The development and evaluation of an individualised gait modification intervention to improve movement function in alkaptonuria patients

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Abstract

Alkaptonuria (AKU) is an ultra-rare genetic disorder which leads to a process called ochronosis, this process discolours and damages the integrity of the joints. Ochronosis within the joint leads to several symptoms including joint pain, premature osteoarthritis and a decline of joint health until eventually total joint failure. These symptoms directly impact mobility, gait and consequently the patient's quality of life, however, there is limited data focussing on the effects of AKU on gait. Mechanical loading at the joint contributes to the ochronosis process, joint damage and progression of the disease. Treatment options currently include nitisinone, however the adverse side effects of long-term use remain a concern. A gait modification intervention is a non-invasive method which has the potential to reduce the loading in the joints which could delay the progression of the disease and delay the time before joint replacements are required.

The work within this thesis firstly describes and characterises gait using novel methods to help understand the progression of the disease and its specific gait mechanisms. The gait of 36 AKU patients between 16-70 years under no treatment were analysed. Gait deviations from normality were discovered in patients as young as 16 years old and a sharp increase was seen at 50 years. Joint level descriptions of gait mechanisms revealed the knee joint to be a problematic factor across all age groups in AKU. Driven by the evidence, the knee joint became the focus of the gait intervention's development and design. The thesis also includes development of a novel intervention tool tailored to alkaptonuria patients, which overcomes some of the methodological shortcomings found in related previous research. The 3D Lever Arm method is a simplified, fast computing method which provides the 3D knee moment impulse in real-time to the patient and is designed to create an individualised approach to gait modifications. The 3D lever arm method was compared to the 'Gold Standard' inverse dynamics during normal walking and six well known gait modifications for 16 healthy controls. The new method demonstrated good agreement during normal walking although underestimated the 3D knee moment impulse, most importantly it was able to detect change during the six gait modifications. The protocol also investigated six gait modifications' ability to reduce the 3D knee moment impulse and the effects on adjacent joints. Only four out of the six were effective at reducing the 3D knee moment impulse, with two increasing adjacent joint moments, and the results highlighted a large variation of individualised approaches. The results led to only three out of six gait modifications being acceptable for future guidance during the final intervention study. Finally, using the new intervention tool, a gait modification protocol was designed for AKU patients, however, findings of only one healthy participant are presented. The results showed that the participant was able to reduce the 3D knee moment impulse after the

individualised gait modification intervention and this was also retained when walking overground.

Overall, the findings of this thesis provide the first joint level description of gait in alkaptonuria, develop a gait modification intervention tool and protocol design. These findings provide the vital first steps towards gait modification interventions for alkaptonuria patients with discussions for future research studies.

Research outputs and publications relating to thesis

King, S., Hawken, M., **Shepherd, H.,** Gallagher, J., Ranganath, L. and Barton, G. (2017) Protective effect in females with Alkaptonuria: Relationships between gait deviations and ochronosis. *Gait & Posture,* 57, 149-150. (Appendix 1).

Cox, T., Psarelli, E.E., Taylor, S., **Shepherd, H.R.,** Robinson, M., Barton, G., Mistry, A., Genovese, F., Braconi, D., Giustarini, D., Rossi, R., Santucci, A., Khedr, M., Hughes, A., Milan, A., Taylor, L.F., West, E., Sireeau, N., Dillon, J.P., Rhodes, N., Gallagher, J.A. and Ranganath, L. (2019) Subclinical ochronosis features in alkaptonuria (SOFIA): a cross-sectional study. *BMJ Innovations,* 5 (2-3), 82-91. (Appendix 2).

Shepherd, H. R., Ranganath, L. R., Robinson, M. A. and Barton, G. J. (2017) Gait Deviations in a European Cohort with Alkaptonuria. 16th CMAS Annual AGM Meeting, Salford, UK. April 6th- 7th. *Oral Presentation.* (Appendix 3).

Shepherd, H., Barton, G., Robinson, M. and Ranganath, L. (2018) Self-selected gait modifications to reduce the internal knee abduction moment in Alkaptonuria patients. *Gait & Posture,* 65, S180-S181 27th ESMAC Meeting and Conference, Prague, Czech Republic. September 24th -29th. *Oral Presentation.* (Appendix 4).

Shepherd, H., Ranganath, L. R., Robinson, M. A. and Barton, G. J. (2019) Identifying joint specific gait mechanisms in Alkaptonuria patients. 18th CMAS Annual AGM Meeting, Sheffield, UK. April 25th- 26th. *Oral Presentation.* (Appendix 5).

Shepherd, H., Barton, G., Robinson, M. and Ranganath, L. (2019). Inverse dynamics versus a simplified 3D knee joint moment: a potential method for real-time biofeedback during gait modifications. 28th ESMAC Meeting and Conference, Amsterdam, Netherlands, September 26th – 28th. *Poster Presentation.* (Appendix 6).

Shepherd, H., Barton, G., Robinson, M. and Ranganath, L. (2020). Taking a moment to consider the medial knee thrust: Gait modifications to reduce the 3D knee moment. Virtual ESMAC Meeting and Conference, September 17th – 19th. *Poster Presentation.* (Appendix 7).

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List of Abbreviations

AKU: Alkaptonuria

HGD: Homogentisate 1,2-dioxygenase

HGA: Homogentisic acid

UK: United Kingdom

NAC: National Alkaptonuria Centre

OA: Osteoarthritis

DRI: Dietary Reference Intakes

GGI: Gillette Gait Index

GDI: Gait Deviation Index

CP: Cerebral Palsy

GPS: Gait Profile Score

MAP: Movement Analysis Profile

MDP: Movement Deviation Profile

SOM: Self-Organising Map

SPM: Statistical Parametric Mapping

GRF: Ground Reaction Force

LJMU: Liverpool John Moores University

KAM: Knee Abduction Moment

KL: Kellgren and Lawrence Grading Score

WOMAC: Western Ontario and McMaster Universities Arthritis Index

KFM: Knee Flexion Moment

JCS: Joint Coordinate System

NHS: National Health Service

NRES: National Research Ethical Service

MFRL: Movement Function Research Laboratory

Chapter 1. Introduction

1.1. Introduction to the research

Walking is an integral part of daily living, and to the majority it is considered a simple activity likely taken for granted. Walking provides health benefits, improves cognitive functions and most importantly gives us independence (Lee and Buchner, 2008). Unfortunately for some, certain diseases or conditions can have a detrimental impact causing pain and abnormalities during the seemingly simple task of gait. One of those debilitating diseases is Alkaptonuria (AKU).

Alkaptonuria, often termed as the 'Black bone disease', is an ultra-rare recessive genetic disorder with an estimated incidence of 1:250,000-100,000 worldwide (Phornphutkul et al., 2002). Alkaptonuria is developed by inheriting two copies of the faulty homogentisate 1,2-dioxygenase (HGD) gene, one from each parent. Due to the disrupted catabolic pathway, there is a harmful build-up of homogentisic acid (HGA). When HGA is oxidised, a melanin-like polymer is produced which binds to effectively all fibrous connective tissues and cartilage leading to ochronosis, which is the dark discolouration of the tissues (Introne and Gahl, 1993), hence the name 'Black bone disease'. Due to increased HGA binding and the extensive pigmentation, the hyaline cartilage ultimately becomes stiff and brittle. Further structural joint damage occurs when the stiff pigmentated cartilage becomes impacted and embedded into the subchondral bone which is located directly below the cartilage, and fragments of the brittle cartilage have also been found within the joint's synovial fluid (Taylor et al., 2011).

Although AKU was the first genetic disease to be described back in 1902 by Sir Archibald Garrod, it has only been in the last 10 years that the development of research into AKU began to rise. Alkaptonuria research has recently advanced in the UK, particularly since the National Alkaptonuria Centre (NAC) was established by the Department of Health (National Specialised Services Commission Group, 2013). The NAC is the treatment centre based at the Royal Liverpool University Hospital and first opened to all UK AKU patients in 2012. Since then there have been successful advances in the awareness, diagnosis and research to help better understand the care and treatment requirements for these patients. Research stemming from the NAC began with trying to understand the biochemical changes in AKU which dramatically enhanced the knowledge in this area. Based on the clear movement limitations seen within the patient cohort, and in the hope to broaden the understanding of the disease, the NAC extended to include a clinical gait analysis service in 2013 as part of their regular service.

The decline in joint health leads to premature osteoarthritis (OA) in the majority of AKU patients, and this premature progression in joint disease causes a considerable amount of pain, disability, loss of movement function and a decrease in quality of life (Rudebeck et al., 2020) and every AKU patient will unfortunately experience joint pain. According to previous research there appears to be a rapid increase of symptoms including ochronosis levels and joint pain at the age of 30 years (Introne and Gahl, 1993; Ranganath and Cox, 2011). The pathological changes due to AKU cause alterations in the joint load-distribution and consequently, the load applied to the underlying bone (Taylor et al., 2011). Alkaptonuria research has shown that the initial sites of ochronosis are within the tissues that are anatomically associated with the most mechanical loading, typically the large weight-bearing joints; spine, hips and knees (Taylor et al., 2011). It is expected that increased joint loading would further accelerate joint disease progression and joint decline.

Unfortunately, there is no current cure for AKU. The drug nitisinone is an effective inhibitor of the 2nd enzyme in the tyrosine catabolic pathway reducing the harmful build-up of HGA and therefore considered as a potential therapy for AKU. Nitisinone is offered as an 'off label' drug to patients at the National Alkaptonuria Centre (NAC), and research to support licensing is ongoing. However, the drug has shown potential adverse side effects and long-term use is still being monitored, in addition, there is currently no clear evidence that it reverses or cures AKU symptoms. Alkaptonuria treatment therefore primarily focuses on the management of symptoms.

The relationship between biomechanical factors and pathophysiology of OA has been broadly researched (Mills, Hunt and Ferber, 2013; Teng et al., 2015) and it is widely believed that the joint loading, particularly of the knees and hips contributes to the degeneration of articular cartilage (Miyazaki et al., 2002; Andriacchi et al., 2004). The disease progression of both AKU and OA regularly leads to total joint replacements in many patients (Gabriel et al., 1997). In AKU total joint arthroplasties occur in more than 50% of patients around 50 years of age (Ranganath, Jarvis and Gallagher, 2013). Gait modification interventions aim to teach patients how to modify their gait in a beneficial way that reduces or alters the joint loading. Gait modification interventions are frequently considered as an alternative to surgical interventions, as they are non-invasive and have the potential to delay the progression of the disease and reduce pain. A systematic review identified 14 different gait modifications to reduce the knee loading in OA patients (Simic et al., 2011). The most effective gait modification remains unclear within the literature, and disparity between which knee loading variable is most associated with disease progression exist within research. Previous studies have also been susceptible to sample selection bias and have used healthy young adults to assess the effect of gait modifications, making generalisation to the affected population difficult. Only few studies have taken into account

the effects of gait modifications on other joints and participant symptoms and furthermore the delivery of the gait modifications are susceptible to methodological issues, particularly for heterogeneous sample populations such as AKU.

Despite movement limitations in AKU, there are only two published papers on gait and AKU (Barton et al., 2015; King et al., 2017). This highlights a clear need to characterise and describe gait in AKU to improve the understanding of the disease. Identifying when problems first begin and monitoring their changes will help to support and influence treatment plans and symptom management. Identifying specific gait characteristics will guide and influence the development of novel non-invasive interventions that are specific to AKU. Although AKU is a rare disease, it ultimately leads to, and has similar symptoms of OA. Understanding the functional effects of AKU on gait can also be transitionally applied to the much more common OA, currently affecting around 10 million people in the UK (VersusArthritis, 2018). Having no current cure to this lifelong disease, gait modification interventions that are non-invasive, potentially structure modifying and aim to slow the progression of joint decline are valuable both for the cost burden of surgical interventions and for the patients, by reducing their daily pain and most importantly increasing their quality of life.

Chapter 2. Literature Review

2.1. Introduction

The following literature review presents a comprehensive discussion on the current research and knowledge associated with the aims and objectives of this thesis. Firstly, the literature review will discuss the relevant clinical research relating to alkaptonuria, its treatment and management. This will be followed by a discussion on alkaptonuria's effect on the functionality of gait, and how gait and joint loading parameters contribute to the progression of the disease. Finally, the review will address the current literature investigating the effectiveness of gait modification interventions that aim to reduce the loading of the joints, and ultimately the progression of disease and pain in alkaptonuria patients.

2.2. Alkaptonuria

Alkaptonuria is one of the 7000 known rare diseases (Wakap et al., 2020). A disease is defined as rare if it affects less than 1 in 2000 people within the general population (EuropeanCommission, 2020). Alkaptonuria is often diagnosed shortly after birth and is identified by the presence of dark urine. It is a hereditary disease and the defected gene results in the absence of homogentisate 1,2 dioxygenase (HGD), the enzyme which is responsible for breaking down homogentisic acid (HGA) (Figure 1). The defected HGD gene prevents the catabolism of phenylalanine and tyrosine, which results in a build-up of HGA which is naturally produced by the body in small quantities during catabolism. The usual removal of HGA by urinary excretion is not sufficient to completely remove this substantial build-up of HGA from bodily tissues and fluids. After the oxidation of HGA, a melanin-like pigmented polymer is produced which binds to effectively all fibrous connective tissues and cartilage. Over the years HGA accumulates and the increased levels of HGA pigmented polymers are deposited within the hyaline articular cartilage and connective tissues, this leads to a black/blue discoloration in a process called ochronosis (Introne and Gahl, 1993). Ochronosis occurs in all components of the joint, bone, cartilage, synovium, capsule, ligament and tendon. As well as pigmentation, the mechanical properties of the affected tissues are altered and weakened, and the cartilage becomes brittle. This eventually leads to total joint failure, a collapse of load-bearing joints (in particular the vertebral column, knees and hips) and early disability (Keller et al., 2005). So far, ochronosis has been observed in the 3rd to 5th decade of life and other organs affected are the ears, eyes, cardiovascular system, kidney and glands (Keller et al., 2005).

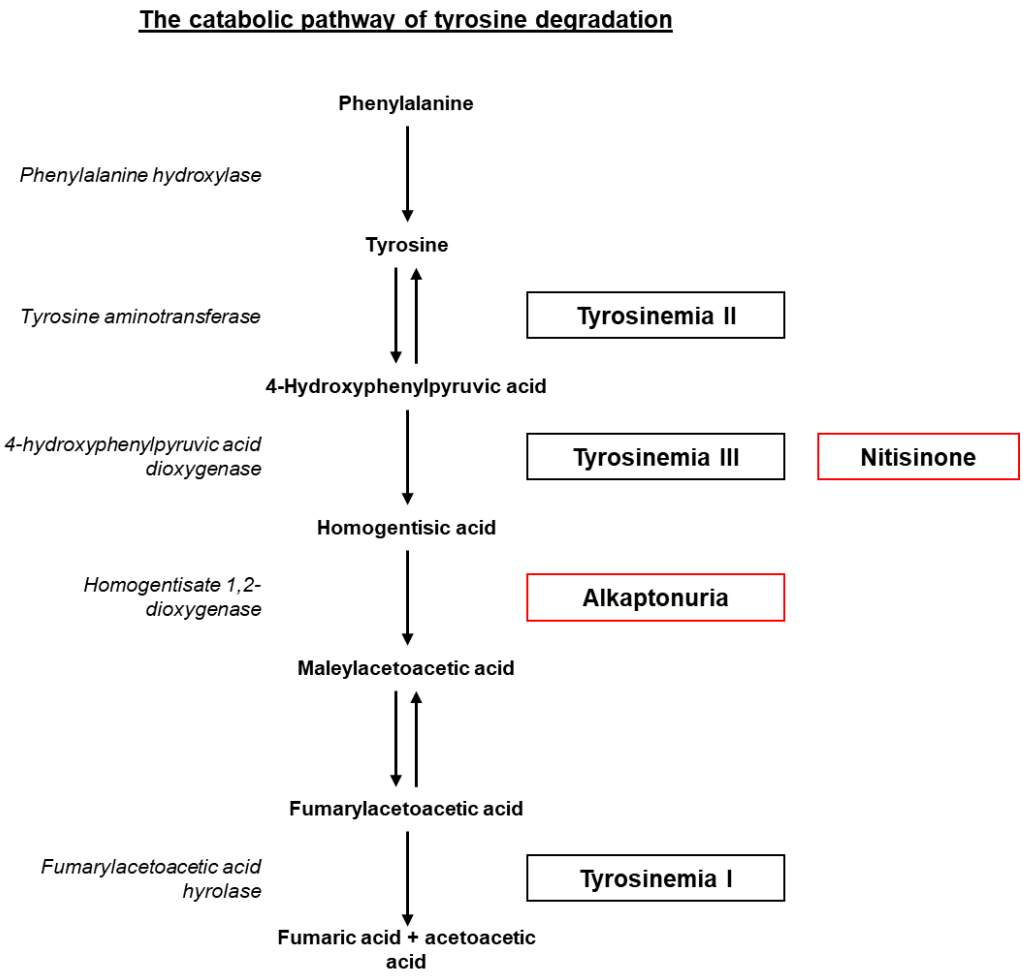


Figure 1: The catabolic pathway of tyrosine degradation. Alkaptonuria causes a deficiency of homogentisate 1,2-dioxygenase leading to a build-up of homogentisic acid. Nitisinone inhibits 4-hydroxyphenylpyruvic acid dioxygenase blocking the formation of homogentisic acid evoking tyrosinemia type two.

2.2.1. Epidemiology

Alkaptonuria is an ultra-rare autosomal recessive genetic condition. There are two copies of every autosomal gene. To develop AKU both copies of the HGD gene need to be faulty. If only one copy of the gene is faulty then the healthy copy is still able to carry out its role. Individuals that have a combination of one faulty copy and one healthy copy become genetic carriers but do not develop the disease or show symptoms. When both parents are genetic carriers it means that their child will have 1 in 4 chance of developing AKU. The various scenarios outlining the autosomal genetic inheritance are shown in Figure 2.

These types of disorders are not typically seen in every generation of an affected family. So far, 1233 AKU patients have been identified worldwide (Zatkova, Ranganath and Kadasi, 2020). The incidence of AKU is estimated at 1 in 250,000 to 1 in 1,000,000 in the majority of populations (Phornphutkul et al., 2002). Geographically the highest incidence has been found in Slovakia, India and Jordan where the incidence can rise to 1 in 19,000 (Zatkova et

al., 2000; Al-Sbou, Mwafi and Lubad, 2012). Due to the hereditary genetic determination of AKU, it is most prevalent in isolated communities where there is reduced genetic variation and an increase in consanguineous marriages occur (Ranganath and Cox, 2011).

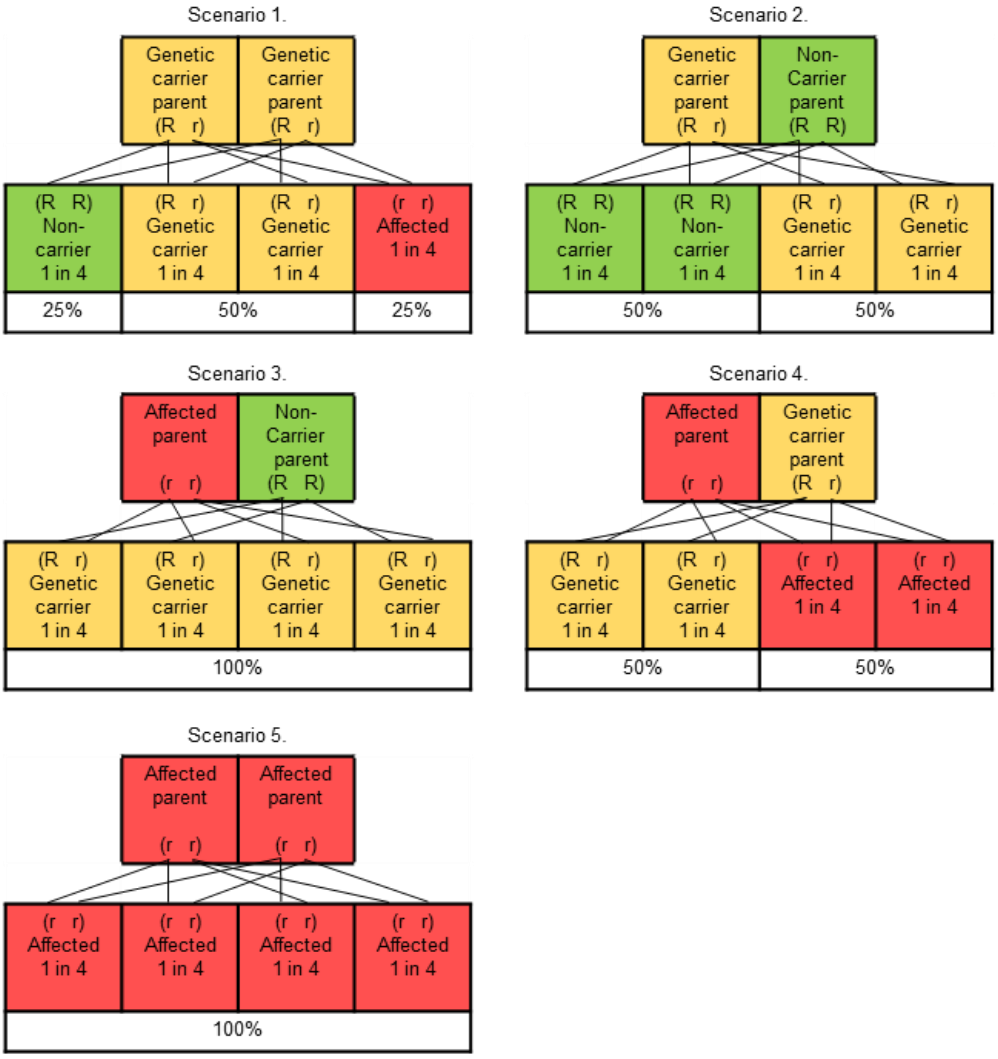


Figure 2: The autosomal recessive genetic inheritance scenarios where (r) represents the faulty copy of the HGD gene, (R) represents the healthy copy of the HGD gene.

2.2.2. Symptoms and diagnosis

It is thought that the distinct clinical features of AKU, homogentisic aciduria, ochronosis and ochronotic osteoarthropathy all develop at different stages of life (Ranganath, Jarvis and Gallagher, 2013). The earliest clinical features of AKU is the urine, which darkens upon standing during oxidation of the HGA pigment and is first noticed when the baby's nappy is black. This is one symptom found in the paediatric age group and is often the first observation, leading to 21% of AKU diagnoses before one year of age (Phornphutkul et al., 2002). Despite these signs, early diagnosis of AKU is still low, and late diagnoses are common. Many are diagnosed after an arthroscopy which has revealed the black, damaged

cartilage and even then, some remain undiagnosed. On average it takes more than four years for a rare disease to be accurately diagnosed (RareDiseaseUK, 2019). Recent work within the AKU Society, dissemination of information, new reliable methods of AKU diagnosis and improvements in AKU medical education have also increased the number of earlier diagnoses. Ochronosis is thought to appear in the third through to fifth decades of life where pigmentation is seen clearly in the eyes and the ears. Large joints, kidneys and the cardiovascular systems are affected and aortic valve stenosis is also frequently observed in AKU patients (Fisher and Davis, 2004). Eventually, ochronotic osteoarthropathy occurs due to the accumulation and deposition of the HGA polymer within the hyaline articular cartilage.

Alkaptonuria is not officially classified as a rare bone disease, it is a disease which severely affects the bones and joints and the structural damage ultimately causes most of the symptoms and pain in AKU. A recent patient survey reported the prevalence of AKU symptoms, and included the patient perspective of the impact of the AKU symptoms (Rudebeck et al., 2020). The study found that joint pain, eye pigmentation, lower back pain, and stiffness were the most common symptoms reported by the patients between 40-74 years old, with joint pain being the most common. Of those symptoms, the patients also perceived joint pain to be the symptom with the highest impact to their life, closely followed by physical disability, spine pain and stiffness. Although AKU has not been found to reduce life expectancy, the progressive nature of the disease causes disability and considerably reduces the quality of life for AKU patients.

2.2.3. Treatment and management in Alkaptonuria

There have been a few therapeutic options that have been tested in the hope to treat AKU and reduce the accumulation of HGA. Ascorbic acid was one of the first to be investigated as a potential treatment, its antioxidant properties could potentially prevent the formation of benzoquinone acetic acid from HGA and therefore reduce ochronosis (Sealock and Silberstein, 1939; Merolla et al., 2012). However, ascorbic acid as a treatment was found to be ineffective particularly *in vivo* with concerns over negative side effects (Wolff et al., 1989; Mayatepek et al., 1998). Presently, there is no clinically approved pharmacological cure for AKU, and treatment currently depends on anti-inflammatory drugs, self-management of pain, diet interventions and joint replacement surgeries. It has been reported that the total joint arthroplasties occur in more than 50% of patients around 50 years of age (Ranganath, Jarvis and Gallagher, 2013).

2.2.3.1. Nitisinone

The relatively new and promising therapy drug nitisinone is typically used to treat hereditary type-1 tyrosinemia. This hereditary condition involves the same metabolic tyrosine degradation pathway and inhibits the HGA producing enzyme 4-hydroxyphenlpyruvate dioxygenase (Figure 1). Nitisinone aims to prevent the build-up of the harmful homogentisic acid in alkaptonuria patients, and several clinical trials through the DevelopAKUre programme are ongoing to assess its effectiveness.

One study monitored the response of a dose of 2 mg of nitisinone given once daily and showed a 95% reduction of urine and plasma HGA concentrations. This result was sustained for 3 years (Suwannarat et al., 2005; Introne et al., 2011). Although nitisinone was shown to be effective in reducing circulating HGA in both human (Introne et al., 2011) and mice studies (Keenan et al., 2015), there was little evidence on the effectiveness of nitisinone on levels of ochronosis, disease severity or rate of progression. More recently, Ranganath et al. (2018) found that as well as decreasing the HGA in AKU patients by >80%, nitisinone reduces the rate of disease progression over a three-year period. To measure disease severity, the AKUSSI assessment tool was developed specifically for AKU. The AKUSSI is a semi-quantitative tool with some features based on both objective and subjective measures including pain-related scores and eye and ear ochronotic pigmentation. Although the AKUSSI was found to be a robust tool to measure disease severity (Langford et al., 2018), other than subjective measures of pain, it does not incorporate specific objective features of joint damage that directly affect mobility.

A dose response relationship was established when carrying out an international, randomised, open-label, no-treatment controlled, parallel group study. With 40 AKU patients during a 4 week study, a clear dose-response relationship was found between nitisinone and the urinary excretion of HGA after 4 weeks, with the highest dose of 8 mg/day showing a reduction of urinary HGA by 98.8% (Ranganath et al., 2016). Although nitisinone is showing signs of becoming a promising drug to delay the onset of ochronosis, nitisinone can also cause several side effects. One concern was the increase in tyrosine levels seen in all doses during the Ranganath et al. (2016) study, as nitisinone interrupts the tyrosine degradation pathway (Figure 1) it results in a significant increase in tyrosine levels. The increased levels of tyrosine in all doses was shown with a less clear dose response relationship than the effect of nitisinone. Although no adverse effects were reported, this study was only short-term, and long-term effects of high tyrosine levels were not monitored. Clinical symptoms reported from long term use of nitisinone used in tyrosemia patients include development of eye lesions (keratopathy) and in some child cases neurocognitive deficits were found, however a direct link to nitisinone remains unclear (Bendadi et al., 2014). Adverse effects have been reported in some AKU patients

including kidney stones, vomiting, and corneal dendritiform keratopathy during a 3-4-month trial (Suwannarat et al., 2005). One case study saw a 22-year-old AKU male on a 2 mg daily dose of nitisinone develop dendritiform corneal keratopathy in both eyes. The development was noticed on the third annual visit to the NAC, however, the AKU patient had reported no symptoms suggesting that this detrimental side effect of nitisinone can occur asymptomatically and potentially unnoticed (Khedr et al., 2018). In addition to its adverse side effects, there is currently no clear evidence that nitisinone reverses the symptoms. Despite this, nitisinone is considered an effective treatment for reducing the effects of the disrupted catabolic pathway seen in AKU and has the most direct effect of reducing HGA. As part of the DevelopAKUre programme, involving 12 European partners, the results of a double-blind clinical trial comparing treatment versus non-treatment over a 4-year period with blood biochemical measures is currently being analysed. In addition to these biochemical measures, research should also consider the long-term effects of nitisinone treatment on several other clinical features. Can nitisinone reduce or delay ochronosis sufficiently, and is this enough to improve mobility and gait function and ultimately increase the AKU patient's quality of life? When considering these harmful side effects, for nitisinone's future usability, the most prominent question posed is - *when should treatment be initiated?* To help answer this question, sub-clinical symptoms of AKU should be further investigated alongside blood chemical indicators. Due to the nature of AKU, gait deviations or abnormalities are considered as a sub-clinical measure of AKU. Analysis into gait abnormalities should include identifying when AKU symptoms first appear, along with their magnitude, to help identify the appropriate age for initiation of nitisinone treatment which maximises effectiveness of the treatment but minimises the risk of long-term side effects. The monitoring of the natural progression of gait deviations in AKU patients will be the first objective of this thesis.

2.2.3.2. Diet and weight loss

Non-pharmacological approaches have considered diet and weight loss. As HGA is derived from protein degradation, theoretically, limiting the amount of dietary protein should decrease the HGA production. Very few studies have investigated the effects of dietary interventions on urine HGA. One study reviewed the medical records of 16 AKU patients aged between 3-27 years. They found that a high protein diet of 3.5 g/kg per day in children for one week led to significant increases in HGA urine excretion when compared to a low protein diet of 1 g/kg per day in children under 12 years (de Haas et al., 1998). Further single case studies found that a protein intake of 0.3 g/kg per day reduced plasma and urine HGA by 25% in one adult, and in a 5 month old child when protein intake was restricted to 3.5 g per day showed an 89% decrease in HGA secretion (Wolff et al., 1989). Although positive effects were observed in these studies, the protein intake restrictions

applied could be considered drastic since the DRI (Dietary Reference Intake) recommends 0.8 g/kg per day for adults and around 11 g per day for babies aged 7-12 months. Severe protein restrictions pose the risk of nutritional deficiencies including vitamin B12, iron and calcium and should be medically supervised. Highly restrictive diets are also hard to maintain and uncooperativeness to a low protein diet was also observed in AKU patients above the age of 12 years (de Haas et al., 1998), possibly due to no immediate visible effects which could reduce motivation, and a perceived disruption to social life. Furthermore, no long-term studies using greater sample sizes of AKU patients have yet been studied, both of which are critical when investigating a slowly progressing disease.

In osteoarthritis (OA) research it has been suggested that the Mediterranean diet can be beneficial to disease progression. One study found that a higher adherence to a Mediterranean diet is associated with a decrease in OA symptoms and increased quality of life (Veronese et al., 2016). The Mediterranean diet typically consists of high consumption of fruits, vegetables, seeds, fish and seafood with olive oil being the main dietary lipid (Davis et al., 2015). This combination lowers the Omega-6 to Omega-3 ratio. Omega-3 fatty acids and polyphenols prevent inflammation and cartilage destruction. In contrast, Omega-6 fatty acids, typically found more so in the western diet, induce the inflammation processes. Another study found a decreased pro-inflammatory cytokine and significant improvements in knee flexion and hip rotation range of motion in the Mediterranean diet group after a 16-week intervention (Dyer et al., 2017). Although these inflammatory responses to diet could be considered transferrable to AKU, the effects have not yet been studied in AKU patients.

Obesity is widely acknowledged as a risk factor for the onset of knee OA (Lau et al., 2000). Although AKU is a genetic disease and not predetermined by risk factors, it could be hypothesised that obesity may contribute to the progression and severity of joint damage in these patients. Obesity increases the mechanical stress of a weight-bearing joint beyond its capabilities. During physical activity for 1 kg of weight loss the knee can experience a four-fold reduction in load (Kuster et al., 1997). This reduction in body weight would directly reduce the magnitude of the ground reaction force vector during movements such as gait, and it is estimated that the magnitude of the ground reaction force contributes 30% of the maximum joint contact forces during level walking, with net muscle forces acting about the knee joint (joint moments) contributing the remaining 70% (Kuster et al., 1997). However, the net joint moments do not consider the muscle co-contractions during gait which contribute to the overall joint contact forces. The positive effects of weight loss on knee OA symptoms and quality of life are strongly evidenced (Christensen et al., 2007), however, its effect of structure modifying capabilities is often conflicting.

2.3. Quantifying gait in clinical populations

Characterising and describing gait patterns in pathological populations has been carried out for decades and there has been extensive research in mobility disorders such as Cerebral palsy, Osteoarthritis, Stroke and Parkinson's (Sofuwa et al., 2005; Gage et al., 2009; Boudarham et al., 2013; Mahmoudian et al., 2017). This has become easier since the introduction of instrumented gait analysis which is a non-invasive procedure objectively quantifying human movement. Frequently, quantitative gait data in a clinical setting are often described and interpreted by trained individuals, and qualitative tests are used to classify patients. The interpretation of these tests are compromised by the subjectivity and the level of training of the analysts (Skaggs et al., 2000). To overcome some of these issues more quantitative methods to classify, monitor and describe gait outcomes have emerged in the literature. These include methods to summarise measures of gait by reducing the complexity and dimensions of gait data, as well as more robust statistical approaches.

2.3.1. Summary measures of gait

A 3D gait analysis provides large amounts of highly complex and interdependent data collated from multiple joints and body segments in three planes of motion at numerous instances in time. Figure 3 highlights the complexity of gait data.

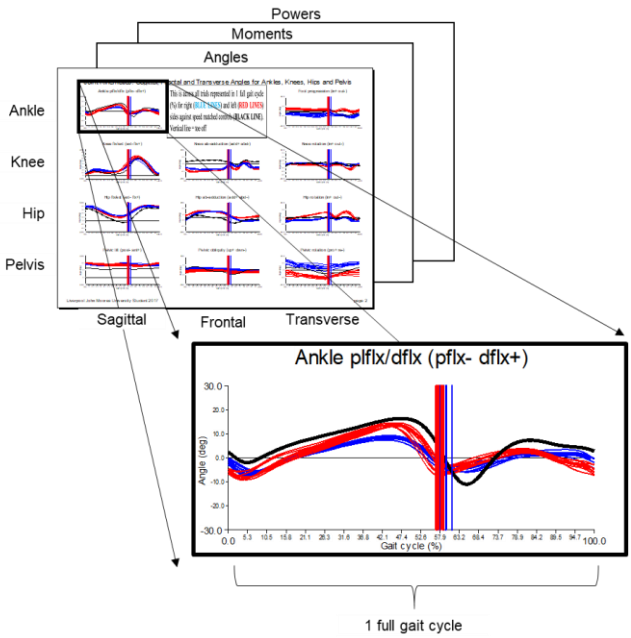


Figure 3: The complexity of gait data can only be captured by quantifying angles, moments in three planes of motion (sagittal, frontal and transverse) and powers at all joints of the lower limbs (ankle, knee, hip and pelvis) across one full gait cycle.

Motion is also coupled across other joints and planes, and each motion occurring at one instant in time can affect other joints at a later point in time. Not surprisingly, methods to reduce the complexity and quickly assess the overall quality of gait and avoid subjectivity of interpretation have been introduced. These methods are single summary gait measures and are now commonly used within clinical practice.

The Gillette Gait Index (GGI) by Schutte et al. (2000) was one of the first to be clinically accepted. The selection of 16 discrete variables were chosen with the help of clinical input and partly for convenience. The variables were those thought to be with closest relevance to that particular gait problem. However, these variables are not generalizable across gait problems or patient groups. The GGI then measured the distance between a set of 16 principal component scores to describe a patient's gait pattern and the average of those scores in a healthy control's gait pattern. Despite its limitations the GGI was the first index measure to be widely used within clinical practice (Romei et al., 2004; Romei et al., 2007) and appears to be the single summary measure most validated (Hillman et al., 2007; Wren et al., 2007).

To overcome the GGI's shortcomings, the Gait Deviation Index (GDI, (Schwartz and Rozumalski, 2008) was presented. The GDI includes multivariate analysis of the joint rotations that efficiently describe gait. By including continuous kinematic plots, the non-generalisability and the subjectivity of choosing discrete gait parameters is removed. The GDI presents the nine kinematic plots as vectors to a singular value decomposition, which extracts and preserves a small number of eigenvectors that account for a large proportion of the information from the original dataset. These eigenvectors are then linearly combined. A Euclidean distance is then measured from control group to subject from any pathological gait condition, this is then scaled to give a GDI score. Typically developing able-bodied controls have a GDI mean of 100±10, within cerebral palsy children it is shown that the GDI decreases from 100 as gait presents more abnormalities, and a decrease of GDI also moderately correlates with an increase in GMFCS (gross motor function classification score) $r = -0.44$ $p < 0.0001$ (Massaad et al., 2014). A comparison of the GDI to the GGI showed a moderate association $r^2 = 0.56$, but a large spread, suggesting that the two measures reflect different aspects of the gait pathology. The GDI also showed a good trend with disease involvement when using the cerebral palsy (CP) classifications. Although the GDI overcame some of the GGI's limitations, its large publicly available normative database was focused on paediatric gait, using a specific biomechanical protocol and marker set, therefore, making this database not fully generalisable across labs, protocols or movements other than gait.

The Gait Profile Score (GPS, (Baker et al., 2009)) is another gait summary measure based on the root mean square difference between a gait variable from a pathological condition

which has been time normalised and the mean data from a reference population calculated across the gait cycle. The GPS is based on the same nine key kinematic variables as the GDI, is mathematically similar to the GDI and calculated across the entire waveform. The GPS showed a strong correlation to the GDI at r =0.995 and showed a low intra-session variability. One advantage of the GPS is the use of the Movement Analysis Profile (MAP) which summarises the information and provides an insight to which variables are contributing to the elevated GPS alongside information on symmetry.

Furthermore, the Movement Deviation Profile (MDP, (Barton et al., 2012)) produces a subject's deviation from normality in the form of a curve across the duration of the gait cycle. This is done through training a Self-Organising Map (SOM, (Kohonen, 1990)) trained with control data to represent characteristics of normal gait using the nine key gait angle curves. When a patient's data is then presented to the trained SOM, the MDP shows the distance from normality at each data point. A single value (MDP_{mean}) can be derived by the mean of the series of deviation values. The MDP had a high correlation with the GDI (r^2=0.927). The advantages of the MDP over the GDI is that the SOM's architecture corrects for any temporal offsets making it more robust. To further advance this method the use of marker coordinates data instead of angle curve data was suggested, the marker coordinate data was first presented to a principle component analysis by Federolf, Boyer and Andriacchi (2013). One advantage of using the marker coordinate position is that it removes the variability of the pre-selection of variables to include in the analysis, a problem seen in the Gillette gait index measure. Secondly, it removes the influence of the Cardan rotation sequences or the differences in joint axes definitions (of which there are multiple combinations). The choice of Cardan rotation sequence can influence the orientation of joint angles and the most appropriate sequence can differ between different movement patterns (Lees, Barton and Robinson, 2010). By using the marker coordinate position as an alternative to angular curve data it removes risk of introducing artefact through secondary calculations (Barton et al., 2015). Overall, the MDP summary gait measure is an excellent tool to reduce the complexity of gait data, monitor disease progression over time and to measure the efficacy of interventions. The MDP summary gait measure will be used to achieve objective one within chapter three of this thesis, by facilitating the mapping of the natural progression of gait deviations in AKU adults.

2.3.2. Discrete parameters vs. Statistical Parametric Mapping (SPM)

Gait summary measures are vital tools for monitoring the progression of diseases, classifying diseases and observing the effectiveness of a treatment or intervention. However, for a more systematic in-depth understanding of gait, joint specific details also need to be described and quantified. A joint level description helps to understand the

patterns that may be seen in the summary measure index scores, and most important help to inform the next steps for potential treatments.

Biomechanical gait data is usually provided in the form of 1-dimensional trajectories both for kinematics and kinetics, for example the knee flexion and extension angle across the whole gait cycle. Due to the waveform nature of cyclical gait patterns, with many time points and many vector components, analysis of this data can be complex. Traditional approaches tend to extract predetermined discrete scalar gait parameters such as peaks, troughs or ranges of motion, these are usually predetermined by informed, yet still subjective opinions of trained individuals. Sometimes these discrete parameters can even be non-predetermined, whereby the gait trajectories are simply visualised, then variables are extracted based on the differences observed. These discrete parameters are then tested for statistically significant differences between pathological gait and a healthy reference. However, discrete parameters are extremely susceptible to regional focus bias, limited to specific events and overlook any continuous effects. This leads to a potential loss or disregard of important data. Parameters extracted this way are also prone to Type I errors as multiple variables are usually tested from the large dataset produced. Often statistical methods such as the Bonferroni correction are made to attempt to avoid false positives. However, this can lead to increases in Type II errors as these multiple variables are often extracted from the same waveform which are likely to be correlated (Pataky et al. 2013).

Statistical Parametric Mapping (SPM, (Friston et al., 2007)) is a hypothesis testing tool. Due to its n-dimensional methodology it has recently been applied to sport and clinical biomechanical trajectory data to address the statistical limitations of the traditional approaches (Castro et al., 2015; Pataky, Vanrenterghem and Robinson, 2015). Statistical parametric mapping was originally used for the analysis of neuroimaging, typically 3D functional MRI and PET images (Friston et al., 2007). The method's major advantage is that it allows analysis over the entire waveform instead of specific data points. If two or more consecutive points of the test statistic profile cross the critical threshold, this is termed a "cluster". The cluster indicates exactly when in the gait cycle there is a significant difference. A single *p* value is given to each suprathreshold cluster, the higher and broader clusters are expected to occur with low probability, therefore will have lower *p* values (Pataky, 2012). Figure 4 provides an example of how and SPM curve is interpreted.

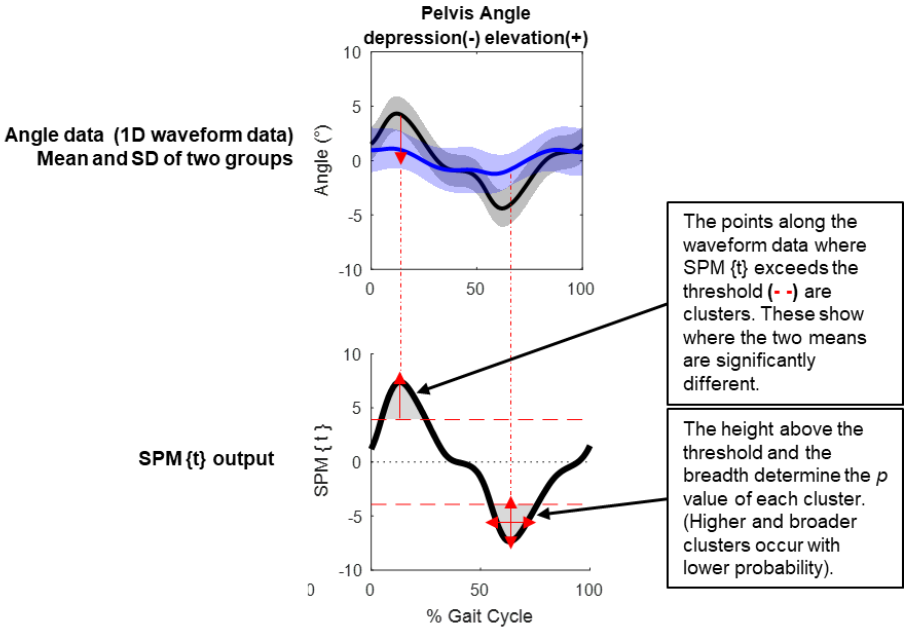


Figure 4: An example of the SPM {t} output curve when comparing angle data (frontal plane pelvis angle) between two groups.

The literature has reported differences in statistical outcomes when analysing the same data sets with traditional approaches and SPM. When assessing ground reaction forces (GRF) between males and females, Castro et al. (2015) demonstrated different outcomes between SPM analysis and traditional approaches which used only discrete peak values. The traditional approach found that males had significantly higher first peak vertical GRF than females, whereas the SPM found that females were significantly higher between 0-5 % of the gait cycle and no significant differences between males and females during the first peak. This suggests that the traditional approaches may miss important differences during parts of the gait cycle that are not analysed (i.e. not a peak value).

A study by Meyer et al. (2018) used SPM to identify the pathomechanics in patients with hip OA and they were able to identify and define abnormalities that can be directly targeted in tailored interventions. They found that patients walked with reduced hip adduction angle and reduced hip abduction and external rotation moments compared to age-matched controls. They also described the reduction in the work generated by the hip abductors. Combining these findings, it is clear that these patients naturally altered their gait kinematics to reduce hip loading, and therefore the demand on the hip abductors. From identifying and describing these gait mechanisms in hip OA patients using SPM, an informed decision can be applied to targeted rehabilitation, hip abductor strength training and gait retraining strategies. One thing to note in the Meyer et al. (2018) study is that the hip OA patients and controls were matched by age and BMI. Some of the differences found between the two groups, particularly in the sagittal plane may be due to differences in

walking speed. This study along with others still only descriptively interpreted the SPM results, simply describing the clusters' height and position along the waveform. When trying to interpret multiple waveform data within patient populations where multiple pathomechanical strategies occur it may be beneficial to systematically rank the clusters to determine which clusters or mechanisms are most important. Overall, SPM provides a more robust statistical analysis when comparing biomechanical trajectory data. To address objective two of this thesis, statistical parametric mapping will be used with chapter four to identify and describe gait mechanisms in AKU.

2.4. Gait and movement function in Alkaptonuria

There is increasing evidence on the structural and pathological changes caused by AKU highlighting a rapid increase of symptoms including ochronosis levels and joint pain at the age of around 30 years (Introne and Gahl, 1993; Ranganath and Cox, 2011). Despite the significant detrimental effects to the joints, there are only small amounts of emerging evidence regarding the effects of AKU on movement function and more specifically gait.

Introne et al. (2011) examined the effect of nitisinone on AKU patients during a 3-year randomised therapeutic trial. A primary outcome measure was total hip range of motion (internal and external rotation) in the worse hip, determined by the greatest loss of rotation at baseline. The hip range of motion failed to show any significant differences between the nitisinone and non-nitisinone group across 10 visits over the 36-month study period. Although the hips are a weight bearing joint and one that is affected by AKU, there was no clear rationale for using hip rotation as a clinical measure stated in the study, even though other joints are also affected such as the knees and spine. Additionally, the internal and external rotation range of motion during gait and typical activities of daily living is minimal, there is also no known evidence to suggest that limited hip rotation is directly related to disease severity and movement function in AKU. In OA research it was found that extension and external rotation of the hip and flexion of the knee to have the strongest correlation with disability (Steultjens et al., 2000), however disability was self-reported by the patients using a questionnaire. Furthermore, the range of internal and external hip rotation is largely determined by the weakness or tightness of the surrounding muscles such as the tensor fasciae latae, piriformis and gemellus superior/inferior which may or may not be solely affected by AKU. Secondary functional outcomes in the Introne et al. (2011) study included Schober's test of spinal flexion, functional reach, timed get up and go and 6-minute walk tests, and these outcomes were significantly worse in the nitisinone group. One explanation for both of these findings is the age range of AKU patients within the study. Although the control group were age matched, the age range ~38-68 years used in this study has been found to be a critical timing for rapid changes both physiologically and structurally in AKU patients (Introne and Gahl, 1993; Ranganath and Cox, 2011). The

Introne et al. (2011) study was the first study to attempt to describe movement and mobility in AKU. Although the secondary outcome measures replicated activities of daily living and are often used in clinical settings, they fail to provide in depth detail on specific joint abnormalities, asymmetry and joint loading during gait.

Gait is one of the most important activities of daily living, and one which is affected by the nature and progression of AKU, reducing the quality of life for AKU patients. At Liverpool John Moores University (LJMU) as part of the National Alkaptonuria Centre's specialised NHS service we have been conducting gait analysis in AKU since 2013. From this work there has to date been two papers published (Barton et al., 2015; King et al., 2017) which we believe are the only specific gait studies in AKU. The Barton et al. (2015) study used the movement deviation profile (MDP, (Barton et al., 2012)) which provides a single number measure of gait deviation from normality (MDP_{mean}) using a neural network trained with 10 healthy controls. When assessed as a function of age they found that the pattern of gait deviations from normality follows a sigmoid shape with an abrupt increase of gait deviations around the second half of the 4th decade of life (Figure 5).

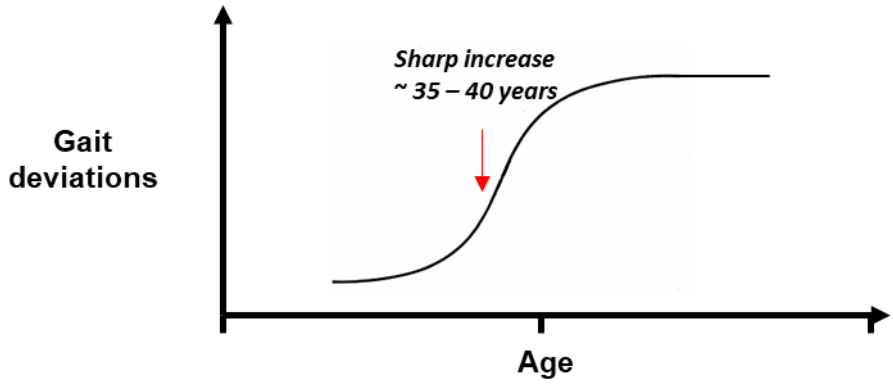


Figure 5: A simplified figure demonstrating the sigmoid pattern of gait deviations from normality as a function of age seen in the Barton et al. (2015) study.

The variation in MDP_{mean} also increased during this stage of life. Additionally, all AKU patients even the younger (<37 years) had higher MDP_{mean} than the control group's MDP_{mean}. The study included subsets of AKU patients; those with and without joint replacements and those with and without nitisinone treatment. A similar pattern of results was found when these groups were considered. This is the first study highlighting the gait deviations from normality in AKU as a function of age. The youngest patient included in the study was only 20 years old and still showing signs of gait deviations, therefore, to truly establish when deviations from normality begin, an investigation into a younger AKU population is vital. Additionally, to truly monitor the natural progression of the disease and its effect on gait and movement function, patients not taking the nitisinone treatment should

be evaluated. These two issues will be addressed in chapters three and four. Gait will be characterised and described in patients from 16-70 years of age to identify if gait deviations are present in younger adults and the AKU patient data analysed in chapters three and four will also be those who were not taking the nitisinone treatment drug, this will allow the monitoring of the natural progression of these gait deviations.

Another study investigated the differences in gait between males and females, again using the MDP_{mean} as an indicator of disease progression and gait deterioration (King et al., 2017). They also considered the relationship between gait deviations and ochronosis. They found that the sharp increase in MDP_{mean} detailed in the Barton et al. (2015) study occurred later in AKU females than in AKU males. Similarly, the ochronosis levels taken from the ear cartilage showed similarly different disease progression in both males and females, suggesting a protective effect in females. It was suggested that hormonal changes may be the reason for these differences and females may benefit from a protective effect. The study provided no direct correlation between ochronosis levels and gait deviations and although the ear cartilage ochronosis gives some indication of disease severity, it may not be well linked to deviations in gait as the ochronosis levels within the joints which are heavily involved in gait. It is clear from the limited amount of studies that there is a need for more evidence and research into the effects of AKU on gait.

From previous literature and the nature of the disease we are aware that AKU affects gait (Barton et al., 2015). However, what these gait deviations are, when they first appear and the cause and effect relationships with the disease progression are still unknown. Gait is a multi-joint, multi-dimensional and cyclic movement, therefore, to comprehensively describe and characterise AKU gait for the first time with appropriate hypotheses, robust statistical methods should be applied. The aim of section one is to characterise and describe gait in AKU for the first time using novel and robust methods. This aim will be address in chapters three and four, through fulfilling objectives one and two.

2.5. Ochronosis progression and mechanical loading

After quantifying and characterising gait in AKU, it is then important to consider the potentially negative effects of particular gait characteristics towards the disease progression and severity. It has been suggested that the presence of HGA alone is not the determining factor in the pigment deposition and ochronosis within the tissue, and that HGA present in healthy cartilage only becomes susceptible to degeneration following focal change (Taylor et al., 2011). A study by Taylor and colleagues compared cartilage samples from AKU pigmented, AKU non-pigmented and patients with OA at various stages of the disease from the knee and hip joints. They observed a distinct pattern of ochronotic pigment binding which initiates in the calcified zone of articular cartilage with focal regions,

then spreads throughout the cartilage. The spread and increase of ochronosis suggests that the initial focal ochronosis may alter the biomechanical properties of their adjacent tissues making it susceptible to pigmentation. These initial focal deposits were in areas that are known to be subjected to the greatest loads during locomotion (Andriacchi, Koo and Scanlan, 2009); typically during gait the knee medial tibial plateau experiences greater loads compared to the lateral knee tibial plateau (Mundermann et al., 2008). Additionally, the pigmentation of the articular surface was central rather than peripheral in the advanced ochronosis. AKU is documented to cause premature OA, and these regions were also associated with the initiations and pathology in primary knee OA following the typical disease process. Determining factors affecting the integrity of the cartilage found from OA research which may overlap in AKU pathology are the subchondral bone turnover, chondrocyte function and biomechanical stresses. Despite the overlap in pathologies, the Taylor et al. (2011) study also found the AKU pigmented cartilage was >5-fold greater in the average Young's modulus than the AKU non-pigmented and OA cartilage, indicating increased cartilage stiffness. This increased stiffness would be more susceptible to further pigmentation in response to tissue injury or mechanical damage even during normal loads. In addition, there is also remodelling of the calcified cartilage and underlying bone leading to an aggressive reabsorption and complete loss of the subchondral plate. This process has not been previously seen in other pathologies including OA.

Conversely, the AKU mouse models show a non-uniform pigmentation across the cartilage, with no end stage 'blanket pigmentation' observed, even in the advances stages (Taylor et al., 2012). Some suggested explanations for these differences were the reduced lifespan of the mice as this reduces the tissue's exposure to mechanical loading and reduces accumulation of HGA polymers to deposit. Furthermore, the mice's quadrupedal locomotion and therefore loading compared to the bipedal human locomotion disperses the load bearing mechanical stresses experienced by the joints.

One more key indicator that the ochronosis is associated to mechanical forces or loading was found following an autopsy (Helliwell, Gallagher and Ranganath, 2008). Aforementioned cardiac problems such as aortic valve stenosis is frequently found within AKU patients. During the autopsy little pigmentation was found in the venous part of the heart, compared to the arterial part where higher blood pressures occur (Helliwell, Gallagher and Ranganath, 2008). Interestingly in the liver, where HGA metabolism occurs, there are no reports showing the development of ochronosis, agreeing with the previous study by Taylor and colleagues that HGA presence alone does not cause ochronosis.

Although there is evidence to suggest that mechanical loading may contribute to the location and distribution of ochronosis within the tissues, and the preferential sites of pigmentation deposition are within the joints and aortic valve, there still remains some

heterogeneity between individuals. However, non-invasive interventions that aim to modify gait, in a way which reduces joint loading in AKU could be a valuable tool for delaying treatment such as costly joint replacements.

2.6. Gait modifications to reduce joint loading

The studies within this thesis aim to be the first in the world to investigate the effects of gait modification interventions on joint loading in AKU patients. Therefore, due to the limited research in AKU and gait, and the shared pathomechanics the following review of the gait modification literature will focus on knee osteoarthritis research.

2.6.1. Knee osteoarthritis pathomechanics

Although AKU is a rare disease, it ultimately leads to, and has similar symptoms of OA. The disease progression of both AKU and OA regularly leads to total joint replacements in many patients (Gabriel et al., 1997). Knee osteoarthritis is a degenerative process which leads to deterioration of the articular surface and eventually leads to a loss of the articular cartilage, osteophyte formation and joint space narrowing. The relationship between biomechanical factors and pathophysiology of OA has been broadly researched (Mills, Hunt and Ferber, 2013), and it is widely believed that the joint loading, particularly of the knees and hips contributes to the degeneration of articular cartilage (Miyazaki et al., 2002, Andriacchi et al., 2004). Similar, to AKU patients, it is seen predominately in the large weight bearing joints such as the knees, suggesting that the mechanical loading is a risk factor, it is expected that increased joint loading would further accelerate joint disease progression and joint decline for both patient groups.

2.6.2. Knee joint moments and disease severity in OA

In an attempt to reduce the loading of weight bearing joints and delay the need for costly joint replacements, research, particularly in knee OA has investigated the influence of load-reducing gait modification strategies. Gait modification interventions are considered a non-invasive and conservative alternative, which aim to reduce the risk of disease onset and/or delay the progression. Unfortunately, it is difficult to directly measure loads applied to the joint surfaces *in vivo*, and so as an alternative, the internal joint moments are widely used as an indirect measure of the net joint loading about the knee. The internal joint moment is the intrinsic turning force acting about a lever arm produced by the muscles and passive joint components to resist the external forces applied to the body.

The incidence of knee OA presenting in the medial compartment of the joint is 5-10 times higher than the lateral compartment (Ahlback, 1968), this together with the understanding that the internal knee abduction moment (KAM) is a determinant of the medial and lateral

load distribution (Schipplein and Andriacchi, 1991) logically led to a number of studies investigating the internal KAM parameters as risk factors for knee OA. Previous studies have found the internal KAM parameters, in particular the 1st peak of the moment profile during the stance phase to be a key factor in the risk of disease progression and pain, associated with radiographic OA severity (Sharma et al., 1998; Miyazaki et al., 2002; Foroughi, Smith and Vanwanseele, 2009) and OA's structural features (Creaby et al., 2010). This led to the peak internal KAM becoming a valid and reliable proxy for the medial knee joint loading (Zhao et al., 2007).

Gait is a cyclical and repetitive movement, yet the peak KAM only provides a measure of load at one instant during the whole movement. It has been suggested that knee KAM impulse (area under the knee moment curve) may give a more comprehensive estimation of the total load applied to the joint as it incorporates the magnitude and duration across the entire stance phase. One study directly compared the peak KAM and KAM impulse's ability to distinguish between measures of disease severity in medial knee OA (Kean et al., 2012). Through an analysis of covariance they found that KAM impulse was significantly different between different severity groups determined by the Kellgren and Lawrence grading scale (KL), (Kellgren and Lawrence, 1957) and alignment groups, whereas peak KAM was not able to distinguish significant differences between the groups.

Hall et al. (2017) considered KL grading of severity, joint space narrowing and KAM parameters to investigate relationships using linear models. Their results found no association within the mild severity group (KL <3). Within moderate severity (KL >3) an increased impulse was associated with increased pain (measured using the Western Ontario and McMaster Universities Arthritis Index (WOMAC), (Bellamy et al., 1988) however within severe disease (KL >4) an increased impulse was associated with decreased pain. This highlights the complexity of the disease, heterogeneous samples and the potential modifications adopted by the severe group to change load distributions in response to pain.

In another cross sectional study by Henriksen, Aaboe and Bliddal (2012) used mixed linear regression analyses to determine relationships between KAM variables, pain and severity and were adjusted for age, gender and walking speed. The less severe group showed negative relationships with KAM variables and pain intensities. The more severe group showed no relationship between peak KAM but a positive relationship between KAM impulse and pain intensity. A limitation to these studies is the cross-sectional design, particularly when assessing pain and symptoms. As with AKU, causal relationships must be made with caution as symptoms may have preceded changes in dynamic knee loading and vice versa.

Although associations and relationships between KAM parameters and disease severity were found, the literature still lacked the direct comparisons between joint moments and the internal medial contact forces applied to the joint surface. To establish this comparison, *in vivo* measurements are needed which are difficult to investigate, or musculoskeletal models which require detailed individualised information. One unique case study used a force-measuring knee implant to directly measure the medial knee contact force, this was then compared to the internal KAM during three different walking trials of normal, medial knee thrust and using a walking pole (Walter et al., 2010). They found that the significant reductions in the 1st peak KAM during the medial knee thrust and walking pole trials compared to normal walking trials, did not coincide with any significant reductions of the 1st peak medial contact force. Conversely, over the entire stance phase similar significant reductions from normal for both walking pole and medial knee thrust were seen in both the KAM angular impulse and the medial knee contact force impulse, suggesting that impulse followed the medial knee contact forces more closely than the 1st peak KAM's. Their reduction in 1st peak KAM during different gait patterns, and no reduction in the medial knee contact force is likely to be due to an increase in the peak external knee flexion moment (KFM) which was also measured. This suggests that frontal plane moments alone cannot solely predict the medial contact forces applied to the joint. This study provided vital insights to the loading applied to the articular surfaces on the knee joint, however due to the complications of instrumented knee implants, studies have used only small numbers and have only been possible on those patients who have undergone knee arthroplasty. Additionally, this study was performed with participants 3.5 years after their knee arthroplasty operation, and therefore did not represent the loading prior to the disease development.

Another study by Erhart-Hledik, Favre and Andriacchi (2015) agreed that KAM parameters alone may not be sufficient enough to predict the knee joint loading environment. Firstly, they found that higher peak KAM is associated with lesser cartilage thickness in the medial tibial regions with a Pearson coefficient of determination at R^2 =0.30, but no associations in patients with less severe OA. Interestingly, they also found the peak external KFM to be associated with cartilage thickness in the posterior region of the medial tibia in the less severe OA group. To further the understanding of this, a subset of patients completed pain questionnaires (WOMAC) and these results showed that a decrease in peak external KFM was significantly associated with a decrease in pain. This could suggest that firstly, increased external KFM may initially contribute to the early stages of disease progression, as only found in the less severe OA group. External KFM may then decrease at the onset of pain and continue to decrease as intensity of pain and disease severity increases.

Furthermore, Roberts et al. (2018) investigated the associations between regional subchondral trabecular bone microarchitecture and joint moment parameters, and included peak moments in all three planes. Contrary to previous findings, their results showed that the peak external rotation moment was significantly and most strongly associated with the 3D micro architectural parameters such as the bone volume fraction and the structure model index score, particularly in the anterior/medial regions. These findings again highlight the importance of considering the net sum of all three knee loading moments acting upon the joint during gait. Although strong correlations were found, the rotation moment is subject to artefacts from cross-correlation and the rotational knee moment curve is one that is often overlooked during typical clinical gait interpretations.

2.6.3. Expression of joint moments in various coordinate reference systems

Throughout the literature the frontal plane loading is reported inconsistently. Some report the external knee adduction moment, some the internal knee abduction moment. The direction of the moment (abduction/adduction) is based on the knee joints position in the frontal plane, relative to the force vector. If the force vector is positioned medially to the knee the external forces (GRF) act to adduct the knee joint, therefore causing an equal and opposite internal abduction moment to counteract this motion. If the force vector is positioned laterally to the knee the external forces act to abduct the knee joint, therefore causing and equal and opposite internal adduction moment to counteract this motion. For the purpose of this thesis the internal (KAM) refers to the internal knee abduction moment.

In addition to the reporting of the KAM, discrepancies between which joint moment parameters are the most important when indirectly measuring joint loading are apparent. One technical methodological discrepancy between studies, and one not often clearly stated is the reference frame in which the moments are expressed in.

Significant differences were found in all joint moment profiles and were more prominent in the frontal and transverse planes when expressed in alternative reference frames when analysing normal gait (Schache and Baker, 2007). These reference frames included three orthogonal frames: laboratory frame, anatomical frame of proximal segment and anatomical frame of distal segment, and one non-orthogonal frame was the joint coordinate system (JCS). Another study evaluated the differences between an orthogonal reference system expressed in an anatomical axis about the bimalleolar axis and a rotation of this reference system. On average the rotation of the reference system was approximately 15° about the long axis of the segment coordinate system. In the knee, they found significant differences in both frontal and sagittal plane peak moments (Manal et al., 2002).

The Walter et al. (2010) *in vivo* study also highlighted difficulty of expressing the moments in different coordinate systems and yielded different results. When the shank coordinate system was rotated by ± 25 °about the superior axis of the shank, this caused large variations in the correlation results between knee moment parameters and medial knee contact forces.

The International Society of Biomechanics recommend the JCS as a standard convention for the description of 3D kinematics, it is also recommended to provide joint moments within the same reference frame as the 3D kinematics (Wu and Cavanagh, 1995). However, it is clear that caution must be taken when comparing results between studies and which reference frame is most appropriate for the expression of the net moment vector remains a debate with limited discussion on the issue. One way to remove this dispute is to consider using the total 3D joint moment. When combining all three orthogonal moment components throughout the gait cycle the total 3D moment's magnitude will remain the same regardless of reference frame used. To the author's understanding no other literature has considered the total 3D moment as a representation of the total knee loading during gait. One study combined the external adduction and flexion moments into a single vector and extracted the magnitude and orientation of the vector defined in the transverse plane of the tibial anatomical frame during the 1st half of the stance phase (Chehab et al., 2014). They used two age groups of healthy participants: young (29.1 ± 4.7 years) and old (50.1 ± 5.6 years). Despite there being no significant differences between groups for the peak KAM and peak KFM, there was a significant difference between the magnitudes of the unified measure with the older group showing an increase.

Gait is a 3D movement and therefore the knee joint loading is a 3D problem but often the sagittal and transverse moments are not considered. The results from these studies highlight the potential contribution of all three joint moment components to the full knee loading environment during the stance phase. Discrete joint moment parameters such as 1st peaks can only describe instantaneous measures and can vary depending on the reference frames they are expressed in. To combat these issues new ways of expressing the total 3D knee moment to better describe or estimate the combined load experienced by the knee joint over the full gait cycle should be considered. The aim of section two within this thesis is to develop a real-time biofeedback method for a treadmill-based intervention. Chapter five will report the development of a new method, which considers the methodological issues reported above, the new method will be evaluated through objectives three and four.

2.6.4. Gait modifications to reduce the internal knee abduction moment

Despite the conflicting evidence regarding the associations between internal KAM parameters, disease progression and total mechanical loading described above, the majority of gait modification interventions continue to exclusively focus on the reduction of internal KAM parameters specifically the 1st peak of the internal KAM as a key variable to measure efficacy of an intervention.

Joint moments are calculated through inverse dynamics, typically through the link segment model. Mathematically, there are two ways of reducing the net joint moment; reducing the magnitude of the forces acting in the link segment model or reducing the perpendicular moment arm length. Typically, gait modification intervention studies primarily focus on mechanically modifying the latter. The reduction of the moment arm length can be achieved in two ways; by moving the centre of the knee joint closer to the force vector or the force vector closer to the knee joint centre.

A systematic review by Simic et al. (2011) identified 14 different gait modifications. The most prominent are out toeing, in toeing, walking cane use, increased step width, medial knee trust, reduced step length and lateral trunk sway. It was found that they all caused different effects to the dynamic loads measured by internal KAM, at varying phases of the gait cycle.

2.6.4.1. Gait Modification: Speed

Altering gait speed affects the frontal plane and vertical centre of mass acceleration which ultimately influences the GRF magnitude. Decreasing gait speed from 1.2 m/s to 0.8 m/s had no effect on peak KAM in healthy controls, however a positive linear correlation was found between gait speed and 1st peak KAM within the OA sample, more so in the mild knee OA group (Mundermann et al., 2004). However, others found no significant reductions in peak KAM when gait speed was reduced (Zeni and Higginson, 2009). Other studies looked at the effect on increasing speed, they more consistently reported significant increases in 1st peak KAM and a reduction in the 2nd peak KAM (Landry et al., 2007; McClelland et al., 2010) and this questions the usability of increasing speed as a joint moment reduction strategy when using the KAM peaks as a criteria.

2.6.4.2. Gait Modification: Walking Aids

Walking aids may reduce the knee moment in a combination of both ways. Firstly, by reducing the force magnitude, this can result from a relief of the upper body mass through the upper limbs via the walking aid. Reducing the moment arm can be achieved by a change in position of the centre of mass or centre of pressure through altered dynamic

motion due to the walking aid. There are a wide variety of walking aids making it difficult to compare across studies. The use of Nordic walking poles showed a significant increase in early stance KAM and no change in late stance (Stief et al., 2008), suggesting that the Nordic walking poles are ineffective at reducing the frontal plane knee moments. Ipsilateral cane use was also shown to significantly increase peak KAM compared to unaided walking whereas contralateral cane use decreased KAM (Chan et al., 2005). Kemp et al. (2008) also found significant reductions in both early and late stance peak KAMs when using ontralateral cane use. Overall, the use of walking aids shows conflicting results, this could be due to the type of aid used. The Nordic poles are typically used bilaterally but involve greater flexion of the shoulders and elbows than cane use, which may alter the positioning of the upper body during gait. Additionally, it has been found that many people self-prescribed the use of walking aids with little education on the appropriate use, the appropriate way being the cane held in the contralateral hand to the symptomatic limb (Van der Esch, Heijmans and Dekker, 2003). Finally, it is difficult to measure how much load is being off-loaded via the walking aid, making it difficult to control for this across participants and studies.

2.6.4.3. Gait Modification: Foot Progression Angle (out toeing/in toeing)

Out toeing, defined as the increase in the foot progression angle showed inconsistent results regarding the 1st peak KAM, however fairly consistently resulted in a reduction of the 2nd peak KAM (Guo, Axe and Manal, 2007; Lynn and Costigan, 2008; Lynn, Kajaks and Costigan, 2008). As the body progresses over the forefoot, the force vector will follow the line of the foot progression, therefore moving the centre of pressure laterally during the stance phase and this shifts the GRF closer to the knee joint centre. Out of the various modifications, increased out toeing appears to be considered the easiest and most subtle modification to implement, making it the most prominently researched. Few long term studies included a 10-week out toe modification intervention with 15 knee OA patients (Hunt and Takacs, 2014). The OA patients' pain scores significantly decreased, alongside reductions in late stance KAM, and patients also reported the programme to be of minimal to moderate difficulty. Similar findings were seen after a 6-week gait retraining programme with 10 knee OA patients, pain was reduced however it was the 1st peak KAM that showed a significant reduction rather than changes in the late stance KAM (Shull et al., 2013).

In contrast to out toeing, in toeing displays more inconsistent results. An in toeing of 27.6° compared to baseline foot progression angle of approximately 10° out toeing demonstrated a significant increase in late-stance KAM in healthy young adults (Lynn, Kajaks and Costigan, 2008). Conflictingly, in healthy older adults there was a significant reduction in early stance KAM but no change in late stance with a 9° in toeing compared to baseline.

This study also evaluated 12 OA patients and found no significant changes in any of the KAM values with an 11.9° in toeing compared to normal (Lynn and Costigan, 2008).

2.6.4.4. Gait Modification: Step Width

Increasing the step width, similar to out toeing, is thought to lateralise the centre of pressure. A step width increase of 20 cm reduces KAM peaks during both early and late stance (Fregly, Reinbolt and Chmielewski, 2008). Additionally Reinbolt et al. (2008) agreed that increased step width reduced the KAM throughout stance. Both of these studies were based on computational optimised predictions from a single subject making it difficult to generalise the findings.

2.6.4.5. Gait Modification: Stride Length

Reducing the stride length with a simultaneous increase in step frequency is suggested to decrease the loading at impact (Mercer et al., 2003). When conducting a study with 10 obese females Russell, Braun and Hamill (2010) found by decreasing the stride length by 15% there was a significant decrease in the KAM impulse, with a significant increase in metabolic cost by 4.6%, however no significant difference in the peak KAM or peak impact shock. The reduction in impulse is likely due to the reduced time spent in the stance phase during each step.

2.6.4.6. Gait Modification: Trunk Sway

The trunk sway modification also aims to shift the direction of the GRF during stance. Mundermann et al. (2008) found a significant reduction in the 1st peak KAM when implementing a 10° trunk lean, but no changes in the 2nd peak KAM. Similarly, Gerbrands et al. (2017) found with a 16° trunk sway the 1st peak KAM was reduced by 38%. The trunk accounts for approx. 54% of your total body weight (Plagenhoef, Evans and Abdelnour, 1983), therefore creates a considerable shift of the centre of mass towards the stance limb, reducing the frontal plane knee moment arm length of the stance limb. However, this was measured in young healthy participants. A kinematic strategy easily adopted by a healthy individual may be difficult for an AKU patient due to pain and mobility constraints. To support this (Hunt et al., 2011) described that OA patients found lateral trunk sway particularly difficult to coordinate body segments. One study found that although the trunk lean modification reduced the maximum knee adduction moment, there was increased ipsilateral trunk bending moment and increased contralateral external oblique activity (Nüesch et al., 2016). The majority of AKU patients show signs of spinal degradation, and so any excessive lateral shifts could lead to increased stresses exerted upon the lower back and spine and/or increase pain.

2.6.4.7. Gait Modification: Medial Knee Thrust

One modification which aims to dynamically move the knee joint centre closer to the force vector is the medial knee thrust. This mechanism is typically achieved by internal rotation of the hip and flexion of the knee. A single-subject knee OA study implemented a subject-specific medial knee thrust kinematic strategy based optimised predictions. The optimisations predicted that the gait pattern reduced the 1st peak KAM between 39-54% and the 2nd peak KAM between 34-56%. After nine months gait retraining the patient achieved 1st peak KAM by 39-50% and the 2nd peak KAM by 37-55% (Fregly et al., 2007). Additionally, a study with 20 symptomatic knee OA patients found a reduction of 1st peak, 2nd peak and KAM impulse (29%, 11% and 38% respectively) compared to comfortable walking, however only the 1st peak KAM reduction remained significant after correcting for walking speed. Another study implementing the medial knee thrust found that the reductions were dependent on the reference frame the moments were expressed in (Schache et al., 2008).

It is unknown which of the multiple modifications is most effective at reducing the KAM parameters. When three known gait modifications were implemented (medial knee thrust, toe in and trunk lean) to 20 healthy individuals it was found that medial knee thrust was more successful at reducing KAM than trunk lean and toe in (Lindsey et al., 2020). This disagrees with the findings of Gerbrands et al. (2017) who found the trunk lean to be more superior to the medial knee thrust. Differences could be explained by the degree of kinematic change that were applied. Interestingly despite the overall reduction in KAM found by Lindsey et al. (2020) they also found a large variation in individual response to the three gait modifications with some participants increasing KAM highlighting the need for individual subject-specific approaches.

Often these gait modifications do not occur in isolation. For example, an increased lateral trunk sway shifts the centre of mass laterally. However, depending on the degree of sway, and if the centre of mass moves towards to limits of the base of support, the body will become unstable. To overcome this instability, other kinematic strategies are typically adopted. When using biofeedback to present the trunk lean to healthy participants, without instruction, two additional sub-mechanisms appeared to counteract this instability. One was to increase the step width to widen the base of support which allowed greater lateral displacement of the centre of mass, the other was a minimal shift of the hip/pelvic complex in the opposite direction to the trunk sway with unchanged step width. Both mechanisms still resulted in a reduced KAM peak and impulse (Anderson et al., 2018). Similarly, other studies found an increase in step width during a trunk sway gait modification (Favre et al., 2016; Tokuda et al., 2018), this makes it difficult to confidently conclude that it is just one prescribed kinematic modification that contributes to the changes in KAM parameters.

Despite debatable results in gait speed and KAM parameters, a change in walking speed may contribute to the differences in KAM parameters. A gait modification demands both mental and physical challenges to coordination, only few studies corrected for the changes in speed and some significant findings were lost during this process (Gerbrands et al., 2017). Gait is a multi-segmental movement and these studies highlight that gait modifications are more likely to be a combination of multiple kinematic strategies. Even in healthy participants, additional kinematic strategies were adopted (increased step width and pelvic shift) to facilitate their prescribed kinematic modification (trunk sway). These additional kinematic strategies are likely to increase or become more individualised in pathological conditions such as OA and AKU, when there are heterogeneous samples and additional movement constraints due to pain.

For the majority of studies the primary outcome remains the frontal plane KAM parameters, with some considering the effects of gait modifications on knee loading parameters in the sagittal and transverse planes of motion (Erhart-Hledik, Favre and Andriacchi, 2015; Richards et al., 2018; Roberts et al., 2018). Even fewer have considered the effects of gait modifications on loading profiles in the adjacent joints. One study found no detrimental changes in the hip and ankle kinetics when implementing trunk sway and medial knee thrust compared to normal (Gerbrands et al., 2017). However, this is only two out of the many potential modifications that were analysed, and individual responses were not documented.

The aim of the third study is to design a gait modification intervention for AKU patients. Due to the inconsistencies within the literature on gait modifications and their effectiveness on reducing the knee moment, chapter six will evaluate the effectiveness of well-known gait modifications on reducing the knee moment to achieve objective five of this thesis. The knee moment will be calculated using the method developed in chapter five, which considers the whole stance phase and all three planes of motion.

2.6.5. Gait modification intervention designs

Another consideration for gait modification interventions is how they are implemented or instructed. The majority of studies use real-time biofeedback, an intervention technique that has been used to retrain gait in a variety of different pathologies including stroke, Parkinson's and amputee gait (Burnside, Tobias and Bursill, 1982; Crea et al., 2015; Schlick et al., 2016). In OA, research studies have presented some methodological issues. Firstly, few studies reported the effects of the gait modifications on other joints. Alkaptonuria affects several large weight bearing joints such as the spine and hips, therefore it is important to consider any negative effects to other joints and ensure no harmful increases in loading profiles. Additionally, some have only tested healthy control

participants rather than symptomatic patients making it difficult to generalise to OA or AKU patients.

2.6.5.1. The presentation of real-time biofeedback

There are a few ways of presenting real-time feedback; visual cues, audio and haptic are those most common. One study investigated the differences between visual and audio feedback (Richards et al., 2018). The feedback for both trials represented a target reduction of 10% below 1st peak KAM average baseline level. The visual was presented in a moving yellow band, when the target was reached the band moved into the green area, when it was increased by 10% it moved into the red area. The aim of the audio trial was to walk without hearing any noise. No noise meant that they had reached the 10% target reduction, the pitch and level of noise increased as the participant got further away from the target. Reductions in 1st peak KAM were similar in both conditions; however, audio feedback trials were conducted after visual feedback trials, and so a learning effect could have influenced results. Anecdotally, patients reported frustration in the audio trials, and it was stated that preference was towards the visual feedback.

Both visual and tactile (vibration) feedback based on the 1st peak KAM were presented in real-time to healthy controls along with prior instructions on known gait modifications (Wheeler, Shull and Besier, 2011). The vibration was binned into three levels, when peak KAM's were 80% of baseline a high amplitude vibration was administered, 60-80% a low amplitude vibration, and less than 60% no vibration was administered to the upper arm. The visual feedback provided the baseline for reference and presented the peak KAM during the previous nine steps. Both groups showed a significant reduction in KAM for the gait modifications compared to their baseline, and no significant differences between the two types of feedback. However, the duration of the trial was significantly shorter in the visual trial than the vibration trial suggesting a faster learning response.

2.6.5.2. Indirect feedback versus direct feedback

There are two types of feedback that can be presented to the participant. The indirect feedback is of the kinematic strategies that are understood to modify the KAM described above (implicit instructions). The direct feedback is feedback on the parameter that is being modified, i.e. the KAM (explicit instructions). Typically, in OA research the indirect feedback is presented to the participants, but these have resulted in inconsistent findings. When presented with two modifications, lateral trunk sway and medial knee thrust, (Gerbrands, Pisters and Vanwanseele, 2014; Gerbrands et al., 2017) found that optimal strategies differ between knee OA patients. Two subgroups emerged, based on the strategy that reduced overall KAM peak the most. For 80% of patients the trunk sway was most effective at

reducing peak KAM, for the remaining 20% the medial knee thrust was most effective. This suggests that there is a personal preference and individual selection is important. Systematic reviews compared studies which used direct feedback of the KAM compared to those that implemented indirect feedback of kinematic strategy (Wheeler, Shull and Besier, 2011; van den Noort et al., 2015). Overall, direct feedback tended to yield a higher reduction in KAM parameters than the indirect instructions (Barrios, Crossley and Davis, 2010; Hunt et al., 2011; Shull et al., 2011) suggesting implicit learning is more beneficial (Richards et al., 2017). This is also supported by sports and motor learning behaviour where motor skill learning and retention is often enhanced when using implicit learning (Masters, 1992). Therefore, allowing patients to adopt their own individualised gait modification may have benefit over a prescribed kinematic strategy, it is likely that the patients would adopt a strategy that would be effective, energy efficient and avoid their individual joint pain.

The implicit instructions given to the participant which explain how to modify gait are also important. A study found that when OA patients are given KAM parameters as a direct feedback, but without any instructions or suggestions on how to modify gait, there were no significant reductions in KAM parameters (Richards et al., 2018). After instructions on three known kinematic modifications (toe in, step width and medial knee thrust), together with direct feedback of the first peak KAM, it reduced significantly by 14% compared to baseline. They found that the patients used a combination of toe in and increased step width to achieve this. The results from this study suggest that patients require some prior understanding or training of kinematic strategies to achieve an effective intervention.

As part of the section two, objective five within chapter six will evaluate the effectiveness of well-known gait modifications. This will help to establish which gait modifications to use as guidance or prior instructions to patients during the gait modification intervention. The new method developed in chapter five will provide direct feedback on the knee moment variable, this will hopefully evoke an individualised gait modification adapted to each patient and objective six within chapter seven will determine if an individualised gait modification intervention can reduce the knee moment.

2.6.5.3. Retention

For gait modification interventions to be effective for long-term treatment, they need to be retained. When feedback is removed, Richards et al. (2018) found that after a short break of 10-15 minutes some reduction in the first peak KAM was maintained but the KAM impulse's initial reduction with feedback was not maintained without feedback. This study did not report the length of time each participant was exposed to the gait retraining practice prior to the removal of the feedback.

Due to the repetitive feedback treadmill gait retraining can offer, it is often a preferred method to implement gait retraining. A study by Shull et al. (2013) assessed the effect of a six-week gait retraining programme. A gait modification was established in the first week of training, each week one gait retraining session was given, using a fading feedback design. In between the gait retraining sessions participants were asked to practice their gait modification for 10 minutes per day. After six weeks the first peak KAM was reduced by 20% compared to baseline. All gait retraining sessions, baseline (week 0) and post-training (week 6) sessions were performed on the treadmill. Although a successful reduction of KAM, the gait modification was not recorded during overground walking to assess if it had been retained.

Treadmill walking can produce small differences in gait kinematic and kinetics (Franz et al., 2007), however it provides the advantage of collecting large quantities of repetitive kinetic and kinematics data and can maintain a constant walking speed. Ultimately, to implement a long-term gait modification, it needs to be retained when walking overground. Barrios, Crossley and Davis (2010) used the treadmill to carry out gait retraining using visual feedback of the dynamic knee alignment. Overground trials were collected at baseline (pre-) and with the new modified gait (post- gait retraining). Overall, after 8 training sessions using faded feedback, a 19% reduction in 1st peak KAM was seen. These findings suggest that although the modified gait was performed and practiced on the treadmill, it can be transferred to overground walking. However, a direct comparison between overground and treadmill modified gaits was not performed. To design an effective individualised gait modification to reduce the knee moment, it is important that any gait modification that is established can be retained without feedback and most importantly retained during overground walking. The final objective of this thesis will be to determine if an individualised gait modification can be retained without feedback and during overground walking, this will be reported in chapter seven.

2.7. Summary

Alkaptonuria is a highly debilitative disease which affects the patient's quality of life. Although nitisinone is a promising treatment and effective at improving important blood biochemical markers, the effectiveness of other sub-clinical features of AKU such as mobility and gait are still unknown. Gait is an important part of our daily lives and something that is affected by AKU. To better understand how gait in AKU is affected, it needs to be monitored and described in detail to identify gait abnormalities, when gait abnormalities first appear, which joints are affected the most, and how these mechanisms change with age. As there is currently little joint level description of AKU gait, this should be evaluated using appropriate non-biased hypotheses, and therefore suitable statistical methods need to be used.

It has been shown that mechanical stresses contribute to the damage and progression of AKU, particularly in the large weight bearing joints. The mechanical loading involved during gait is likely to contribute to the rate of disease progression. A non-invasive gait modification strategy may have the potential to reduce joint loading, delay the progression of the disease, reduce daily pain and delay the need for costly and invasive joint replacements. However, the way in which joint loading is currently quantified has many methodological issues, and inconsistencies remain within the literature. Changing the way in which we estimate joint loading during gait, by moving away from single peak values in one plane of motion and moving towards a consideration of all three planes of motion across the entire stance phase may better represent the loading environment during gait. Well researched gait modifications should then be revisited using this 3-dimensional loading approach to see which gait modifications are effective, whilst also considering any negative effects on other joints. Gait is multi-segmental; therefore, an optimal gait modification for an AKU patient is likely to be a combination of subtle movements individualised to their own constraints and pain. Based on the literature, visually presented direct feedback on the kinetic loading appears to yield better results by allowing the patient to create their own kinematic strategy using an individualised approach. Joint pain remains the most common AKU symptom and one which affects daily life the most. An individualised gait modification intervention which effectively reduces the knee loading may have the potential to delay the progression of the disease and most importantly reduce pain and improve quality of life for AKU patients.

2.8. Aims and objectives

The first aim of this research is to characterise and describe gait in alkaptonuria for the first time using novel and robust methods. This aim will be address within section one of this thesis and realised through the following objectives which will be covered in chapters three and four.

1. To use self-organising maps to identify any clusters between AKU and control gait data, and to monitor the natural progression of gait deviations in AKU adults between 16-70 years.
2. To identify and describe joint specific gait abnormalities and mechanisms in AKU patients compared to speed matched controls.

The second aim is to develop a treadmill-based real-time biofeedback method and to design and evaluate an individualised gait modification intervention for AKU patients. This aim will be addressed within section two of this thesis and achieved through the following objectives which will be covered in chapters five, six and seven:

3. To develop a novel real-time biofeedback method (3D Lever Arm) for treadmill-based interventions designed to reduce the knee moment, incorporating all three knee moment components.
4. To compare the simplified 3D Lever Arm method to the inverse dynamics method during normal gait and test its ability to detect changes during gait modifications.
5. To evaluate the effectiveness of well-known gait modifications on reducing the knee moment in healthy controls.
6. To determine if an individualised gait modification strategy using a treadmill-based intervention and the 3D lever arm feedback method can reduce the 3D knee moment.
7. To identify how the individualised gait modification pattern is achieved through an analysis of temporal-spatial and kinematic parameters.

Section 1: Characterising the natural progression of gait deviations from normality in AKU patients

Chapter 3. Identifying gait deviations from normality as a function of age in AKU patients using Self-Organising Maps

3.1. Introduction

Instrumented gait analysis enables us to quantitatively assess gait in pathological populations. Gait analysis objectively provides spatio-temporal measures and kinematic and kinetic measurements over a full gait cycle: the period between two consecutive ground contacts of the same foot (Gage et al., 2009). Using this information gait has been described, characterised and gait patterns have been identified in many common pathological populations, mostly cerebral palsy, osteoarthritis, stroke and Parkinson's (Sofuwa et al., 2005; Gage et al., 2009; Boudarham et al., 2013; Mahmoudian et al., 2017). Due to the pathology of alkaptonuria, many patients experience joint pain, early onset of osteoarthritis and often require several joint replacements. These symptoms result in complex relationships between cause and effect mechanisms that are detrimental to gait and mobility. Despite this, little evidence is available on the functional changes over time, and more specifically the effect of AKU on gait.

Two previous studies investigated the age-related deviations of gait from normality in an AKU cohort from the UK using the MDP (Barton et al., 2015; King et al., 2017). The MDP is a useful tool whereby the whole gait profile is derived into a simple, single number measure. The resultant summary measure (MDP_{mean}) quantitatively shows how much an individual's gait deviates from normal gait (further details of this method are reported in the literature review 2.3.1.). Barton et al. (2015) found an abrupt increase in MDP_{mean} around ages 35-40 years and all AKU patients showed a MDP_{mean} greater than the mean of the controls. However, of the 39 patients in this study, 19 had been taking nitisinone treatment for 1 year, and 13 patients had been taking nitisinone for 1-3 days prior to testing. Previous studies have shown that various AKU symptoms and biomarkers have decreased after just two weeks of nitisinone treatment (Ranganath et al., 2016), which may have also affected functional measures such as gait. Therefore, it is important to monitor the natural disease progression and its effects on gait by analysing AKU patients that are not on the treatment drug nitisinone. Additionally, Barton et al. (2015) found an increase in MDP_{mean} of AKU patients with joint replacements compared to AKU patients without joint replacements (2.70 ± 0.47, N = 14 and 2.24 ± 0.4, N = 25 respectively).The effect of joint replacements on gait deviations is important to consider when mapping the disease progression.

The second study by King et al. (2017) found sex differences between gait deviations and ochronosis in AKU with 34 AKU patients ranging between 19-72 years. They suggested that females may be protected up until ~55 years when the increase coincides with the onset of menopause and the effects of the menopause (osteoporosis). (Further details of both studies are reported in literature review 2.4.). The assessment of younger participants is needed to see if deviations are present at a younger age.

Due to the high dimensionality of gait datasets, data reduction techniques are useful to enable identification of gait patterns, monitor progression of gait over time or to characterise disease severity from gait patterns. One way to firstly determine if AKU gait differs from healthy gait is clustering techniques such as self-organising maps (SOM, (Kohonen, 1990). Self-organising maps simplify datasets with many variables and visually identifies any clusters based on similarities in the datasets presented to it. Previously in cerebral palsy research, a self-organising artificial neural network successfully identified several clusters representing both common abnormal and normal gait patterns using 612 CP patients and 20 normal subjects (Barton et al., 2006). No previous studies have attempted to distinguish AKU gait from normal gait using the lower body movement pattern as a function of the gait cycle.

Alkaptonuria begins at conception; although, in previous reports many symptoms have been shown to appear and increase at ~30 years of age (Introne and Gahl, 1993; Ranganath and Cox, 2011). However more recent studies have shown signs of ochronosis much earlier (Cox et al., 2019), and investigations into when AKU symptoms first appear are still ongoing. The possible new treatment drug Nitisinone has previously been shown to decrease urine and plasma homogentistic acid (HGA) by up to 95% (Introne et al., 2011). But there remain concerns over potential long-term adverse side effects as detailed in literature review 2.2.3.1.

In the pursuit to determine the optimal age to begin nitisinone treatment, which maximises the efficiency on AKU symptoms and minimises the harmful side effects with long term use, identification of when AKU clinical features and symptoms begin including gait abnormalities should be examined. Therefore, it is important that the natural progression of the disease and its effects on gait are investigated over a wide age range, including younger AKU patients. By mapping and clustering the natural progression of gait deviations from normality we can firstly assess if AKU gait is easily distinguishable from normal gait. Secondly, we can identify at what age gait deviations from normality first appear, which would contribute to the important decision when to initiate nitisinone treatment.

3.1.1. Objectives and hypothesis

1. Use self-organising maps to identify any clusters between AKU and control gait data and to monitor the natural progression of gait deviations in AKU adults between 16-70 years.

Based on the limited literature presented on AKU gait, it is hypothesised that self-organising maps will be able to differentiate gait between AKU and healthy controls, additionally when mapping a summary measure over time there will be rise in movement deviations around the fourth-fifth decade of life.

3.2. Methods

3.2.1. Participants

All 36 AKU patients within this study were recruited from the National Alkaptonuria Centre, these patients were part of a larger collaborative study (Subclinical Ochronosis Features in Alkaptonuria SOFIA). The patients at the time of testing were not currently receiving or had previously received any nitisinone treatment with the aim to investigate the natural progression of the disease. All UK patients (excluding Welsh) attending the NAC and receiving nitisinone were not included in the study. Therefore, the AKU patient population included a variety of nationalities including; Belgian, American, Slovak, Latvian, Portuguese, English, Welsh, Swiss, Irish, Romanian, Italian, Polish and Spanish. For comparison, the gait of 20 healthy participants was used. All AKU patient and control characteristics are detailed in Table 1. The 20 healthy participants had no musculoskeletal or neurological injuries or impairments.

Table 1: Characteristics of AKU patients and healthy controls.

	AKU	Controls
N	36	20
Male/female	22/14	8/12
Age range (years)	16-70	22-60
Height (m, mean ± SD)	1.67 ± 0.09	1.70 ± 0.09
Body mass (kg, mean ± SD)	68.4 ± 13.58	73.26 ± 12.95
Joint Replacements		
Knee	8	
Hip	5	
Other		
Meniscus removals	2	
Ankle ligament ruptures	4	

3.2.2. Equipment

A ten-camera motion capture system was used (T10/T160, Vicon Motion Analysis Inc., Oxford, UK). The cameras were centred around two adjacent embedded 600 mm x 400 mm force plates (Kistler 9281B; Kistler Instruments Ltd., Winterthur, Switzerland). The 3-dimensional marker coordinates and ground reaction forces (GRF) under each individual foot were simultaneously recorded in Nexus (V1.85). Kinematic data were sampled at 120 Hz and force data were sampled at 1000 Hz.

3.2.3. Protocol

NHS ethical approval was obtained by the sponsor (Royal Liverpool University Hospital) according to the site agreement and was granted by the NRES Committee (07/Q1505/29). Patients were given the participant information sheet (Appendix 8) and full written consent was obtained for all patients (Appendix 9). The 3D gait analyses for all AKU patients and healthy control participants were performed in the Movement Function Research Laboratory (MFRL) at LJMU. A brief history was taken to note any previous lower limb injuries or surgeries.

In accordance with the Helen Hayes model (Davis et al., 1991) 15 reflective markers (1.7 mm diameter) were attached to the skin or tight-fitting clothing. The markers were placed on the calcaneus, head of the 2nd metatarsal, lateral malleoli, lateral femoral epicondyles, left and right anterior superior iliac spine, and the sacrum, 10 cm wands with reflective markers were also attached to left and right lateral mid-shaft shanks and thighs.

Anthropometric measurements were collected; height was measured on a stadiometer (Seca 216 Mechanical Stadiometer; Birmingham, UK) and body mass on scales (Seca 799 Electronic Column Scale; Birmingham, UK). Additionally, the ankle width and knee width were measured using callipers (Lafayette 01291, Indiana, US). The Vicon plug-in-gait model was attached to the body and thigh wand orientation was checked to ensure the frontal plane knee angle did not exceed ±10°. This ±10° threshold is from the Clinical Movement Analysis Society's guidelines, apart from in extreme malalignment cases any frontal plane angle that is above ±10° is unrealistic, therefore would most likely be the result of a misalignment of the sagittal plane knee axis orientation determined by a misalignment of the thigh wand.

All walking trials were performed barefoot to remove any effects that may be caused by footwear or prescribed insoles. Alkaptonuria patients walked along a 10m walkway at their self-selected walking speed (1.11 ± 0.29 m.s), three successful walking trials were collected for each patient and 2-3 trials were collected for the healthy control participants all walking at a self-selected walking speed (1.28 ± 0.14 m.s). Automatic gait events were

calculated after each trial, the beginning of stance phase was defined when then vertical vector of GRF was greater than the 20 N threshold, gait events were then auto correlated. The walking speed was assessed after each trial using the plug-in-gait calculate gait parameters pipeline which was based on events automatically determined by the force plates.

3.2.4. Data Processing

All the movement data were then labelled and cropped to one gait cycle for each side in Vicon Nexus (V1.85). The optoelectronic marker data and force plate data were then exported to .c3d files and further processed in Visual 3D (V6, C-Motion, Inc., Germantown, MD, USA) where it was filtered using the 6 Hz Butterworth filter and time-normalised to 101 points (% gait cycle). A Helen-Hayes lower limb 7-link model was applied, each segment was assigned with a local coordinate system, the positive *x*-axis pointing to the right, the positive *y*-axis anteriorly and the positive *z*-axis superiorly. The ankle and knee joint centres were defined as the mid-points calculated by half of their measured ankle and knee widths.

3.2.5. *Data Analysis*

3.2.5.1. 1-D Self-organising map

The 15 marker positions in 3D (x,y,z) were exported to an ASCII file (American Standard Code for Information Interchange) to allow the file to be recognised and easily read by multiple platforms. The 15 marker positions in three dimensions resulted in 45 data points over 101 frames (101 frames across the gait cycle). To reduce the dimensionality of gait data and identify any clusters within the data, the 45 marker positions over 100% gait cycle (101 frames) for all control and patient data were presented to a Self-Organizing Map (SOM) in MATLAB 2017a (Mathworks, MA, USA). The neural network organises the data based on patterns and similarity. The neural network classifies input vectors (marker positions) according to how they are grouped in the input space The SOM layer contains neurons and weights, each neuron will have *n* amount of weights where *n* = number of dimensions in the data (in this case 45, (15 x 3)), Each neuron has a specific topological position along a 1D vector. During the training of the data each neuron is examined to calculate which one's weight is most like the input vector; the winning neuron is commonly known as the best matching unit (BMU). The radius of the BMU is determined, this is called its neighbourhood. The weights of neurons within the neighbourhood are adjusted and will move the average position. The position of the output node is based on the adjusted weights as its coordinates on the output map. For a 1D SOM, the weights will change during training and the adjustments of the weights within the neighbourhood ensures that similar inputs are directed to the same nearby neurons (BMU) and the inputs that are different are directed to BMU's further away, meaning the weights are linearly ordered

along the 1D vector (Figure 6) which reflects the distribution of the inputs. Therefore, the SOM layer learns the topology of the presented input space. Qualitative visualisation of gait similarity is then analysed on this 1D topological map.

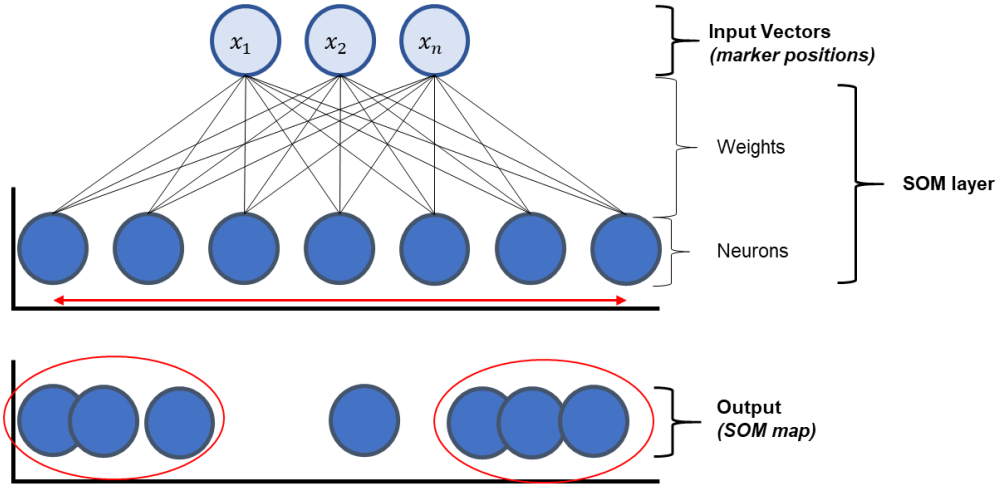


Figure 6: A simplified visualisation of the SOM. The output (SOM) map represents the movement of the adjusted weights during training. The weights determine which neurons will be the BMU's, then as the weights are adjusted during training, they will direct similar inputs to their BMU's and dissimilar inputs further away.

The age of each AKU and healthy control was also added as a visual component of the clustering as the size of the circle on the SOM; older = larger circle, younger =smaller circle. The age was added as a secondary hidden variable, meaning it is not an input variable and the SOM is not influenced by this, but only by the gait data. The addition of the visualisation of age means that it is possible to examine if the gait data is ordered by age.

3.2.5.2. MDP

All 15 markers' coordinate data were normalised to 101 frames (% gait cycle) for each AKU patient and control, then exported from Visual 3D (C-Motion, Germantown, MD) to a .tsv file. Each individual file was then imported to (MATLAB R2017a, Mathworks, MA, USA) to normalise and process the data before it was presented to the MDP freeware program (Barton et al., 2012). This phase involved firstly, the calculation of a linear line fitted onto the progression of the centre of the pelvis during one gait cycle (the means of the X, Y, Z coordinates of Sacrum and the two ASIS's). The coordinates of the markers were then subtracted from the calculated line and divided by its respective standard deviation to give processed marker coordinates which equalises the differences between the different amplitudes of the markers attached to the proximal and distal segments, and emphasises the shape of the marker trajectories rather than the amplitudes. The data is then reshaped from a transformed matrix into a single column for each trial 3 x 4545 rows for AKU patients

and 2 x 4545 rows for controls. All AKU patient columns were added to one data set and all control columns were added to another data set.

A model of normal gait was created by training the self-organising neural network with the control data set in the MDP freeware program (Barton et al., 2012). Both the AKU patient data set and the control data set were then presented to the program and the MDP_{mean} values were derived from the trained neural network model.

Finally, the mean deviation from normal was calculated by averaging MDP_{mean} values from the three trials from each AKU patient and two trials for each of the controls. The MDP vertical axis is presented with the same units as the input data, as the input data is the marker coordinates that are divided by their standard deviation during the normalisation process the unit becomes arbitrary. These arbitrary MDP_{mean} values were then plotted against age. A linear regression analysis was ran on the data to determine the effect of age on MDP_{mean} using the software package SPSS 25 (IBM SPSS statistics data editor, Armonk, New York). A median filter was applied to the data with a window sizes between 5-7 samples. This was to better identify any transitional increase in deviation from normal gait over a small age range.

3.2.5.3. Movement Deviation Profile: Control group validation

The control group used in this study consisted of 20 participants between the ages of 22-60 years, in the attempt to match the distribution of the AKU patients (16-70 years) for comparison. The MDP_{mean} results show that there is a no increase of gait deviation from normality with age within the healthy control group, however based on normative data there is expected to be some change even with healthy aging. One explanation for the lack of change in gait deviations with age is that all of the control data was used to train the SOM to define normality. To get the MDP_{mean} of each of the controls, the control data is then presented to the MDP again as test data. This means the MDP is trained with the same data as the test data. The algorithm chooses the best matching set of weights in the control data space for each of the 101 rows of data rather than the average normality of the controls (Barton et al., 2012).

To distinguish if there is any influence of age on MDP_{mean} within the control group, they were split into two subgroups: Older, consisting of 8, 31-60 years, 4 females and 4 males, and Younger, consisting of 12, 22-28 years, 8 females and 4 males. A separate neural network model was then used whereby the Younger control group was used to train the neural network and then the Older control group MDP_{mean} was calculated. This was then repeated using the Older group to train the neural network and then the Younger group MDP_{mean} calculated, meaning that the test control data presented to the MDP was not the same control data used to train the SOM.

3.3. Results

3.3.1. SOM

Figure 7 shows the 1D SOM, a 1D layer of 54 neurons, this configuration is the end-result of training the neural network. From a qualitative visual inspection of the 1D SOM, there is a very minimal separation between gait patterns of the AKU patients and healthy controls, there is a slight grouping of the controls on the right and the AKU patients on the left, however, with multiple overlaps this is not a distinct pattern. There is also a minimal effect of age in the AKU, with the older AKU patients (larger circles) appearing more so on the left. However, there is not a distinct pattern suggesting that age is not a strong determinant of gait similarity.

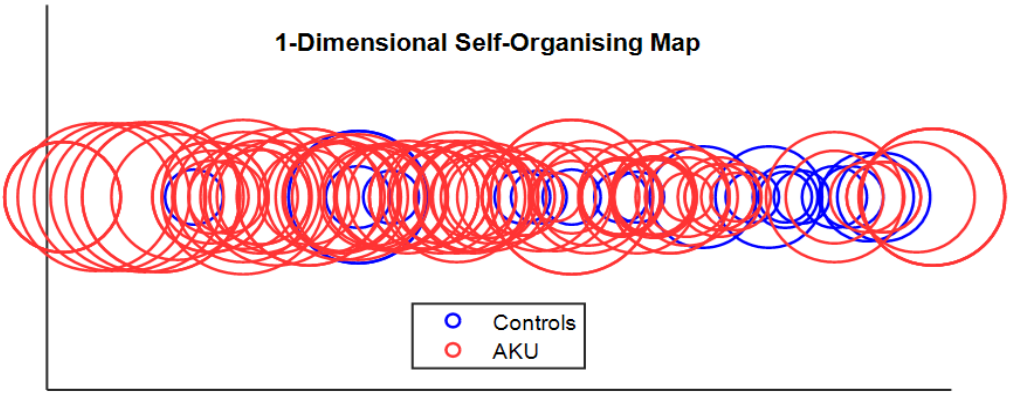


Figure 7: 1D cluster plot to visualise any clusters between AKU (red) and control (blue) gait patterns. The size of the circle indicates the age of each individual (circle size increases with age).

3.3.2. MDP Overall

Figure 8 shows that the MDP_{mean} increases with age, a linear regression established that age could significantly predict the MDP_{mean}, $F(1, 34) = 11.70$, $p = 0.002$ and age accounted for 23.4% of the explained variability in MDP_{mean}. On visual assessment of the MDP_{mean} plot (figure 8), results show that all but two of the 36 AKU patients has higher gait deviations from normality than the mean of the controls (1.64 MDP_{mean}), and 23 out of the 36 AKU patients' $MDP_{mean,}$ including the younger AKU patients were outside the mean ± SD range of the controls (1.64 ± 0.2 MDP_{mean}). Relatively large gait deviations from normality were also found in the three youngest patients at 16 years (1.96, 2.08 and 2.28 MDP_{mean}). The median filtered curves show more clearly a steep incline in gait deviations from normality around the age of 50 years which then continues to gradually increase. The median curves also indicate larger variations in the MDP_{mean} after 50 years.

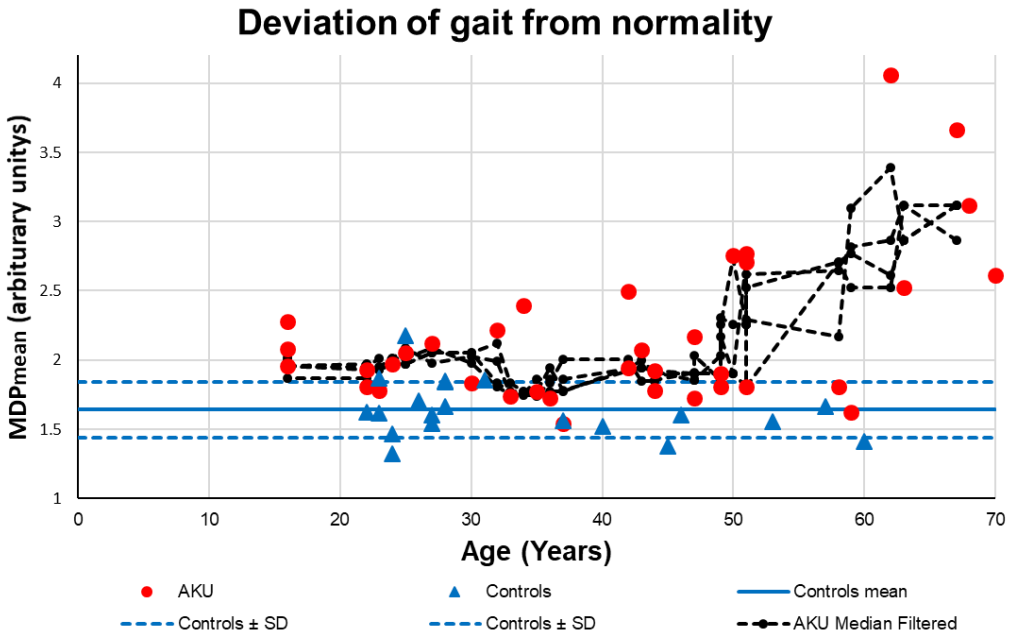


Figure 8: Gait deviations (MDP_{mean}) of AKU patients and controls as a function of their age. The (MDP_{mean}) values of patients were also median filtered in windows of 4-7 to visualise any trends.

When the AKU patients were split into 3 groups based on the changes in the curve profile and stages of life by decade, the 3 groups were: Young, 3rd decade of life and below (16-29 years), Middle, 4th and 5th decade of life (30-49 years) and Old, 6th decade of life and above (50+ years). There was an incremental increase of % MDP_{mean} scores that were above the controls' mean and SD (1.64 ± 0.2 MDP_{mean}), in the Young group 22% were above the controls' mean and SD, 50% in the Middle group and 77% in the Old.

3.3.2.1. MDP no joint replacements

To account for AKU patients that have had previous joint replacement surgery, Figure 9a shows the MDP profile when those patients are removed. The MDP median filtered curve shows a sharp increase in MDP_{mean} at 50 years but no continued gradual increase after 50 years. The 7 patients with joint replacements aged between 42-70 years. Their MDP_{mean} was greater (2.63 ± 0.79, *N*= 7) than the AKU patients above 42 years with no joint replacements (2.22 ± 0.59, *N* = 13). After a descriptive interpretation of Table 2, there is no clear pattern between type of surgery, joint affected or symmetry and $MDP_{mean.}$ Dates of surgery were not available.

Table 2: The demographics, MDP_{mean} and brief description of the surgery of the 7 patients that have undergone lower limb surgeries or injuries that may have affected gait.

Patient	Sex	Age (years)	Brief description of surgery	**MDP_{mean}**
1	Male	42	Right knee replacement	**2.50**
2	Female	44	Bilateral meniscus removal and patella realignment	**1.78**
3	Male	51	Bilateral Achilles tendon ruptures Bilateral knee replacement	**1.81**
4	Male	62	Bilateral knee replacement Left hip replacement	**4.06**
5	Male	63	Right Achilles tendon rupture Bilateral knee replacement Bilateral hip replacement	**2.53**
6	Female	68	Left knee replacement	**3.12**
7	Male	70	Bilateral hip replacement	**2.61**

3.3.2.2. Sex differences

Figure 9b shows the MDP_{mean} plotted against age for males. The median filtered curve shows a sigmoid shape with a sharp increase in MDP_{mean} at 50 years, with increased MDP_{mean} in the younger participants. Figure 9c shows the MDP_{mean} plotted against age for females. The median filtered curve does not follow the same sigmoid shape as seen in Figure 9b instead shows a flat line. However only 2 females were above 50 years of age.

The % of MDP_{mean} scores that were above the controls' mean and SD (1.64 ± 0.2 MDP_{mean}) was calculated for both males and females. The results showed 77% of the 22 males aged between 16-70 years showed MDP_{mean} scores that were above the controls' mean and SD, and 43% of the 14 females aged between 22-68 showed MDP_{mean} scores that were above the controls mean and SD. AKU patients that were over 50 years and with joint replacements where then excluded, results remained similar, with 75% of the 12 males aged between 16-49 years showed of MDP_{mean} scores that were above the controls mean and SD and 45% of 11 females aged between 22-47 years showed MDP_{mean} scores that were above the controls' mean and SD.

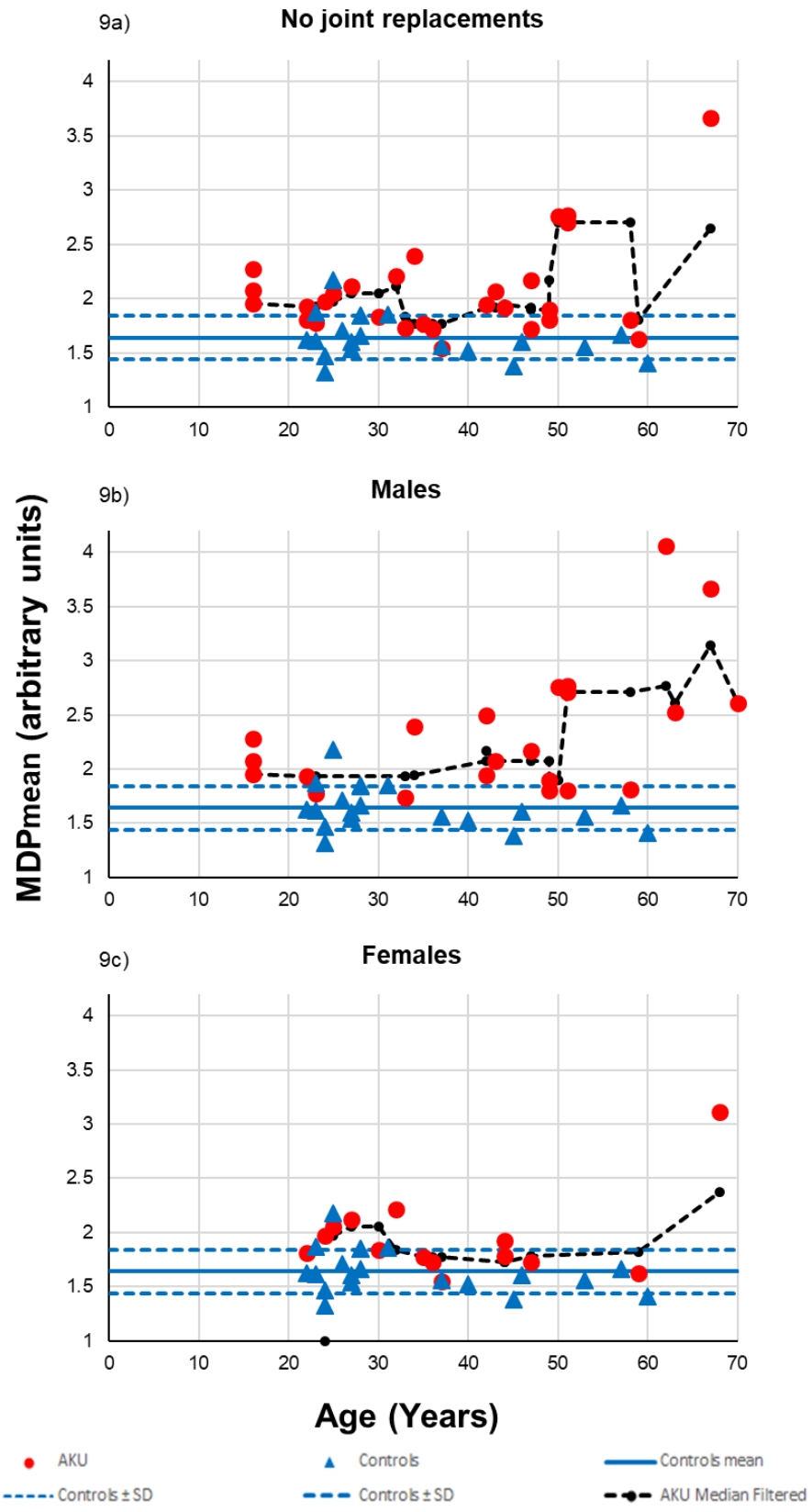


Figure 9: Gait deviations (MDP_{mean}) of AKU patients and controls as a function of their age. The (MDP_{mean}) values of patients were median filtered to a window of 5 to visualise any trends (9a) AKU patients without joint replacement surgery, (9b) males, (9c) females.

3.3.3. Movement Deviation Profile: Control group validation

When the Younger control group was used to train the neural network and the Older control group was presented, the Older control group $MDP_{mean} = 1.74 \pm 0.30$. When the Older control group was used to train the neural network and the Younger control group was presented, the Younger control $MDP_{mean} = 1.95 \pm 0.29$. The results show a small difference between the two MDP_{means} (MDP_{mean} difference = 0.21), with a minimal decrease in MDP_{mean} with age amongst the control group, suggesting that there is little or no gait deviations occurring as a result of ageing within the healthy controls. A limitation to this finding is that the group sizes are not equal (8 older group, 12 younger group), and more so the spread of the Older control group (31-60 years) is much larger than that of the Younger control group (22-28 years).

3.4. Discussion

The objective of this study was to identify any clusters within the AKU and control gait patterns using a self-organising map. Contrary to the hypothesis, upon visual inspection of the 1-D SOM (Figure 7), there is minimal but no definitive separation between AKU gait and control gait. Similarly, there is minimal but no distinct grouping by age. In contrast, Carriero et al. (2009) were able to classify children with spastic diplegia CP and identify their gait abnormalities using principal component cluster analysis. Aside from a different pathological condition being investigated, the variables presented to the CP study were discrete kinematic and temporal parameters at specific time points within the gait cycle. These parameters were typically recognised CP characteristics and suggests that distinct gait patterns exist in CP gait. The advantage of the SOM in this study is that the data presented to the SOM were the marker coordinate positions over the full gait cycles as opposed to predetermined gait parameters, and it focuses on gait patterns as a whole rather than specific variables of interest. Additionally, well-established CP gait patterns such as ‘crouch gait’ can have large ranges of kinematic differences with up to 40 degrees knee flexion. Therefore, the results suggest that any kinematic changes in AKU patients are more subtle than those with CP, with more heterogeneity within the sample. It must also be noted that AKU gait has not yet been described in the extensive detail that other pathological gait patterns such as CP and stroke have. Therefore, pre-determining discrete variables to present to the clustering analysis would be difficult.

The non-definitive separation may also indicate a mixture of variable gait deviations, and the gait abnormalities may differ in symmetry. Other than the evidence that AKU affects the weight bearing joints primarily (Taylor et al., 2011) and more ochronosis is seen in sites of known mechanical loading, little is known about the development of ochronosis. It is also unknown which limbs are affected first (dominant or non-dominant), or how the

contralateral limb may behave after a joint replacement or symmetry of affected joint. The SOM and MDP tools, although useful at predominantly identifying any distinct differences between the two groups, are not specific enough to detect the cause and effect relationships of gait mechanisms. The patient group was a heterogeneous group, and joint replacements were not taken into consideration during the SOM analysis. Overall, there were 13 joint replacements within seven AKU patients (Table 2).

The second part of the objective was to monitor the natural progression of gait deviations in AKU adults between 16-70 years. This objective was to help identify the earliest age that gait deviations from normality appear in AKU patients who were not currently taking any nitisinone treatment, and to determine the magnitude of those gait deviations from normality. The most important finding is that gait deviations appear even in the three youngest patients at 16 years old, this is the first time that this has been seen in AKU patients under 19 years old. Additionally, 22% of the younger patients aged 16-29 years had a MDP_{mean} higher than the controls' mean and SD. This differs from the original belief that symptoms did not begin until ~30 years (Ranganath and Cox, 2011). Agreeing with this study, a cross sectional study using a subset of 30 of the same patient group as this study (Cox et al., 2019) found pigmentation in one of the youngest AKU patients at 16, showing that ochronosis can begin as young as 16 years. Circulating serum HGA was also found to be elevated at 16 years and increases with age. qAKUSKI scores which reflect morbid clinical features such as joint and spinal pain were also increased at 16 years. Interestingly, the MRI analysis for both the spine and knee joint did not show degradation in those younger than 30 years.

Compared to the previously published studies (Barton et al., 2015; King et al., 2017), this study included younger AKU patients, and to monitor the natural progression all participants in this study were not taking nitisinone. However, there were both similarities and differences across the studies. The results from this study show a sharp increase of MDP_{mean} at around 50 years old, this differs slightly from the hypothesis and the previous findings by Barton et al. (2015) where the sharper MDP_{mean} increase was seen earlier at 30-40 years, however, they did report a slight secondary rise at 50 years which was less pronounced due to the large variability in the older group. One explanation for this slight difference is the patient population in each study is that the Barton et al. (2015) study included only UK patients attending the NAC, all of these patients were taking the trial treatment drug nitisinone. Although this would be expected to delay the onset of ochronosis and subsequently gait deviations, the differences may suggest that nitisinone, although reducing HGA levels, it is not delaying the functional gait problems seen in AKU. Lifestyle and diets may also drastically change between the mixed European cohort in this study compared to the UK cohort in the previous study. It is thought that the Mediterranean diet

which includes omega-3 fatty acids, polyphenols and is rich in fibres, provides an anti-inflammatory effect (Morales-Ivorra et al., 2018). This anti-inflammatory response may protect the joints and delay the progression of the disease in the European cohort. However, the diet was not measured within this study.

This sharp increase at 50 years coincides with the Cox et al. (2019) study's MRI analysis. The Pfirrman scores (Griffith et al., 2007), showed a similar sigmoid shape with an increase of spinal disc degenerations at around 40-50 years. Additionally, the knee WORMS score (Peterfy et al., 2004); a semi-qualitative method scoring structural abnormalities in the knee from MRI analysis stays relatively low but then increases to only be associated with age after the middle of the fourth decade. These findings suggest that the spinal and joint degradation could possibly contribute to the sharp decline of gait function as shown by the increased MDP_{mean} at around 50 years old.

The findings from this study slightly agree with sex difference reported in the (King et al., 2017) study, whereby, when only looking at <50 years (the age at which we see a sharp MDP_{mean} increase), 75% of males had an MDP_{mean} above the controls mean and SD, and females only 43%. This agrees that females may be slightly protected throughout the 3rd to 5th decade. This protection may be due to their hormonal status, but more studies would be needed to confirm this protective mechanism. Additionally, caution must be taken as AKU males and females were not age matched for comparison. The three youngest patients at 16 years were all male, is it difficult to conclude if females would show the same high MDP_{mean} at 16 years. King et al. (2017) found a sharp increase in the 6th decade in females, this was not supported by the findings from this study. However, only 2 females compared to 9 males were above 50 years in this cohort. More female AKU patients above 50 years would be needed to draw direct conclusions between sexes within this age bracket.

It has been reported that total joint arthroplasties have occurred in around 50% of patients over the age of 50 years, with patients often having multiple joints replaced (Ranganath, Jarvis and Gallagher, 2013). To account for joint replacement surgeries, all AKU patients that had received joint replacements or surgeries that may have affected gait were removed from the dataset and the MDP_{mean} was reanalysed. This resulted in seven patients being removed, only two of which, were under 50 years. Figure 9a shows the median filtered curve drop after 60 years. This drop suggests that those patients with previous joint replacements or injuries contribute to the higher $MDP_{means.}$ This could be due to the surgeries themselves affecting the kinematics post-operatively. A systematic review of 10 studies following knee arthroscopy that included a healthy reference group concluded that it was unclear whether gait parameters returned to normal (Sosdian et al., 2014). There could also be asymmetry or compensation strategies on contralateral limbs. Additionally, AKU is

a continuous disease, affecting all joints, therefore, when one limb is replaced, there is also ongoing disease progression occurring in other joints. Similar to the sex differences there was limited number of AKU patients with and without joint surgeries that were age-matched to demonstrate clearly the effects of joint replacement on gait deviations from normality in AKU patients. As shown in Table 2 of those seven patients there is no distinct pattern between type of surgery/injury and their $MDP_{mean.}$ Furthermore, to fully understand the effect of joint replacements on gait, age matched AKU patients and controlled pre- and post-surgery gait analysis data are needed.

These findings suggest that gait deviations occur young at 16 years at the same time as the first signs of ochronosis, circulating serum HGA and reported joint and spinal pain. When joint and spinal degradation begin later in life this coincides with a sharp decline in gait function. It is difficult to conclude from these results the primary and secondary problems. The gait deviations in the younger group may be contributing to the progression of the disease and degradation of the joints. Additionally, gait modifications could be adopted by the patients to avoid pain after the joint degradation or post-joint replacements surgeries.

Although AKU is an ultra-rare disease, with only 1233 AKU patients identified worldwide (Zatkova, Ranganath and Kadasi, 2020), the sample size of a European cohort in this study is still small. Patients from the UK were not included in this study as almost all patients have access to and are taking nitisinone treatment. The aim of the study was to map the progression of the disease, therefore the 36 AKU patients were spread across a large age range (16-70 years), this was good for monitoring changes as a function of age, however it means any further grouping of patients becomes difficult. Difference between males and females and patients with and without joint replacements are difficult to conclude due to small numbers in each group and not all were closely age matched, therefore more participants would be needed in each group. Similarly, our youngest AKU patients were 16 years however the youngest healthy controls were 22. Therefore, it is difficult to definitively conclude that the deviations seen in the 3 youngest were due to AKU. Deviations from normality were seen in 16-year-old AKU patients indicating for the first time that younger AKU patients show symptoms. Therefore, to further assess when gait problems begin, and to determine the optimal age to begin nitisinone treatment paediatric data would need to be analysed

3.5. Conclusion

This study did not find distinct clusters between AKU and healthy control gait, indicating that AKU changes may be more subtle compared to other mobility disease such as CP or that the AKU patient group may show a large variation in the gait deviations due to the

heterogenous nature of the disease. This study also investigated the natural progression of gait deviations as a function of age in alkaptonuria patients without nitisinone treatment. For the first time gait deviations were seen in patients as young as 16 years despite previous reports that symptoms do not appear until ~ 30 years of age. There was also a sharp increase in gait deviations at 50 years, with some sex differences however more age-matched participants are needed to provide adequate sample sizes when grouping the data and understand the effects of joint replacements on gait. Finally, all but two patients showed deviations from normality. Gait is complex, so therefore, to further characterise gait in patients with AKU an in-depth analysis should be done to identify and understand the joint specific gait deviations contributing to the increased MDP_{mean} scores, this would provide a better understanding of the specific gait mechanisms adopted by AKU patients through the progression of age and disease. This will be addressed in the next chapter.

Chapter 4. Identifying joint specific abnormalities in AKU gait as a function of age using Statistical Parametric Mapping

4.1. Introduction

The previous chapter identified gait deviations from normality in the majority of AKU patients, even within the youngest patients at 16 years old. The MDP is an effective tool to reduce the dimensions of gait data and monitor the natural progression of the disease. The next step is to identify those joint specific gait deviations, and the gait mechanisms which contribute to the high MDP_{mean} scores.

Gait has been extensively described in movement disorders such as cerebral palsy, stroke and osteoarthritis (Kim and Eng, 2004; Gage et al., 2009; Heiden, Lloyd and Ackland, 2009). Despite AKU's detrimental structural damage and painful limiting symptoms, there is currently no previous literature known to the author which has described gait in AKU patients at joint level. To describe gait in AKU for the first time, a nonbiased approach is required, as we do not yet know where the differences between normal gait and AKU gait lie. When describing or analysing gait patterns, traditional approaches using discrete parameters which are zero-dimensional data are subject to both Type I and Type II statistical errors. To overcome these issues and to identify any gait abnormalities in AKU, one-dimensional Statistical Parametric Mapping (SPM) will be used to combine and compare all clinically relevant one-dimensional data; angle, moment, power and force trajectories over the entire gait cycle. Statistical parametric mapping is a robust statistical approach to biomechanical waveform data which reduces the statistical errors and bias by using a 1D model of randomness instead of 0D. A similar non-directed null hypothesis approach by Meyer et al. (2018) was conducted using SPM, they were able to identify and define abnormalities that can be directly targeted in tailored interventions for hip OA patients. Statistical parametric mapping was used to compare the differences between hip OA patients and healthy controls on all hip kinematic and kinetic waveforms using a hypothesis without the need for prior data reduction. The results highlighted some pathomechanical strategies naturally adopted by patients with hip OA to reduce the hip joint loading. From the description of gait mechanisms further informed clinical rehabilitation decisions can be made for these patients.

The Meyer et al. (2018) study only focused on the deviations at the hip joint for hip OA patients. However, gait is a complex problem, with all joints interacting and contributing to the progression of movement. Alkaptonuria is a multi-joint problem, with ochronosis seen at the major weight bearing joint such as the knees and hips. To understand the interaction all lower limb joints should be investigated.

Due to the nature of AKU, the evidence suggesting that mechanical loading contributes to the progression of joint damage (Taylor et al., 2012), and similarities to OA, any differences in joint moments will be monitored closely. As mentioned in the literature review (chapter 2.6.1) the internal joint moment is the turning force acting about a lever arm produced by the muscles and passive joint components to resist the external forces applied to the body. To help to truly interpret differences a comprehensive comparison of angle, moment, power and GRF data is important. The angle data will help to identify any mechanisms or compensatory movement patterns directly related to changes in joint moments. Joint powers indicate how the structures within the body (both muscles and passive structures) generate or absorb energy and may provide information on potential damage to surrounding joint structures. Finally, ground reaction force is one of the forces acting upon the link segment model contributing to the summation of the net joint moments, therefore, it is important to interpret any differences in the ground reaction forces between AKU and healthy controls to determine potential contributions to differences in joint moments.

Before we implement gait modification interventions it is important to understand the pathomechanics of how AKU patients naturally ambulate, how these change with age, and how patients have adapted to the disease and to pain. Any specific gait abnormalities identified in this study can then be addressed in a targeted gait modification intervention. Therefore, the non-directed null hypothesis is that there are no significant differences between AKU gait and healthy control gait.

4.1.1 Objective and hypothesis

1. To identify and describe joint specific gait abnormalities and mechanisms in AKU patients compared to speed matched controls.

Using the statistical parametric mapping the hypothesis for this chapter is that there are significant differences in the angle, moment, power and force vectors between AKU gait and healthy control gait across all three age groups.

4.2. Methods

4.2.1. Participants

All 36 AKU participants were the same as in chapter three. For comparison, the gait of 21 healthy controls between 19-60 years were used and recruited based on convenience sampling. The controls consisted of 8 males and 13 females who had no musculoskeletal or neurological injuries or impairments. See Table 3 for participant characteristics.

Table 3: Characteristics of AKU and healthy controls.

	AKU	Controls
N	36	21
Male/female	22/14	8/13
Age (years, mean ± SD)	41 ± 16	33 ± 12
Height (m, mean ± SD)	1.67 ± 0.09	1.71 ± 0.09
Body Mass (kg, mean ± SD)	68.4 ± 13.58	74.81 ± 12.29
Joint Replacements		
Knee	8	
Hip	5	
Other		
Meniscus removals	2	
Ankle ligament ruptures	4	

4.2.2. Protocol

The data collected from the previous chapter was analysed in further detail for this chapter to investigate the joint specific differences in the waveform data. 3D motion capture and force plate data were collected during 2-3 barefoot walking trials. Alkaptonuria patients walked at their self-selected walking speed across a 10-metre walkway. See chapter three equipment (3.2.2), protocol (3.2.3) and data processing (3. 2.3) for specific methodological details.

For a speed matched comparison, the control group were asked to repeat the protocol at two different speeds: self-selected (1.28 ± 0.13 m/s) and slow (0.98 ± 0.14 m/s), these two speeds were collected to represent the typical walking speed range seen in AKU patients

2D video cameras (Basler, 640-210 and 1000-48, Ahrensburg, Germany) were used to capture the frontal and sagittal planes of motion, the 2D video was used to qualitatively describe any upper body malalignments that may support the quantitative findings.

4.2.3. Data analysis

4.2.3.1. Comparisons

To monitor the changes as a function of age the AKU patient data were split into 3 age groups (Young 16-29 years, Middle 30-49 years and Old 50+ years). These groups were based on the groupings used in the previous chapter, and the changes in the MDP profile which showed a different rate of change at 30 years and 50+ years. The statistical analysis

which was performed considers the entire waveform and so does not correct for the differences that may be due to walking speed. Patients with more established disease severity are likely to walk slower, and it has been previously found that speed has a greater effect on kinematics than age or gender (Røislien et al., 2009). Therefore, the mean and standard deviation of walking speed was measured for each AKU age group to identify which groups should be compared. Each AKU age group were compared to the control group with the closest walking speed, either self-selected or slow. See Figure 10 for the comparisons made.

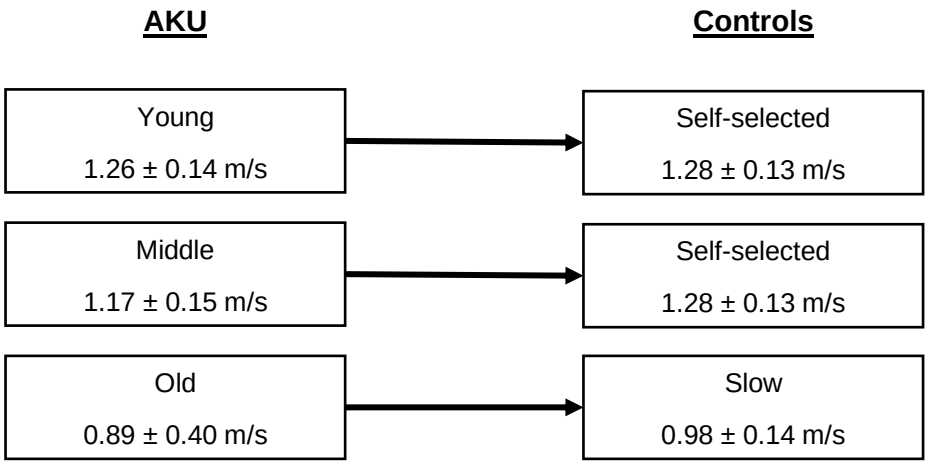


Figure 10: A schematic diagram representing the comparisons made between the AKU and control groups.

4.2.3.2. Statistical Parametric Mapping

To make the comparisons between AKU and healthy control gait data, 1-Dimensional analyses were implemented using the open source spm1d code (v.M0.1, www.spm1d.org) in Matlab (R2017b, 8.3.0.532, Mathworks Inc., Natick, MA, USA). The spm1d an open source package was used for one-dimensional statistical parametric mapping. A two-sample t-test was performed to compare the differences in the mean joint angles, moments and powers between AKU patients and the healthy controls. Typically, the threshold in which we measure the *p*-value against is alpha = 0.05 (95% level of confidence), however, to avoid excessive type 1 error caused by multiple comparisons alpha was set at 0.00238 (0.05/21) to correct for the 21 comparisons for each age group. The 21 gait curves that were compared are shown in Table 4.

Table 4: The gait curves of both sides used in the comparison between AKU patients and healthy controls.

Angles	**Moments**	**Powers**
Ankle plantar/dorsiflexion	Ankle plantar/dorsiflexion	Ankle
Ankle in/out toeing	Knee flexion/extension	Knee
Knee flexion/extension	Knee abd/adduction	Hip
Knee abd/adduction	Knee rotation	
Knee rotation	Hip flexion/extension	
Hip flexion/extension	Hip abd/adduction	
Hip abd/adduction	Hip rotation	
Hip rotation		
Pelvic tilt		
Pelvic obliquity		
Pelvic rotation		

For each comparison the univariate *t*-statistic (SPM {t}) was calculated at each data point of the waveform. For each comparison a critical threshold was calculated, with alpha set at 0.00238, which means that only 0.00238% of equally smooth random data would exceed this threshold. The two-group means were considered significantly different if the SPM {t} curve exceeded this threshold. The points along the waveform data at which SPM {t} exceeded this threshold are known as a cluster and provide the information about when in the gait cycle the two means significantly differed. A *p*-value for each cluster was calculated, this indicated the probability of determining a cluster with similar proportions when evaluating equally smooth random data. An example of the interpretation of a SPM {t} curve is shown in Figure 11.

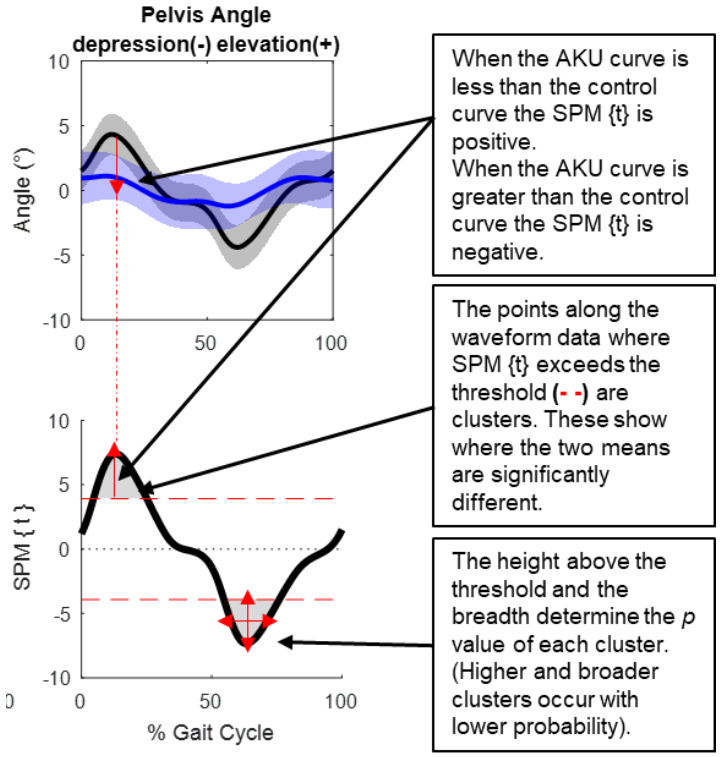


Figure 11: An example of how to interpret the SPM {t} results. Above the mean and SD of two gait curves (AKU blue and control black) and below is the SPM {t} curve result.

4.2.3.3. Ranking of clusters

The SPM1D produces an SPM{t} curve. The SPM results provide a single *p*-value for each suprathreshold cluster. The implemented height-threshold and cluster-breadth procedure (Penny et al., 2011), means that a very high and/or broad cluster occurs with low probability, a lower *p*-value. Therefore, each of the suprathreshold clusters were ordered with respect to their *p*-value.

Firstly, all curves for all 3 groups were visually assessed for significant differences identified by suprathresold clusters, any curves showing no significant differences i.e. no clusters were not further analysed.

Clusters and their respective *p*-values from the angles, moments and powers curves were split into the age groups (young, middle and old) then the *p*-values were ordered from smallest to largest.

4.2.3.4. Ground reaction force vector field analysis

A vector analysis on the entire three component GRF was performed to identify significant differences between AKU patients and healthy controls in the 3 groups. The vector field analysis was not carried out on the angle, moment and power data due to the need to explore the joint mechanisms. Based on the previous chapter's increased MDP_{mean} scores,

multiple differences were expected within the kinematic data, these would have direct effects on the moment and powers data. The vector field analysis was conducted only on the GRF, as there were expected to be less differences than in the angle, moment and power data. Therefore, the vector field was analysed first and further explored using post hoc analyses if the results showed significant differences between the AKU groups and speed matched controls. All GRF data were normalised to each individual's body mass and normalised to % stance phase. A 2-sample Hotelling's T^2 test was used followed by *post hoc* t-tests on individual GRF components to determine the relative contributions of each force component to the Hotelling's T^2 results.

4.3. Results

4.3.1. Overall description of results

Upon first inspection of the results in Table 5, 6 and 7 we see that the amount of significant differences between AKU and control gait curves increases with age (Angles: Young = 1, Middle = 2 and Old = 8 and Moments: Young =1, Middle = 1, Old = 3).

The young and middle groups display significant differences only in the sagittal plane for angles, moments and powers. The old group show significant differences in all three planes of motion within the angle curves, predominantly frontal plane differences within the moment curves and showed no significant differences in the power curves.

The young group only showed significant differences between AKU and healthy controls at the knee joint. The middle group showed significant differences at the knee and hip whereas the old group showed significant differences at all lower limb joint levels, ankle, knee, hip and pelvis. The knee joint moment showed significant differences across all three age groups in both the sagittal and frontal planes.

Table 5: The ranking of significant differences derived from SPM between AKU and healthy control gait angle curves.

Angles						
Group	Rank	*P* Value	Joint	Plane	% Gait cycle	Description
Young	1	1.0E-03	Knee	Sagittal	35-42	Increased extension
Middle	1	4.0E-04	Hip	Sagittal	82-100	Reduced flexion
	2	2.2E-03	Hip	Sagittal	22-26	Increased extension
Old	1	3.0E-14	Foot	Transverse	0-68	Increased out toeing
	2	4.9E-11	Knee	Frontal	7-55	Increased abduction
	3	8.2E-05	Pelvis	Frontal	55-76	Reduced depression
	4	1.0E-04	Pelvis	Frontal	5-25	Reduced elevation
	5	7.7E-04	Hip	Frontal	55-72	Increased adduction
	6	1.1E-03	Ankle	Sagittal	62-68	Reduced plantarflexion
	7	1.6E-03	Foot	Transverse	92-100	Increased out toeing
	8	1.9E-03	Ankle	Sagittal	3-6	Increased dorsiflexion

Table 6: The ranking of SPM results of the significant differences between AKU and healthy control gait moment curves.

Moments						
Group	Rank	*P* Value	Joint	Plane	% Gait cycle	Description
Young	1	1.4E-07	Knee	Sagittal	35 - 42	Increased flexion moment
Middle	1	6.6E-04	Hip	Sagittal	55-57	Reduced flexion moment
Old	1	0	Knee	Frontal	38 - 55	Reduced abduction moment
	2	8.9E-15	Knee	Frontal	11 - 25	Reduced abduction moment
	3	0.0016	Hip	Transverse	58 - 59	Reduced external moment
	4	0.0024	Knee	Frontal	98 – 98	Increased abduction moment

Table 7: The ranking of SPM results of the significant differences between AKU and healthy control gait power curves.

Powers						
Group	Rank	*P* Value	Joint	Plane	% Gait cycle	Description
Young	1	7.7E-05	Knee	Sagittal	42 - 45	Increased generation
Middle	1	0.0022	Knee	Sagittal	56-56	Reduced absorption

4.3.2. Joint specific gait deviations in the Young AKU patients

Figure 12 displays the results of the SPM analysis of the kinematic and kinetic waveforms. AKU patients walked with increased knee extension at mid-terminal stance (35-42% gait cycle) ($p = 0.001$). At the same period of the gait cycle they had an increased knee flexion moment ($p < 0.001$). Knee power absorption was also increased during this period of the gait cycle although this was not significant. This is followed by a significantly greater power absorption at 42-45% gait cycle ($p < 0.001$) than the speed matched controls.

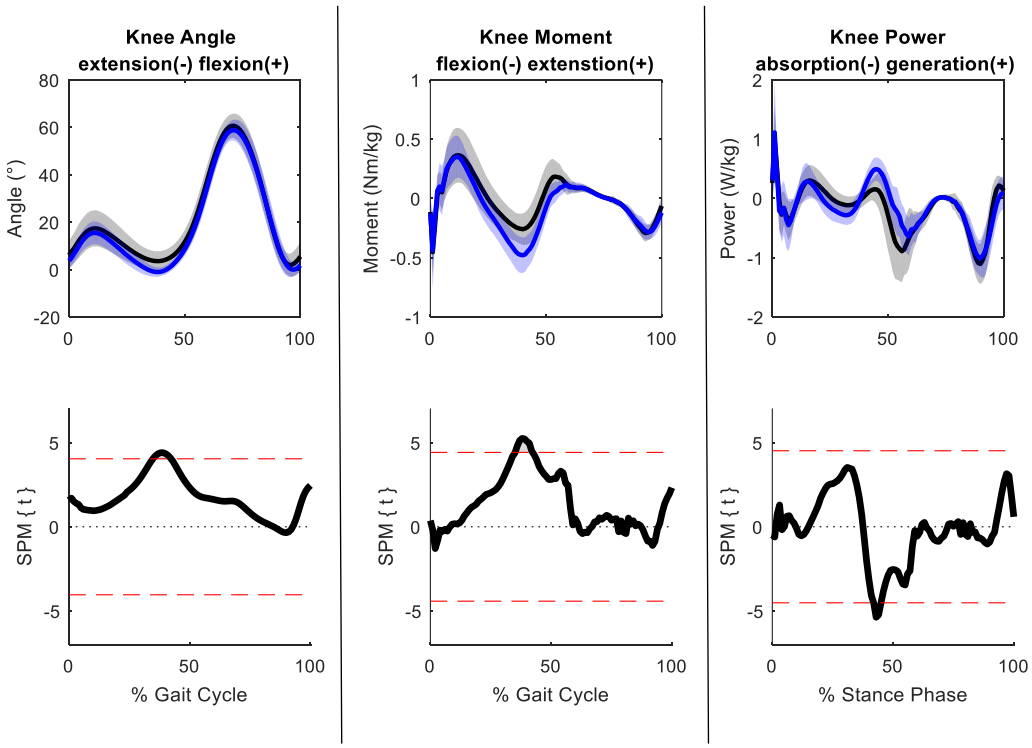


Figure 12: The kinematic and kinetic curves where significant differences occurred between the Young AKU patients and controls. For each curve the top panel represents averaged curves for the AKU Young (blue) and speed matched controls (black). The bottom panel shows the t-statistic (SPM {t}). This represents an inference curve with a threshold at a specific t (dashed red line). When SPM {t} exceeds this threshold, significance is reached with *p* values reported.

4.3.3. Joint specific gait deviations in the Middle AKU patients

The largest significant difference between AKU middle group and healthy control group was the reduced hip flexion at terminal swing (82-100% gait cycle) $p < 0.001$. The second largest angle difference was the offset to extension during stance, which was significantly different between 22-26% gait cycle $p = 0.002$. At 55-57% of the gait cycle at terminal stance we see a reduced hip flexion moment $p = 0.001$ with a simultaneous reduced knee power absorption at 56% gait cycle $p = 0.002$ (Figure 13).

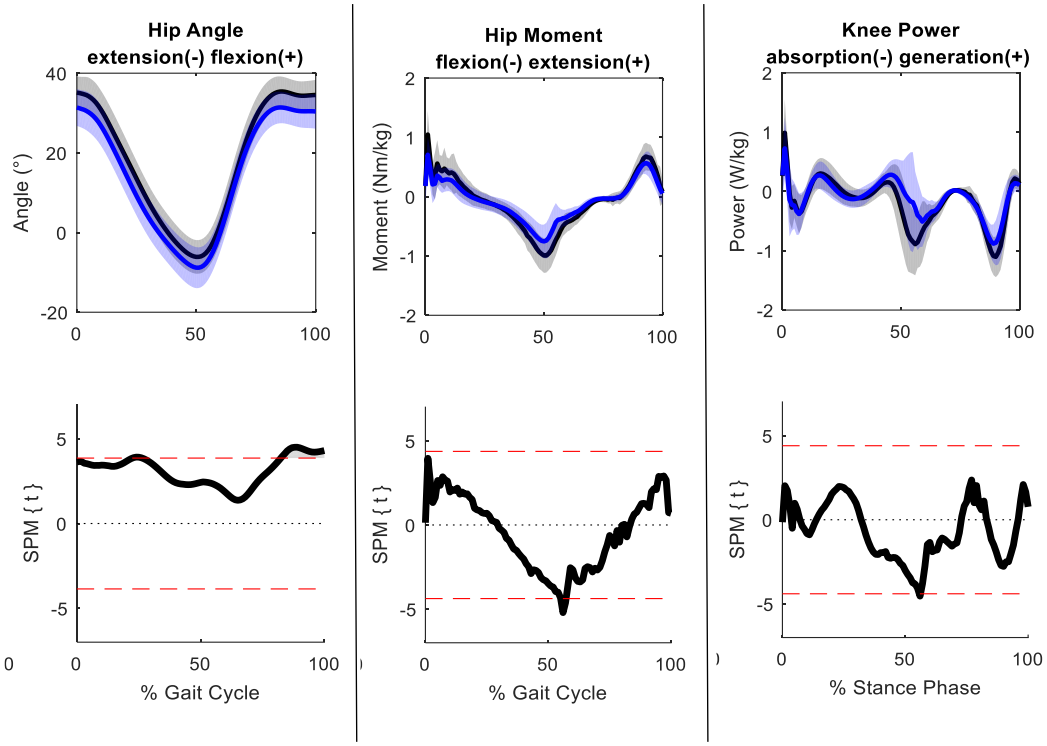


Figure 13: The kinematic and kinetic curves where significant differences occurred between the Middle AKU patients and controls. For each curve the top panel represents averaged curve for the AKU Middle (blue) and speed matched controls (black). The bottom panel shows the t-statistic (SPM {t}). This represents an inference curve with a threshold at a specific t (dashed red line). When SPM {t} exceeds this threshold, significance is reached with *p* values reported.

4.3.4. Joint specific gait deviations in the Old AKU patients

Figure 14 shows the largest significant difference between the AKU old group and the healthy control group in the transverse plane foot progression angle between 0-68% gait cycle $p < 0.001$, suggesting increased out toeing throughout the stance phase. Secondly, there is increased knee abduction between 7-55% gait cycle $p < 0.001$. There are significant differences shown in the frontal plane pelvic obliquity; reduced depression 55-76% gait cycle and reduced elevation 5-25% gait cycle $p < 0.001$. There is also increased hip adduction during 55-72% gait cycle and reduced plantarflexion during 62-68% gait cycle during push-off.

The largest significant difference between the AKU old group and the healthy control group in the moment curves is the reduced knee abduction moment $p = 0$ between 38-55% of the gait cycle, indicating the second half of the stance phase. The second largest difference is during 11-25% of the gait cycle indicating reduced knee abduction moment during the first half of the stance phase $p < 0.001$.

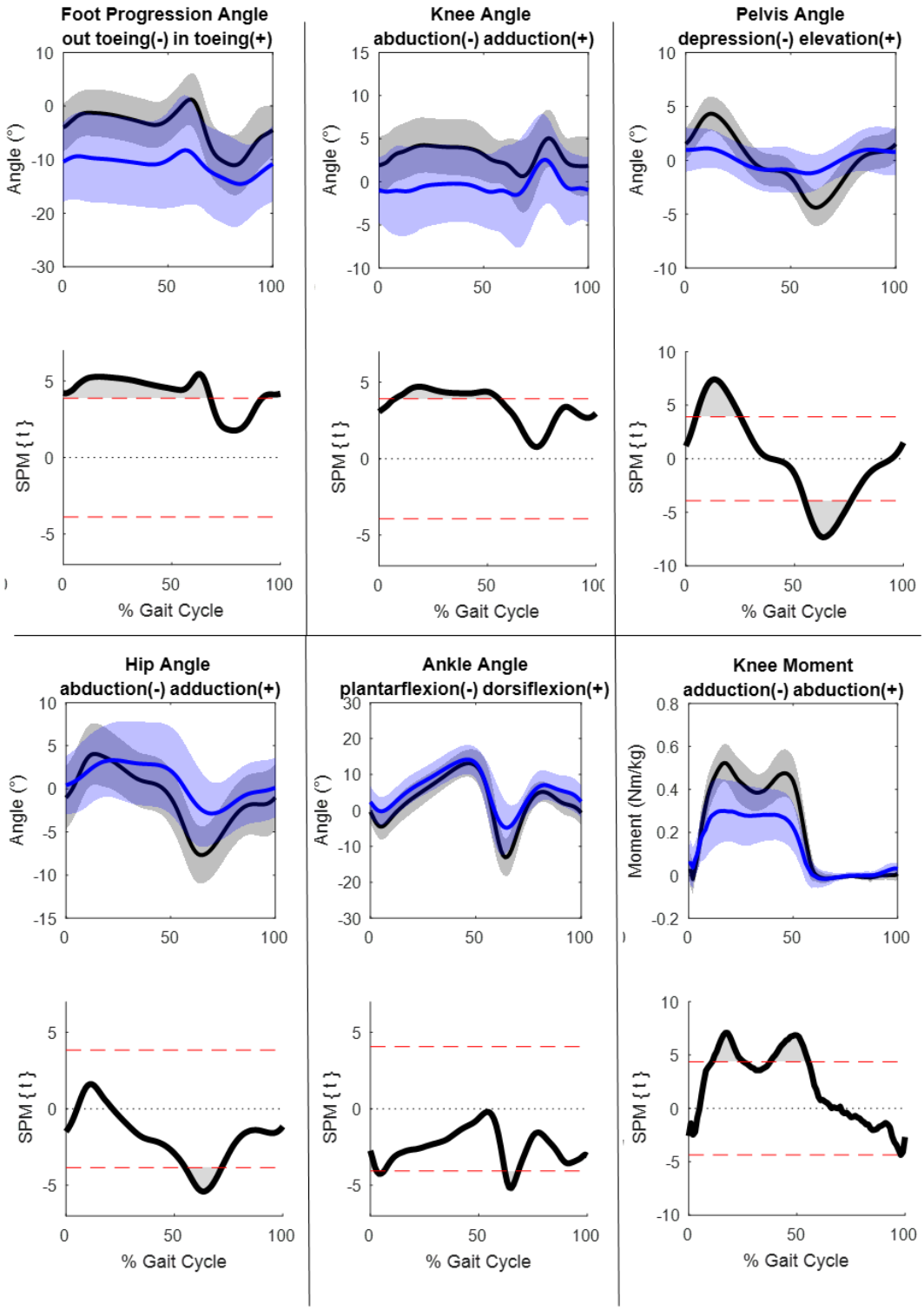


Figure 14: The kinematic and kinetic curves where significant differences occurred between the Old AKU patients and controls. For each curve the top panel represents averaged curve for the AKU Old (blue) and speed matched controls (black). The bottom panel shows the t-statistic (SPM {t}). This represents an inference curve with a threshold at a specific t (dashed red line). When SPM {t} exceeds this threshold, significance is reached with *p* values reported.

4.3.5. Ground reaction force vector field

The Hotelling's T^2 GRF waveform analysis showed no significant differences between AKU and control GRF waveform in both the Young and Middle group (Figure 15a and 15b). Significant differences were seen in the Old group at 100% of the gait cycle, showing the T^2 waveform greater than the critical threshold (Figure 15c). At 100% of the stance phase the forces are at the lowest as the foot is close to toe off, when the forces are low they are most susceptible to noise and crosstalk, therefore the significant differences at 100% may be due to errors and not represent a meaningful difference, based on this, the analysis was not taken further.

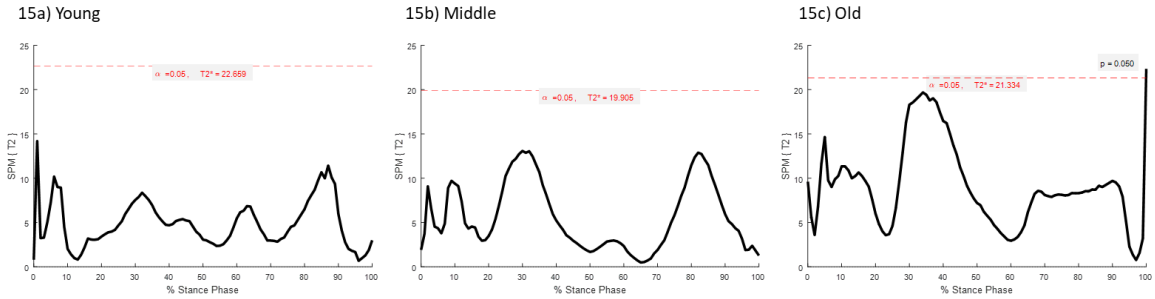


Figure 15: a) Young group, b) Middle group and c) Old group Hotelling's T^2 trajectory (SPM{T^2}), The ground reaction force vector field did not differ between controls and AKU for the Young and Middle groups and a significant difference in the Old group at 100% stance.

4.4. Discussion

The previous chapter highlighted the natural progression of gait deviations in relation to age in AKU patients using a summary measure of gait. This study aimed to expand this further by identifying the joint specific deviations and mechanisms of AKU gait. This is the first study known to the author to describe AKU gait at joint level. Firstly, the hypothesis was accepted as there were significant difference between the gait vectors of AKU and healthy controls. In general, the amount of significant differences between AKU and healthy control gait curve profiles were seen to increase with age, coinciding with the previous chapter whereby MDP_{mean} scores (deviation from normal) increased with age.

4.4.1. Young AKU group

The deviations seen in the young are clearly linked. The increased knee extension during mid- to terminal stance leads to the knee joint centre being more posterior to the GRF vector than normal, increasing the extension moment arm and resulting in an increased internal flexion moment. The younger group also exhibited a reduction of the second rocker, indicating an early heel rise and leading to an excessive plantarflexion knee extension coupling, these two deviations both occur at the same period of the gait cycle

(35-42% gait cycle). However, the difference between the two means (AKU and controls) in the sagittal plane ankle angle was not significant. During the same period of the gait cycle the power curve for the knee joint is typically negligible as the GRF stabilises the knee in extension and muscular contribution is minimal. However, in AKU gait we see an increase in power absorption followed by a significant increase in power generation. As the knee is in increased extension compared to normal, the increased flexion moment is likely to be a result of the passive resistance of the posterior soft tissue structures of the knee which may also absorb the power during elongation of the soft tissue. As the knee joint goes into flexion, the passive structures are no longer stretched, and the release may contribute to the increased generation of power which occurs directly afterwards at 42-45% gait cycle.

These deviations from normal at the knee joint are likely to put additional strain on the passive structures, particularly within the posterior supporting ligaments, which are also susceptible to AKU ochronosis related damage. Thickening of Achilles tendons, ruptures and tears of knee and ankle ligaments during normal activities have been previously documented in AKU patients (Phornphutkul et al., 2002; Manoj Kumar and Rajasekaran, 2003). These sagittal plane deviations at the knee joint may contribute to the increased MDP_{mean} identified within the younger AKU patients (16-29 years) reported in chapter three.

4.4.2. Middle AKU group

The largest significant difference between the AKU middle group and the self-selected speed controls was the reduced hip flexion during terminal swing (82-100% gait cycle), in preparation for initial contact. During stance the hip is also offset to extension, significantly so during 22-26% gait cycle. With an offset to extension during terminal stance (although not significant) one would expect to find an increased hip flexion moment due to a larger moment arm in the posterior direction. However, we see a reduced hip flexion moment compared to the control group at 55-57% gait cycle, and at the same point in time we see a reduced knee power absorption at 56%. One explanation for this is a forward trunk lean, which would bring the force vector more anteriorly, shortening the moment arm in the hip in the sagittal plane. Spinal disc degradations were seen at the ages of 40-50 years (Cox et al., 2019), which could result in structural changes and orientation of the trunk during gait, however, trunk position was not measured during this study. After qualitatively analysing the 2D video in the sagittal plane, there were signs of abnormal trunk posture. Only four out of the 16 AKU patients in the middle group showed normal trunk posture, 11 out of the 16 had signs of thoracic kyphosis, and two out of the 16 showed clear signs of an anterior trunk tilt.

4.4.3. Old AKU group

In the old group, we see a shift away from sagittal plane deviations. There are no sagittal plane moment differences, and the sagittal plane angle differences are not highly ranked. The largest difference between AKU and healthy controls is the reduced frontal plane knee abduction moment. Due to the minimal significant difference within the 3 component GRF waveform analysis at 100% of stance phase with minimal practical significance, we can assume the moment is influenced by a change in moment arm rather than the GRF vector magnitude. There are several angular differences revealed by the SPM analysis that present mechanisms to support this notion. Firstly, the old group show increased out toeing between 0-68% gait cycle throughout the whole duration of the stance phase (0-60% gait cycle). Out toeing alters the line of the GRF vector's progression along the line of the foot during the stance phase, this moves the GRF vector laterally bringing it closer to the knee joint centre, reducing the moment arm in the frontal plane, therefore reducing the internal knee abduction moment. The old group also showed an increased external hip rotation which would also support the out toeing; however, this was not significantly different compared to the speed matched controls.

Another mechanism identified, was the increased knee abduction angle along with the increased hip adduction, which suggests a valgus knee alignment. This brings the knee centre medially closer to the GRF vector, therefore, also reducing the frontal plane moment arm, consequently reducing the frontal plane knee abduction moment.

The old group also show a reduction in pelvic elevation and depression, indicating a reduced range of pelvic obliquity motion throughout the gait cycle, this is likely due to spine stiffness and lower back pain limiting the range of motion. Lower back pain is a common symptom reported by 88.9% AKU patients aged between 40-74 years (Rudebeck et al., 2020). Additionally, they show a decreased plantarflexion at push off which may be linked to a thickening of the Achilles tendon, which would reduce or alter its mechanical role in the progression of gait.

4.4.4. Differences between the planes of motion

These results show that the deviations from normality shift between anatomical planes as age increases. Sagittal plane moments are often overlooked in OA research however, Erhart-Hledik, Favre and Andriacchi (2015) found that the external first peak flexion moment showed the greatest association with degeneration of the posterior tibial region in the less severe-subgroup of OA patients. This suggests that sagittal plane moments have a substantial influence of the force that acts upon the joint. Although the increase in the AKU younger (less severe) group is the internal peak flexion moment in the second half of stance, it still highlights the involvement of the sagittal plane moments, and the potential

damage it may cause to the integrity of the AKU knee joint. Interestingly, Erhart-Hledik, Favre and Andriacchi (2015) also found that a decrease in external peak knee flexion moment was significantly associated with an increase in pain (R =-0.272, p = 0.049) in OA patients. Our older AKU group did not show any significant differences in the sagittal plane knee moments, suggesting a decrease from the younger AKU group's findings. The removal of the increased sagittal plane moments could be in response to structural damage and pain. However, pain and structural damage were not measured in this study.

In the younger and middle AKU groups we see no significant differences in frontal plane knee moments compared to controls. In agreement to this, previous studies have shown no differences in the internal knee abduction moments in the early stages on knee OA (Foroughi, Smith and Vanwanseele, 2009). However, high internal knee abduction moments are often associated with severe OA as an indicator of medial compartment loading. In contrast, our older and more severe AKU group had decreased internal knee abduction moments. One explanation is the difference in the frontal plane knee alignments seen in both conditions. Severe OA have shown increased varus alignment (Meireles et al., 2016), however the old AKU group showed increased valgus alignment. This suggests opposite frontal plane knee alignment resulting in opposite loading profiles (OA increased knee abduction moments, old AKU decreased knee abduction moments). Although AKU leads to premature OA, there are some underlying physiological differences between the two diseases as well as between gait profiles.

As well as valgus knee alignment contributing to the knee abduction moment, the most highly ranked angle deviation was the out toeing in the old AKU group. It is likely that out toeing has been adopted, potentially subconsciously, as a self-selected gait modification to decrease the frontal plane knee moments in response to reported pain (Rudebeck et al., 2020) and increased structural joint damage (Cox et al., 2019) seen the older AKU patients. Additionally, out toeing may also be a natural change occurring during healthy aging as the internal hip rotators become weaker, or it may be adopted to increase the base of support and therefore increase stability. Although out toeing is a deviation from normality it has a beneficial consequence by reducing the frontal plane knee moment. The AKU patients in this study were speed-matched instead of age matched therefore the difference between out toeing may be smaller when compared to age matched controls.

A self-selected gait modification suggests that it is an achievable movement pattern for these patients, even with the constraints of the AKU disease. Additionally, there appears to be no negative consequences of this movement pattern, such as increased moments in any of the other joints. However, due to the multiple deviations that occur within the older group across multiple planes of motion, it is difficult to conclude how much a single kinematic gait modification such as out toeing influences the knee moments, and whether it

is an isolated movement. Specific kinematic gait modification and their effect on knee moments would have to be further investigated, this will be evaluated in chapter 6 of this thesis.

Despite monitoring gait changes across age groups in AKU, it is difficult to determine what came first. An adopted gait compensation or modification in response to increased pain and structural damage or increased structural damage and pain due to an altered gait pattern. What we do know is that AKU is progressive with age and potentially worsened by mechanical loading, even by loads seen during normal gait. If we were to implement an effective intervention to reduce the mechanical loading at the knee earlier within younger patients it may have the potential to delay the progression of the disease within the knee, reduce the pain and delay the need for costly and invasive joint replacements.

There were a few limitations to this study. Firstly, only lower extremity kinematics and kinetics were measured, the role of the trunk and upper body were only qualitatively analysed using the 2D video. A 3D quantitative description of the upper body would be insightful to gain an understanding of the full body movement patterns and their effects on the knee joint moments in AKU, particularly in the middle AKU group. Although we are aware that pain, disease severity and structural damage increases with age (Cox et al., 2019; Rudebeck et al., 2020), we do not have the direct associations with gait deviations. The AKU patients were split into three groups based on their age ranges, however, there still remains large inter-patient variation in each age group indicated by the large standard deviations seen across the waveform data. This is also supported by the lack of distinct clusters seen in chapter 3 which may suggest variable gait deviations within the AKU cohort. The large variations in each group indicate that alkaptonuria gait is heterogenous and cohort analysis may not have identified all of the movement patterns and compensation strategies.

4.5. Conclusion

To describe AKU gait in detail we took an unbiased approach to identify the differences between AKU and speed-matched healthy control gait. The study successfully identified gait abnormalities and mechanisms in AKU gait fulfilling the objective. Key findings include the knee joint showing significant differences in all three age groups identifying the joint as an important factor in AKU gait abnormalities. Additionally, there was an apparent shift from sagittal plane deviations to the frontal and transverse plane as age increased, demonstrating that AKU gait is affected in all three planes of motion. Finally, a large reduction in the frontal plane knee moment was seen in the old AKU group and potential mechanisms contributing to this were described. A potential self-implemented gait modification (out toeing) which reduces the knee moment was identified driven by pain and

structural damage in the older group. Based on these findings other potential gait modifications and their effect on the knee moment in all three planes should be investigated further, in the hope to implement a successful load-reducing gait modification earlier in the progression of the disease.

Section 2: The development of a real-time biofeedback method for treadmill-based gait interventions in AKU patients

Chapter 5: Inverse Dynamics versus a 3D lever arm approach: the technical development of a method for real-time biofeedback during gait modification interventions

5.1. Introduction

The majority of biofeedback methods during gait retraining in osteoarthritis research use specific indirect kinematic parameters, which are thought to influence the knee moment, in particular the KAM. However, indirect feedback requires prior knowledge and evidence of which kinematic variables influence the joint moment, these kinematic variables are outline in chapter 2.6.3. Additionally, prescribing a specific kinematic strategy may not be well received by patients. Variations in pain experienced, current compensations and perceived effort by patients may cause an avoidance of a particular strategy. Gerbrands et al. (2017) found personal preference a key factor when choosing a modification. Allowing patients to determine their own gait modification strategy overcomes these problems. To implement this, direct feedback (feedback on the outcome variable aimed to change, in this case the 3D moment impulse) has been shown to be more successful than indirect feedback (feedback on a variable that is known to influence the outcome variable, in this case a kinematic change) (Richards et al., 2018). This concept is further emphasised in sports, where motor skill learning and retention is greater when using a direct feedback versus an indirect feedback approach (Masters, 1992). When enhancing motor learning to prevent ACL injuries, Benjaminse et al. (2015) found that explicit instructions which direct attention to the desired outcome or the effects of the movement was more successful than implicit instructions on the just movement itself. By using direct feedback, the participant or patient can develop their own individual kinematic strategy. This is particularly important for the heterogeneous AKU patient population.

Joint moments are typically calculated using the inverse dynamics method. This uses Newton-Euler equations and a link-segment model to calculate the sum of the individual moments produced by the joint reaction forces, ground reaction forces and the muscle and soft tissue forces that produce the joint moment. The moment vector is generally resolved into three planar components; sagittal, frontal and transverse. This method is thought of as the ‘gold standard’ in clinical gait analysis. For the knee joint moments, the inverse dynamics approach uses kinematic and kinetic data from the foot segment and ankle joint,

and the shank segment and knee joint as well as the inertial parameters of the body segments to give precise estimations of the knee joint moment's magnitude.

To provide direct feedback of the KAM during a gait modification retraining intervention, the typical inverse dynamics method poses some problems. The measurement is complicated, usually calculated offline and requires several variables for computation. Current real-time software and models available on the market such as the Human Body Model (HBM, Motekforce Link, Amsterdam, The Netherlands) come with some limitations. The HBM provides calculations of joint angles, joint kinetics and muscle forces in real-time, however, the knee is modelled as a hinge, therefore is given one degree of freedom. The reason for this decision is that this method is simpler and more time efficient for the real-time calculation of muscle function and estimations of muscle forces (Glitsch and Baumann, 1997). Thus, ab/adduction and internal/external rotations are set as constants due to their small ranges of motion during gait, this disregards the interpretation of the frontal and transverse plane knee moment. This constraint may be representative of non-pathological gait, however AKU gait shows structural deformities which cause abnormal out of plane movements. This was evidenced in chapter three in the older AKU group who demonstrated increased knee abduction throughout the stance phase.

Those that have provided real-time feedback on the knee joint moments have often used their own in-house biomechanics software to compute the inverse dynamics (Richards et al., 2018). One study used a real-time estimation of tibiofemoral contact forces using OpenSim, prior to real-time capabilities the protocol required model calibrations, which involved initial data collection and offline data processing totalling to 1.5 hours of preparation before the system was ready for real-time feedback (Pizzolato et al., 2017b). When just computing inverse kinematics and inverse dynamics in real-time without the time consuming addition of contact forces Pizzolato et al. (2017a) encountered some issues with filtering. Time delays caused by the filtering affected the signals' frequency in both time and magnitude, these are then combined in the calculation of inverse dynamics causing larger distortions in the joint moments. Additionally when the kinematic and kinetic data have different filter cut-offs this can lead to artefacts within the moment calculation (Kristianslund, Krosshaug and van den Bogert, 2012).

A simplified approach is the lever arm method, which estimates the joint moment by calculating the product of the 3D GRF vector and the perpendicular distance (moment arm length) between the axis of rotation (the knee joint centre) and the GRF. There are mathematical differences between the lever arm method and inverse dynamics and (Winter, 2009) outlined the mathematical errors of this simplified approach: The mass-acceleration and the moment of inertia-angular acceleration products of the stance limb are not included in the lever arm approach. The method only uses the ground reaction force

vector which is a summation of the mass-acceleration products of all segments. The effects of the other contributing joints are not subtracted at each joint from the ground upwards. Therefore, errors are negligible at the ankle, small but significant at the knee and large at the hip (Wells, 1981) and errors continue to increase with the ascent up the body. If the lever arm method was to be extended to the neck, the projection of the GRF during gait would mean a very large moment arm and an unrealistic neck moment that is several times larger than what is typically seen at the lower limb joints. Secondly, the lever arm approach cannot estimate joint moments during the swing phase due to the lack of GRF vector. Despite the mathematical errors of this method, it is simple and computationally fast, and it could have the potential to be a method for a real-time biofeedback stimulus.

Two studies used the simpler lever arm method during gait modification interventions, although both studies calculated the lever arm only in the frontal plane. To calculate the knee joint centre Wheeler, Shull and Besier (2011) used the position of the lateral femoral condyle plus half the knee width medially offset in the frontal plane. They used the 1st peak of the KAM as their direct feedback, which was calculated as the cross product of the position vector from the knee joint centre to the centre of pressure and the ground reaction force in the frontal plane. The 1st peak KAM was computed in the first 40% of the stance phase. The second study did not clearly state their methods used (Shull et al., 2011). Whilst these two studies used this approach during an intervention, one study compared the two methods. Lewinson, Worobets and Stefanyshyn (2015) directly compared the raw moment magnitude as well as the peak KAM between inverse dynamics and the simplified lever arm approach. They only included the frontal plane moment and used the mediolateral and vertical ground reaction force (GRF_x and GRF_z respectively), and the mediolateral and vertical distances from the knee joint centre to the centre of pressure (r_x and r_z respectively) using equation (1).

$$EKAM_y = r_z GRF_x + r_x GRF_z \qquad \textit{Equation (1)}$$

The results showed poor agreement between the two methods, low correlation was found (r=0.24, p=0.63), and a Bland-Altman plot showed that the mean difference was 14.2 Nm. The lever arm approach consistently underestimated the KAM, compared to the inverse dynamics. However, the general shape of the curves was the same. Lewinson, Worobets and Stefanyshyn (2015) subsequently went on to compare the two methods when a lateral wedge was introduced in an attempt to induce a change in KAM. When assessing the % change between the two methods a moderate correlation was found (r =0.55, p=0.03), the Bland-Altman plot test revealed a mean difference of -5% between the two methods, and individual values were typically within one standard deviation. The results suggested a moderate agreement, with moment reduction being larger in the inverse dynamics. Differences between these two findings could be due firstly to the coordinate system that

the joint moments are expressed in. Previous studies have shown that the magnitude of peak KAM can significantly differ between the coordinate systems used at the shank (Schache and Baker, 2007; Schache et al., 2008). Additionally, the lever arm method (used within this study) and those previously mentioned only used a 2D approach and used the lab-based coordinate system. The 2D approach assumes that the shank is always perpendicular to the lab floor in the sagittal plane and no rotation occurs. Both assumptions are violated during gait and affect the calculation of the magnitude of the moment. Another study used the 3D cross product approach by taking the 3D distance of the knee joint centre to the centre of pressure and multiplying it by the 3D GRF. They then calculated the peak KAM and KAM impulse and compared these values with the inverse dynamics values. They reported high correlation between the two methods $r > 0.9$ and absolute differences were less than 10% (Rutherford and Baker, 2018). These results demonstrated that using the 3D cross product method yields a better comparison to the inverse dynamics than the lever arm method in just the frontal plane. However, this method was not analysed during modified gait.

The peak KAM's are often used as proxy to the knee joint forces due to its associations with the medial compartment loading (Zhao et al., 2007; Foroughi, Smith and Vanwanseele, 2009). However, an *in-vivo* study found the KAM angular impulse to have a better association with the medial knee contact forces than the 1st peak KAM (Walter et al., 2010). The impulse incorporates both the magnitude and duration of the moment throughout the stance phase. Additionally, the knee loading is a 3D problem, as recent studies have shown reducing the KAM does not always result in a reduction in the medial compartment forces (Walter et al., 2010). Differences in the two is likely a product of increases in the sagittal plane moments (Erhart-Hledik, Favre and Andriacchi, 2015) or even transverse plane differences (Roberts et al., 2018). Therefore, a direct feedback of joint loading using a single measure which incorporates all three planar components of the joint moments would be beneficial, enabling focus on 3D joint moment reduction, rather than solely in the frontal plane.

Additionally, during inverse dynamics the reference frame in which the knee joint moments are expressed can also cause significant differences within the parameters analysed (Manal et al., 2002; Schache and Baker, 2007). This technicality is eliminated when using the 3D knee moment vector. To overcome the limitations within previous literature, whilst being aware of the errors outlined by (Winter, 2009), this chapter aimed to design a new 3D lever arm approach. This method would present a single simple variable; a 3D moment impulse, which considers all three components of the joint moment, more closely representing the total 3D moment applied to the knee during each stance phase. The

method would aim to be applied during real-time gait retraining to give direct feedback of the knee loading during the stance phase only.

5.1.1. Objectives

1. To develop a novel real-time biofeedback method (3D Lever Arm) for treadmill-based interventions designed to reduce the knee moment, incorporating all three knee moment components

Objective 1 will be addressed under 5.2. development of the lever arm method.

2. To compare the simplified 3D lever arm (LA) method to the inverse dynamics (ID) method during normal gait, and test its ability to detect changes during gait modifications

Objective 2 will be addressed under 5.3 comparison of the 3D lever arm and inverse dynamics. Based on the previous literature, the hypothesis within this chapter will be that the 3D lever arm method will compare well to the inverse dynamics' method during normal and modified gait.

5.2. Development of the 3D lever arm method

The simplified 3D lever arm method was created with the D-Flow system (Motek Medical, Amsterdam, The Netherlands). The 3D lever arm method uses a simplified equation for the calculation of the 3D knee moment which assumes that the GRF and the perpendicular distance from the GRF and the knee joint centre are the main contributors to the magnitude of the moment. The equation uses the F=md approach whereby the GRF force vector is multiplied by the perpendicular distance to the joint centre (moment arm).

The D-Flow system software is connected to the M-GAIT treadmill (Motek Medical, Amsterdam, The Netherlands). The D-Flow editor was used to create an application which calculated the 3D moment impulse. The building blocks of a D-Flow application are modules which receive inputs, perform some processing and generate outputs (Figure 16).

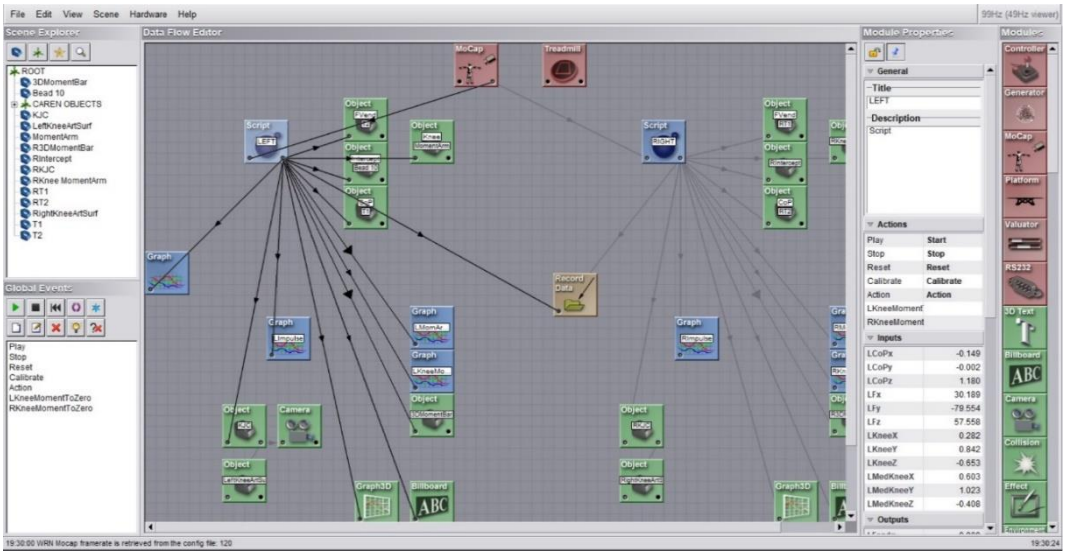


Figure 16: The D-Flow editor interface.

D-Flow receives both marker position data and force data streamed live from Vicon Nexus (Vicon Motion Analysis Inc., Oxford, UK). The specific inputs from Nexus required for this application were the centre of pressure position (CoP_x, CoP_y, CoP_z), the ground reaction force vector (F_x, F_y, F_z) and the lateral and medial knee marker positions ($Knee_x$, $Knee_y$, $Knee_z$ and $MedKnee_x$, $MedKnee_y$, $MedKnee_z$ respectively) which were retrieved via the MoCap module. Within the script module (Figure 17), the 3D knee moment impulse was calculated for both the left and right sides using the inputs outlined above, the script module uses the Lua language for coding (the full script is reported in appendix 10). The details of the calculation are described below.

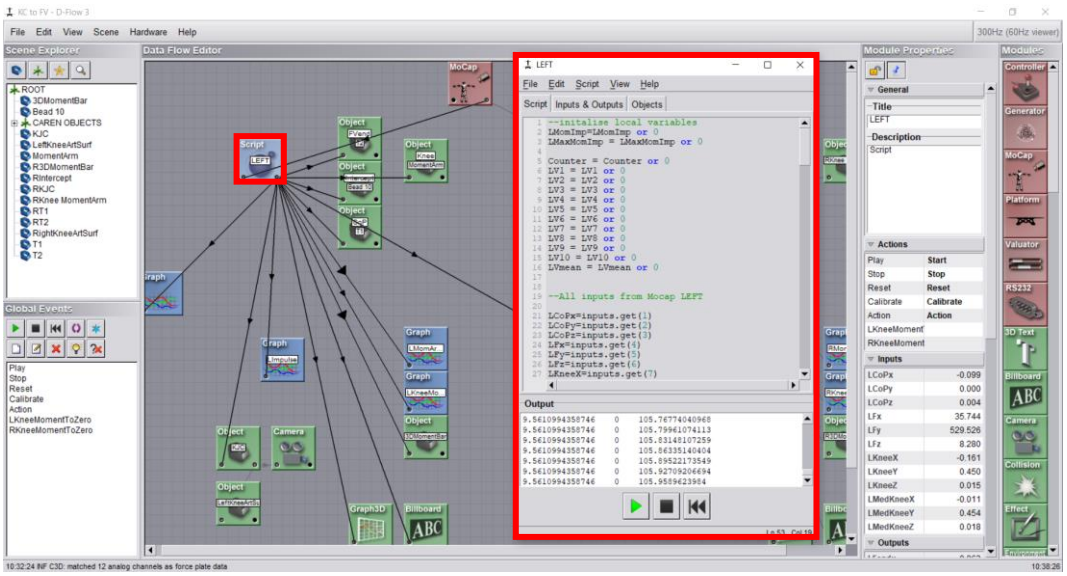


Figure 17: The script module within the D-Flow Editor.

5.2.1. Calculation of the 3D knee moment arm

Firstly, within the script module the knee joint centre (KJC) position was calculated as the midpoint between the lateral (LatKnee) and medial (MedKnee) epicondyle using equation (2)

$$KJCx = \frac{LatKneex + MedKneex}{2} \qquad \text{Equation (2)}$$

$$KJCy = \frac{LatKneey + MedKneey}{2}$$

$$KJCz = \frac{LatKneez + MedKneez}{2}$$

For the visualisation of the GRF vectors and subsequent calculations the force components were scaled. The force components received from Nexus are given in newtons, to help visualise the GRF vector, graphical objects were placed at the CoP and the end of the GRF vector (Fend). D-Flow assumes that numbers which are assigned to objects are given in metres. As the newtons are high values e.g. 785 N for an 80 kg participant, to keep the GRF within visual view of the screen, this number was divided by 1000 to give 0.785 m. The GRF end point position (Fend) was found by adding the CoP position to each of the scaled force components (x,y,z) to give a position in metres.

The CoP, Fend with the KJC created a triangle (Figure 18), whereby the lengths of its sides were found using Pythagoras theorem equation (3). Force vector length (FVL) equation (4), CoP to KJC length equation (5) and Fend to KJC length equation (6). The angle (Θ) between the Fend and CoP to KJC was found using the Cosine rule equation (7).

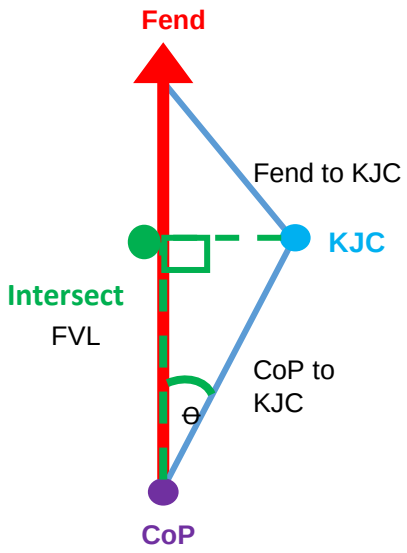


Figure 18: A visual representation of the triangle between the Fend, CoP and KJC with the angle between the FVL and CoP to KJC, and moment arm intercept from the KJC.

$$a^2 + b^2 = c^2$$ *Equation (3)*

Equation (3) was rearranged to find the triangle lengths

$$\text{FVL} = \sqrt{Fx^2 + Fy^2 + Fz^2}$$ *Equation (4)*

$$\text{CoP to KJC} = \sqrt{(KJCx - CoPx)^2} + (KJCy - COPy)^2 + (KJCz - CoPz)^2$$ *Equation (5)*

$$\text{Fend to KJC} = \sqrt{(Fendx - KJCx)^2} + (Fendy - KJCy)^2 + (Fendz - KJCz)^2$$ *Equation (6)*

$$c^2 = a^2 + b^2 - 2abcos\theta$$ *Equation (7)*

Where a = FVL, b = CoP to KJC, c = Fend to KJC and θ = the angle between FVL and CoP to KJC.

Trigonometry was then used to calculate the moment arm length equation (8) and the length of the CoP to the point of the moment arm intersect along the force vector equation (9).

$$Sin\theta = \frac{o}{h}$$ *Equation (8)*

*Where **o** = moment arm length, **h** = CoP to KJC and **θ** = the angle between FVL and CoP to KJC*

$$Cos\theta = \frac{a}{h}$$ *Equation (9)*

*Where **a** = length to point of moment intersection from CoP, **h** = CoP to KJC **θ** = the angle between FVL and CoP to KJC*

To determine the coordinates of the moment arm intersection perpendicular to the GRF from the KJC the ratio of the FVL and the CoP to the point of intersect length was calculated by dividing the intersect length by the FVL then multiplied by the force vector length and added to the CoP for the intersect coordinates (I_x, I_y, I_z) equation (10).

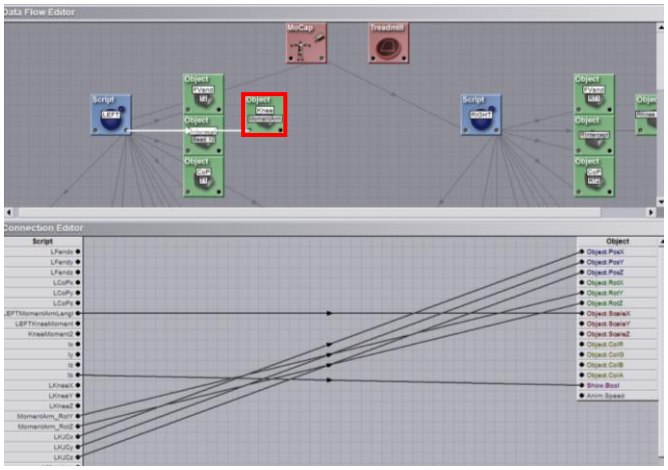
$$Ix = Ratio * (Fendx - CoPx) + CoPx$$ *Equation (10)*

$$Iy = Ratio * (Fendy - CoPy) + CoPy$$

$$Iz = Ratio * (Fendz - CoPz) + CoPz$$

D-Flow does not have a function or module which allows the visualisation of a line between two points. Therefore, to visualise the moment arm, the object module was used, and a thin cylinder shape was created (Figure 19a). The cylinder was scaled to the moment arm length and rotated about y and z axis using the positions of the intersect and KJC (Figure 19b).

19a)



19b)

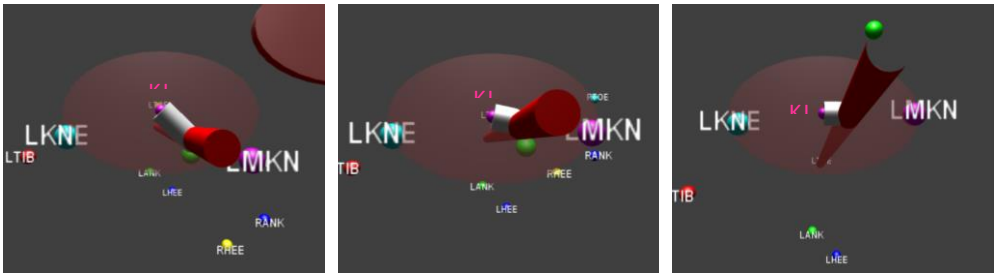


Figure 19: The visualisation of the moment arm. 19a the object module to create the cylinder, 19b a birdseye view of the knee surface to visualise the moment arm and the GRF vector at different stages throughout the stance phase.

The 3D knee moment impulse was calculated by multiplying the moment by the change in time (seconds) between each frame and added to the previous impulse in real-time. The impulse value cumulatively increases throughout the stance phase as more data points are summed as time increases (Figure 20). The impulse was then reset at the beginning of each swing phase and the maximum value was provided. This maximum value represents the impulse across the stance phase. The swing phase was determined while the 3D knee moment = 0 as there was no force vector data provided for the calculation. The force vector had a threshold of 20 N to avoid inaccurate values when the force is close to zero.

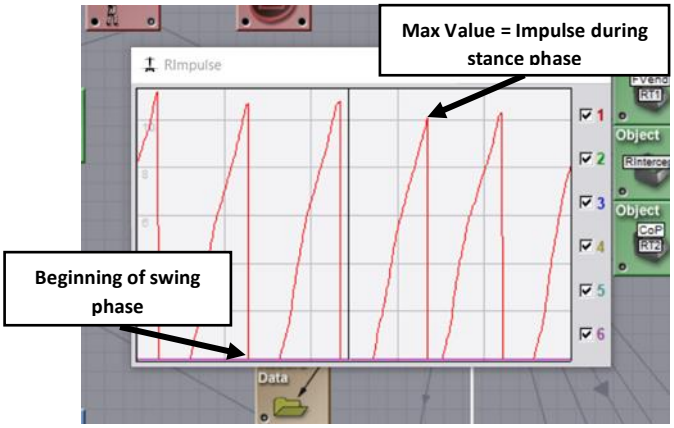


Figure 20: The summation of the moment impulse at each frame during the stance phase.

5.2.2. Visualisation of the 3D knee moment impulse

The 3D knee moment impulse was presented at the end of each stance phase as a horizontal line segment on a step wise graph until the next toe-off when the new impulse was shown. To avoid any asymmetries during the intervention, both left and right impulse values were projected onto a large screen approximately two metres in front of the participant's position on the treadmill (Figure 21).

Figure 21: The participant's position on the treadmill in relation to the screen which presents the visual feedback.

5.2.3. Calculating and visualisation of a target reduction

An adjustable target parameter was also implemented into the visualisation. This was a solid line at a 10% reduction from their baseline 3D impulse measure. The 3D moment impulse was averaged over the last 10 steps of the data recorded from the normal walking trial and multiplied by 0.9 to give a 10% target 3D impulse reduction value to input into the visualisation (Figure 22). A 10% reduction was chosen based on previous studies which reported that a 10% target reduction in KAM is achievable without performing excessive movement patterns during the gait modifications (Shull et al., 2013; Hunt and Takacs, 2014), Richards et al. (2018) also found that a 10% reduction in KAM was achievable with knee OA patients.

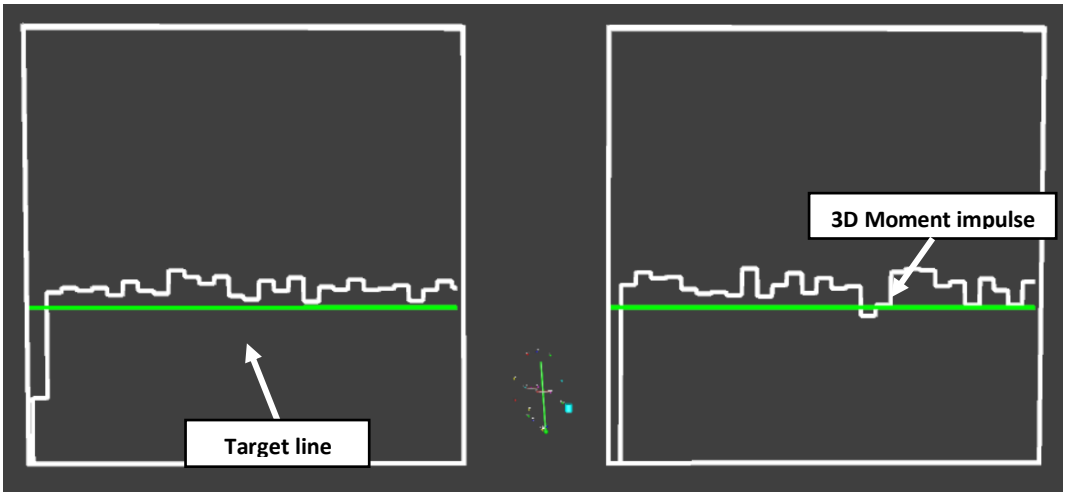


Figure 22: Example of the visual feedback display. Continuous history of the 3D moment impulse from the previous gait cycles which always end at toe-off. A target line which represents a 10% reduction from their baseline was also displayed to the participant.

5.3. Comparison of the 3D lever arm and inverse dynamics

The intended application of the new method would be to provide the real-time feedback to re-train gait during the intervention; however, it would not replace the assessment of the joint moments done offline using the 'Gold Standard' inverse dynamics. Therefore, the research question is: does the 3D lever arm method compare well to the inverse dynamics' method? If the two methods show good agreement, and is able to detect changes during gait modifications, the 3D lever arm method could provide a simplified real-time direct feedback method to use during gait modification interventions, which incorporates the three components of the knee with one value of feedback.

5.4. Methods

5.4.1. Participants

To compare the two approaches 16 healthy participants were recruited from Liverpool John Moores University students with no previous or current injuries that may have affected their gait. They were aged between 23-38 years with 8 females and 8 males. Full participant characteristics are shown in Table 8. Each participant made a single visit to the Movement Function Research Laboratory at Liverpool John Moores University. They were provided with an information sheet (Appendix 11) and were asked to sign a consent form (Appendix 12). Ethical approval for this study was granted by Liverpool John Moores University Research Ethics Committee (SPS REC ethics number: M20SPS001).

Table 8: Participant characteristics.

Variable	
N	16
Male/Female	8/8
Age (years, mean ± SD)	26.4 ± 3.8
Height (m, mean ± SD)	1.77 ± 0.10
Body Mass (kg, mean ± SD)	75.7± 13.9

5.4.2. Protocol

This study was a methods-comparison study design, whereby the data for both methods was collected simultaneously. Each participant's height and body mass were measured. For the Helen Hayes model and inverse dynamics calculation, the knee and ankle widths were measured to later calculate the knee joint centre within Visual 3D. Participants wore their own trainers and tight fitted clothing. The reflective markers were attached to the lower limbs according to the Helen Hayes Marker set (Davis et al., 1991) with the addition of two knee markers placed on the medial epicondyles. To capture the upper body motion, additional six markers were placed on the right and left shoulder (acromion), the clavicle, sternum, cervical 7^{th} and thorax 10^{th} spinous processes.

The M-GAIT split belt treadmill (M-GAIT, Motek Medical, Amsterdam, The Netherlands) was used and forces from the two force plates under the left and right belts, running at the same speed were sampled at 1000 Hz. To collect kinematic data, 15 Vicon motion capture cameras were used (12 Vero and 3 T160, Vicon Motion Analysis Inc., Oxford, UK) sampled at 120 Hz. Familiarisation of treadmill walking was undertaken for 2.5 minutes. The treadmill was set at 1.2 m/s walking speed for all participants. The speed was controlled to allow for easier comparison between the two method and speed has also been found to affect the knee moment during gait modifications (Simic et al., 2011; van den Noort et al., 2015). After the familiarisation period, the normal walking trial was recorded for 30 seconds.

5.4.3. Gait modification trials

Prior to testing all participants were given a gait modification information sheet (Appendix 13). This outlined each gait modification along with illustrative images. All participants were given the chance to ask any questions regarding each of the gait modifications. The participants were then asked if they understood each gait modification before continuing, verbal confirmation of understanding was given. The gait modifications were toes in (in), toes out (out), short stride length (short), lateral trunk sway (sway), medial knee thrust (thrust) and wide base gait (wide). A description of each modification is given in Table 9.

Table 9: Gait modification descriptions.

Gait Modification	Description
In	A decrease of the foot progression angle
Out	An increase of the foot progression angle
Short	A decrease in step length
Sway	A translation of the trunk over the stance limb
Thrust	An internal rotation of the hip along with a flexion of the knee during stance
Wide	An increase in step width

Each participant's baseline impulse was measured during the normal walking trial (method described in 5.2.5). The 10% reduction of the baseline impulse was calculated and displayed on the screen as shown above in Figure 22. Each participant was told to complete each gait modification whilst aiming to get as close to or below the target white line indicating the 10% reduction target. No other form of feedback was given during each modification. For all walking trials the treadmill speed was set to 1.2 m/s to control for walking speed. Participants were given 2.5 minutes to familiarise, then both Nexus and D-Flow kinematic data were recorded simultaneously for 30 seconds at 120 Hz.

5.4.4. Data processing

For the 3D lever arm method, the 3D moment was calculated in D-Flow and filtered using a low pass 6 Hz Butterworth filter. Data were exported to a text file (.txt) and then normalised to body mass.

For inverse dynamics labelled marker positions and force data were exported directly from Nexus to a c3d. file. Data were filtered using a 6 Hz Butterworth filter. The three knee joint moment components were calculated using inverse dynamics and normalised to body mass in Visual 3D (V6, Visual3D, C-Motion, Germantown, USA). The three moment components were exported to a text file (.txt) and 3D knee moment was calculated using equation (11).

$$3D\ knee\ moment = \sqrt{(Mx)^2 + (My)^2 + (Mz)^2} \qquad \textit{Equation (11)}$$

The impulse of the 3D knee moment during the stance phase was calculated for both the 3D lever arm method and the inverse dynamics. Stance phase for each side was defined when the force was above a 20 N threshold. The 20 N threshold is considered as the 'Gold Standard' threshold value to remove noise from the force signal (Zeni Jr, Richards and Higginson, 2008).

5.4.5. Statistical analysis

Paired *t*-tests were used to compare the mean 3D impulse between the two methods for each condition. Paired *t*-tests were then used to compare the mean percentage change from normal, during each gait trial.

A Pearson's 2-tailed correlation were used to assess the relationship of the mean between the two methods. Similarly, a Pearson's 2-tailed correlation were used to assess the relationship of the percentage change between the two methods for each gait trial. This analysis determines the direction and strength of the relationship between the two methods.

To observe the agreement between the two methods a Bland-Altman plot was used (Bland and Altman, 1986). The x-axis represents the mean of the two measurements and the y-axis is the difference between the two values. The mean of the difference is calculated and plotted along with the two lines of agreement which is the upper and lower 95% confidence interval to represent the bias. As there is no *a-priori* limit of agreement for these two methods, a good agreement was determined when 95% of the values are between the upper and lower lines of agreement. When there is more than 50% of the values above outside of the limits of agreement, this indicates that there is no agreement between the two methods (Giavarina, 2015).

5.5. Results

5.5.1. 3D moment impulse

Table 10 shows the summary results of the mean 3D impulse difference between the Inverse Dynamics (ID) method and the 3D Lever Arm (LA) method for each gait trial. During all seven gait trials there were significantly strong positive correlations between the ID and the LA methods. There were also significant differences in the mean 3D moment impulse between the two methods for all seven gait trials, with the LA method significantly lower than the ID method.

Table 10: The summary of the results of the 3D moment impulse mean between the two methods.

Gait Trial	**ID** Mean ± SD	**LA** Mean ± SD	Mean difference ± SD (ID – LA)	*T*-test *P* value	Correlation *r* value	Correlation *p* value
Normal Impulse (Nm/kg.s)	0.31 ± 0.06	0.26 ± 0.06	0.05 ± 0.01	**<0.001 ***	0.976	**<0.001 ***
In Impulse (Nm/kg.s)	0.27 ± 0.02	0.22 ± 0.05	0.05 ± 0.01	**<0.001 ***	0.966	**<0.001 ***
Out Impulse (Nm/kg.s)	0.26 ± 0.04	0.21 ± 0.04	0.05 ± 0.02	**<0.001 ***	0.966	**<0.001 ***
Short Impulse (Nm/kg.s)	0.24 ± 0.05	0.19 ± 0.04	0.05 ± 0.02	**<0.001 ***	0.931	**<0.001 ***
Sway Impulse (Nm/kg.s)	0.29 ± 0.07	0.25 ± 0.06	0.04 ± 0.02	**<0.001 ***	0.956	**<0.001 ***
Thrust Impulse (Nm/kg.s)	0.28 ± 0.09	0.26 ± 0.09	0.02 ± 0.02	**<0.001 ***	0.964	**<0.001 ***
Wide Impulse (Nm/kg.s)	0.25 ± 0.05	0.22 ± 0.04	0.03 ± 0.02	**<0.001 ***	0.897	**<0.001 ***

During the normal walking trial, the LA and ID method were strongly and positively correlated ($r = 0.976$, $p < 0.001$), (Figure 23a). The Bland-Altman plot (Figure 23b) shows good agreement between the two methods with >95% within the confidence intervals.

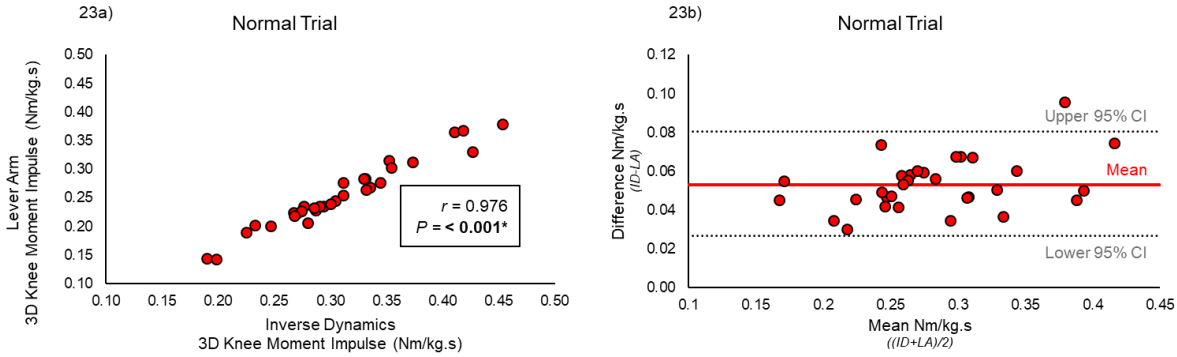


Figure 23: a) the correlation between the lever arm method and the inverse dynamics method's calculation of the 3D knee moment impulse. b) the Bland-Altman plot showing the agreement between the two methods when measuring the 3D knee moment impulse, the red line shows the mean difference and the dotted black lines show the upper and lower 95% confidence intervals.

5.5.2. Percentage change during gait modifications

Table 11 shows the summary results of the mean percentage change in the 3D knee moment impulse from normal gait to each gait modification for the ID method and the LA

method. There were significantly strong positive correlations between the ID method and the LA method. For the sway, thrust and wide trials, the ID method had a significantly larger % change in 3D knee moment impulse from normal than the LA method. In addition, for the medial knee thrust trial the ID method saw a negative percentage change compared to normal, and the LA method saw a positive percentage change compared to normal.

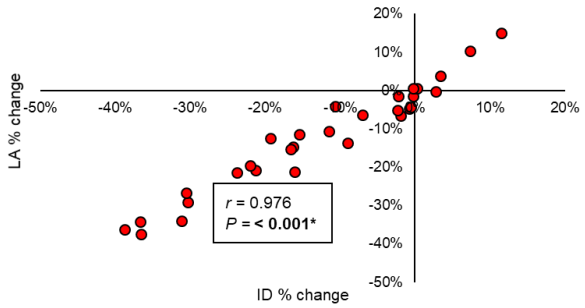
Table 11: The summary of the results of the mean % change in 3D moment impulse from normal between the two methods during each gait trial.

Gait Trial	ID % change from normal Mean ± SD	LA % change from normal Mean ± SD	Absolute difference between ID and LA (%) Mean ± SD (ID – LA)	*T-Test* *p* value	Correlation *r* value	Correlation *p* value
In	-11.77 ± 2.62	-11.39 ± 2.55	-0.39 ± 3.18	0.503	0.976	**<0.001 ***
Out	-13.52 ± 1.88	-14.61 ± 2.24	1.10 ± 4.43	0.178	0.941	**<0.001 ***
Short	-22.87 ± 2.07	-24.52 ± 2.12	1.65 ± 5.28	0.093	0.896	**<0.001 ***
Sway	-4.58 ± 2.58	-1.87 ± 2.72	-2.71 ± 6.13	**0.020 ***	0.915	**<0.001 ***
Thrust	-8.83 ± 4.66	2.14 ± 5.49	-10.97 ± 10.29	**<0.001 ***	0.941	**<0.001 ***
Wide	-16.29 ± 2.73	-10.87 ± 2.67	-5.42 ± 6.60	**<0.001 ***	0.905	**<0.001 ***

Figures 24 shows the correlation between the LA and ID methods when calculating the percentage change during each of the gait modifications trials. For some individual cases, the LA and ID methods differed and were opposite in the direction of % change. These are those values which fall into quadrants two and four, highlighted on the Figures 24a-24f by the dashed blue boxes. In toeing and short strides showed no opposite values. Out toeing showed one value, trunk sway showed two values, medial knee thrust showed six values and wide base showed four values.

For the agreement between the two methods, in toeing, out toeing and wide all show good agreement between the two methods when calculating the percentage difference from normal. Short strides, trunk sway and medial knee thrust demonstrated a moderate agreement between the two methods, for all trials > 90% of values were between the limits of agreement.

24a)



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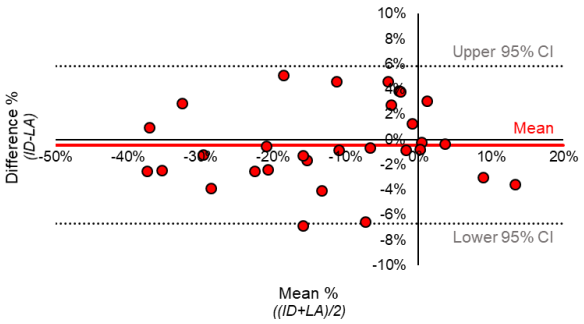

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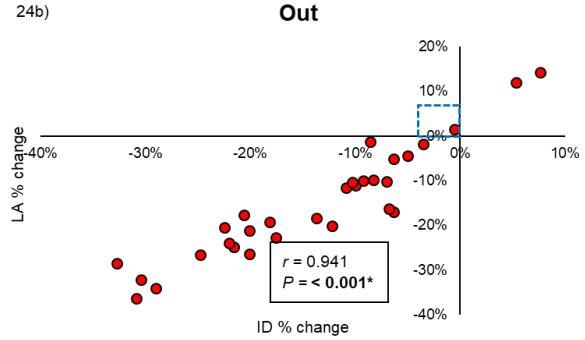
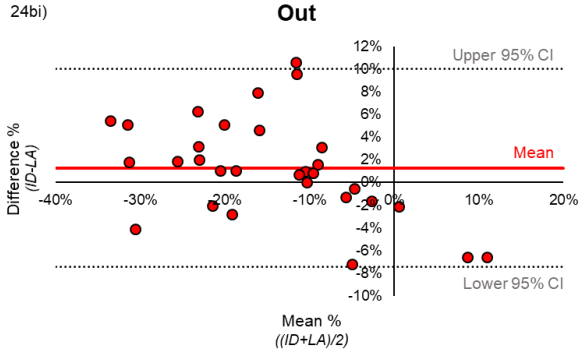
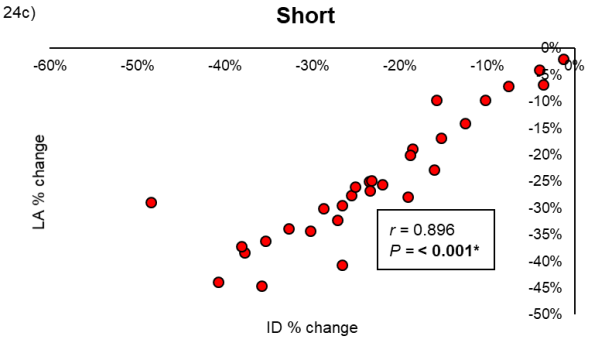


24bi)



24c)



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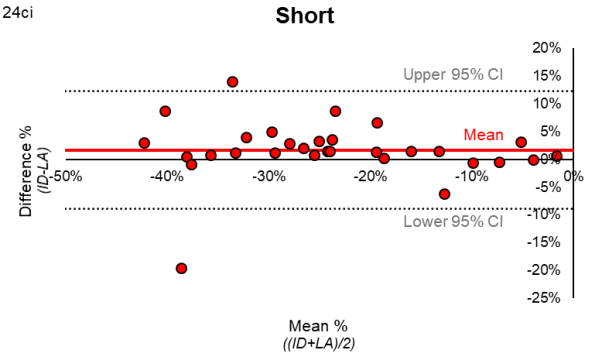
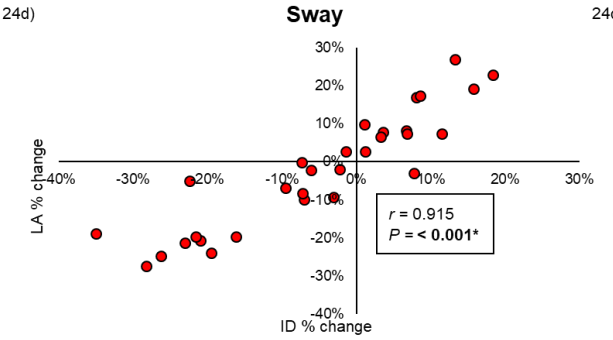


24d)



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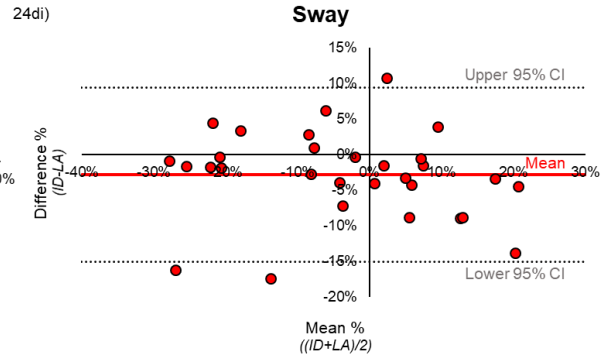

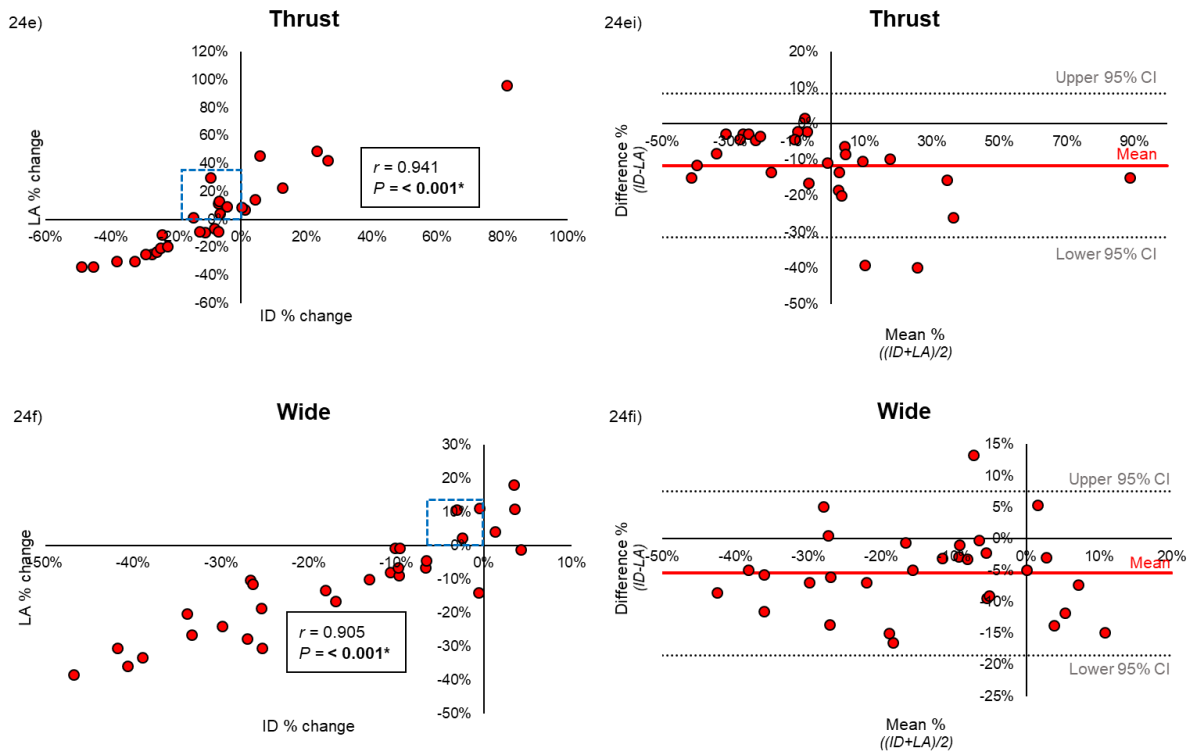

Figure 24: a-f) The correlation between the 3D lever arm method and the inverse dynamics method when calculating the % difference from normal for each of the gait modification trials. ai-fi) the Bland-Altman plots showing the agreement between the two methods when calculating the % difference from normal for each of the gait modification trials. The red line shows the mean difference and the dotted black lines show the upper and lower 95% confidence intervals.

5.5.3. Absolute differences (smallest and largest)

To demonstrate the agreement between the two methods, the smallest and largest absolute differences of the 3D knee moment impulse between the two methods are shown in Figure 25. All of the gait trials, for all participants were reviewed to find the smallest and largest differences. The individual participant and gait trial (Wide) which presented the smallest absolute difference of the 3D knee moment between the two methods is shown in Figure 25a (absolute difference (ID-LA) = 0.001 Nm/kg.s), the individual participant and gait trial (Sway) which presented the largest absolute difference of the 3D knee moment between the two methods is shown in Figure 25b (absolute difference (ID-LA) =0.098 Nm/kg.s).

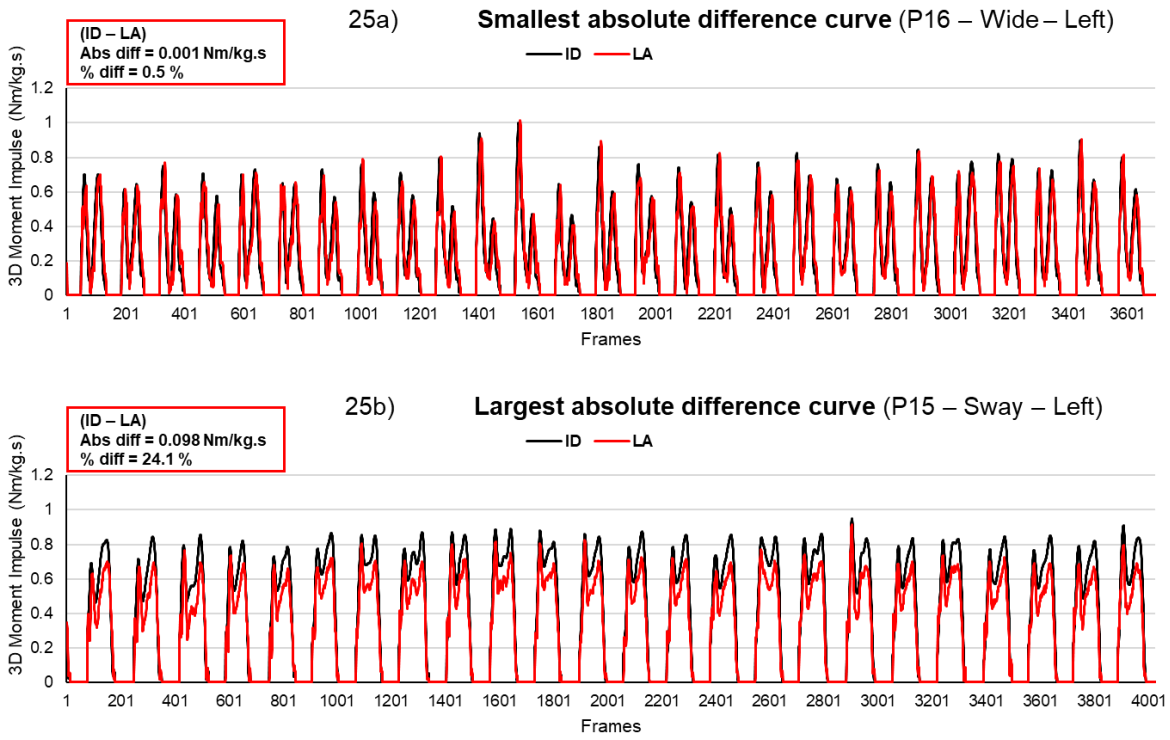

Figure 25: The Inverse Dynamics and 3D Lever Arm 3D knee moment curves. 25a shows the curves that give the smallest absolute difference in 3D knee moment impulse between the two methods. 25b shows the curves that give the largest absolute difference in 3D knee moment impulse between the two methods.

5.6. Reference frames for the expression of the knee joint moments

Throughout the literature the reference frame used to express the lower limb joint moments are often not described and the difference between the reference frames is not considered. There are four reference frames that can be used to express a joint moment. Three are orthogonal: the proximal reference frame (proximal), the distal reference frame (distal) and the laboratory frame (lab). The fourth possible option is the non-orthogonal, which is the joint coordinate system (JCS). There is currently no consensus on which should be used, as they are all mathematically correct. This makes it difficult to compare data across studies and may also affect the results of gait intervention studies. Previously, Schache and Baker (2007) compared the lower limb joint moments when expressed in the four reference frames. They found significant differences in the knee joint moment profiles during gait in all three components, specifically the 1st peak internal extensor moment, 1st peak internal valgus moment and the peak stance external rotator moment. They came to the conclusion that the non-orthogonal JCS is the best references frame based on the biomechanical meaning of the joint moment. The International Biomechanics Society (IBS) recommend the JCS for describing joint kinematics (Wu et al., 2005), and it was also found that it is important to describe joint kinematics and kinetics in the same reference frame (Gagnon, Desjardins and Larrivé, 2001; Derrick et al., 2020). As the new 3D lever arm method uses

the 3D knee moment, as opposed to the separate knee moment components, it is important to investigate the effect of the four references frames on the expression of the 3D knee joint moment.

5.6.1. Data Analysis

Right sided data during the normal walking trial (speed 1.2 m/s) for one participant were chosen for analysis. The knee moments were calculated using the standard inverse dynamics method and were then expressed in four reference frames: the proximal segment anatomical frame, the distal segment anatomical frame, the laboratory frame and the joint coordinate system (JCS). Data were normalised to body mass and all inverse dynamics calculations were made in Visual 3D (V6, Visual3D, C-Motion, Germantown, USA), the knee moments in the sagittal, frontal and transverse planes for all four reference frame conditions were then exported to a .txt file and the 3D moment was calculated in Excel for all conditions.

5.6.2. Results

The sagittal plane knee moment (Figure 26a) shows that during the first half of stance the internal knee extension moment is less in the distal frame, compared to the proximal, lab and JCS. During the second half of stance the internal knee flexor moment is less in the distal frame than the proximal, lab and JCS. In the sagittal plane proximal the proximal and JCS moment curves are close (curves overlap). Out of the three planes the smallest differences are seen in the frontal plane (Figure 26b). The differences primarily occurred during the 1st and 2nd peaks. The 1st peak abduction moment was larger in the distal frame than in the proximal, lab and JCS. The the 2nd peak abduction moment was smaller in the distal frame than the proximal and lab, but similar to the JCS. In the transverse plane (Figure 26c), during the first half of stance, the proximal frame shows a peak internal rotation moment, where the distal, lab and JCS all give an external rotation moment. The JCS and distal also show a larger external rotation moment during the second half off stance compared to the proximal and lab. Additionally, in the transverse plane the distal and JCS moment curves are close (curves overlap). Interestingly, the 3D knee moment removes almost all differences between the four references frames (Figure 26d).

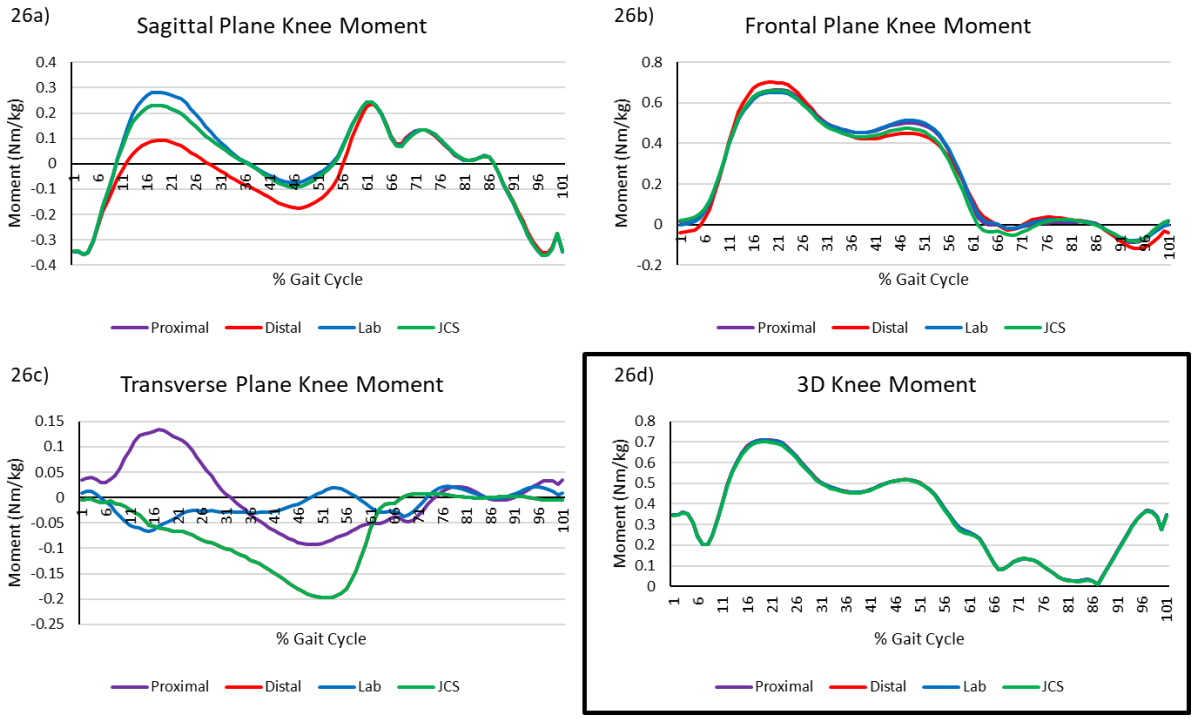

Figure 26: The knee moments expressed in the four reference frames (proximal, distal, lab and JCS) for the sagittal plane (26a), frontal plane (26b), transverse plane (26c) and the 3D knee moment (26d).

5.7. Discussion

The first objective of this chapter was to develop a novel method to provide real-time direct feedback for gait modification interventions. The 3D LA method was developed to provide a direct feedback of the variable that is intended to be changed/reduced by implementing a gait modification. It also provides an adjustable target reduction which can be individualised based on each participant or patient's baseline measures. The direct outcome variable that is used in the method is the 3D moment impulse. It remains unclear which KAM parameter (1^{st} or 2^{nd} peaks) is most effective and displaying too many variables for a patient to interpret during an intervention would be difficult. The moment impulse provides magnitude and duration of the moment throughout the stance phase and may provide a better representation of total knee load. However, this was not tested during this study. Thirdly, the new 3D LA method provides a 3D moment which includes all three moment components in all three planes.

To maintain symmetry during gait retraining both left and right values are presented in a simple step plot, showing the history of previous steps. It also has advantages in that less variables and data processing is needed for the calculation of the 3D LA method, just the force vector and only the four knee markers are needed to be seen at all times by the cameras. This reduces any problems with the marker sets that require all markers to be seen at all times to build the model necessary for inverse dynamics.

5.7.1. Comparison of the inverse dynamics approach and 3D lever arm approach

The second objective of this chapter was to compare the new 3D lever arm approach to the 'gold standard' inverse dynamics approach. Firstly, the shape of the curves matches very closely (Figures 25a and 25b). Similar to the 3D cross product findings by Rutherford and Baker (2018) there were strong positive correlations between LA and ID methods for the mean 3D moment impulse for all gait trials. However, the correlation only provides information regarding the association between the two methods. To understand the agreement between the two methods, the Bland-Altman plots were interpreted. During the normal walking trial there was good agreement between the lever arm method and inverse dynamics method when calculating the 3D knee moment impulse.

For the 3D lever arm method to be an effective tool for gait retraining it must have the ability to detect changes in the outcome measure when gait is modified. There were strong positive correlations between the two methods when calculating the percentage change from normal for each gait modification. All gait trials show differences of less than 10%, apart from the medial knee thrust trial (10.97%) between the two methods when calculating the % difference from normal walking. Previously a 10% reduction of the knee moment is often used as a target value during gait modifications interventions (Favre et al., 2016; Richards et al., 2018), therefore anything larger than this could mean differences were due to the method rather than the gait modification. The Bland-Altman plots also demonstrated moderate to good agreement between the two methods with >90% of all values lying within the limits of agreement. These results demonstrate that the LA method is able to detect changes in the 3D moment impulse changes during gait modifications.

Throughout all gait trials the LA method has a reduced mean 3D impulse suggesting a underestimation of the 3D moment impulse calculation compared to the ID method and the absolute differences of the mean 3D moment impulse range from 0.001 Nm/kg.s to 0.098 Nm/kg.s). There are mathematical differences between the two methods which could explain this underestimation. One difference is that the link-based model gives the masses and moments of inertia located at the centre of mass of each segment and inverse dynamics uses mass of each segment within the calculation. However, when segmental masses were removed from the inverse dynamics calculation the difference was minimal during the stance phase, and only clearly noticeable during the swing phase. Figure 27 presents the results the 3D knee moment of the right knee for one participant cropped to 10 strides as an example. The segmental masses were scaled down to 0.001 kg for the right thigh, shank and foot within Visual 3D (the model would not build if 0 kg was entered, therefore a low value of 0.001 kg was used instead). The original values for each segment were: thigh = 6.69 kg, shank = 3.11 kg and foot = 0.79 kg. On visual inspection of Figure 27

there is minimal difference between the ID – segmental masses and ID – no segmental masses during the stance phase, however during the swing phase the moment is reduced to 0 Nm/kg when the segmental masses are removed. This difference would make very minimal difference to the 3D moment impulse calculation as the swing phase is not included.

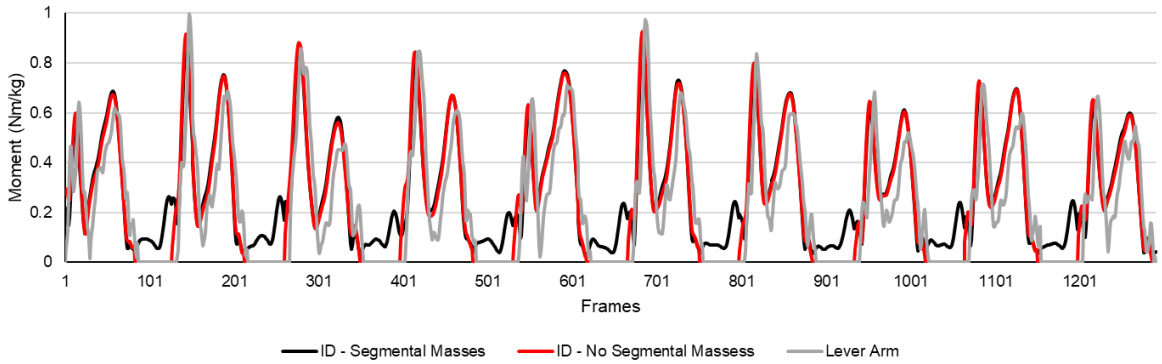

Figure 27: The 3D knee moment for the right knee of one participant during 10 strides. The results demonstrate the small difference when the segmental masses are removed during the calculation using inverse dynamics.

Another difference is that the LA method uses the ground reaction force vector, which represents the algebraic summation of the mass-acceleration products of all segments. Inverse dynamics, corrects for this at each joint by subtracting the effects as the calculation moves from the ground upwards, taking into consideration the inertial forces in the segments below the joint. Hence why the errors increase as the further up the body in the LA method, showing minimal effects in the ankle, small but significant in the knee and large at the hip (Wells, 1981). Therefore, this method may not be appropriate to use at the hip joint, however this was not measured in this study.

5.7.2. Comparison of the reference frames for the expression of the knee joint moment.

It is clear from Figure 26d that any differences between the four reference frames are removed when the 3D moment is calculated. Schache and Baker (2007) reasoned that the JCS better represents the joint rotation action of the muscles, if the joint rotations are calculated using the JCS. However, for any subsequent calculations from the moments such as joint powers an orthogonal reference frame should be used. A joint moment represents the net force of the muscle groups and passive structures that cross the joint. The direction of the joint moment (i.e. flexion/extension) indicates the 'winning' side, however, it does not necessarily represent the anatomical action of that 'winning' muscle, consider the co-contractions or give information on the connective tissue. In addition, due to the anatomy of muscle groups and contractions during movement, the actions of

different muscle groups will not be acting solely about a principal axis. Determining the 'winning' muscle groups is important in some aspects of clinical practice such as cerebral palsy when abnormal muscle activation timings are negatively affecting movement patterns. When the 3D moment is calculated the information regarding the directional component or the isolation of the 'winning' muscle group is removed. Alkaptonuria affects all aspects of the joint, cartilage, ligaments and tendons therefore the ultimate goal for AKU patients is to reduce the total load that is experienced by the joint during the stance phase of gait, and the directional component of the moment becomes less of a priority. Both methods are blind to the effect of co-contractions which increase the joint force. The 3D moment represents the total muscle force acting upon the joint during stance, reducing the 3D moment reduces the muscle forces acting upon all aspects of the joint. A limitation to the 3D lever arm moment impulse is the loss of directional information normally available through the moment components. By examining a 3D moment, it is no longer possible to identify the acting muscle groups during a particular part of the gait cycle. When considering the AKU patient group, the aim is to reduce the total knee moment acting about the joint in the hope to reduce the damage caused by mechanical loading. By only focusing on one plane (the frontal plane) there is a risk of increases in the moments in the other unmonitored planes (sagittal and transverse) during gait modification interventions.

Although the two methods show good agreement when calculating the 3D knee moment impulse and when calculating the percentage difference from normal, there is no *a-priori* limits of agreement based on the two methods, this would help to further interpret the agreement between the two methods. Additionally, the 3D moment is used as a primary outcome measure for the training tool. The gold standard inverse dynamics will still be calculated offline, where the three planar components can still be assessed. The effect of previously studied gait modification on the 3D knee moment will be further explored in the next chapter. Like other methods which use the moments as a proxy measure of the joint contact forces, the 3D moment impulse still does not provide us with the actual joint contact forces acting upon the articular cartilage, how well this combined 3D variable is associated to the *in vivo* contact forces should be further investigated. Furthermore, the 10% target for the reduction is based on previous studies using the KAM, not the 3D knee moment, the 10% reduction may not be achievable in the 3D knee moment. Finally, although the target is individualised to each participant based on their baseline measure, the clinical relevance of a reduction in the 3D knee moment in AKU patients is unknown, investigating this would lead to a more informed decision to provide a target reduction.

5.8. Conclusion

The 3D LA method was successfully developed which quickly computes a single simple variable which represents the total 3D knee joint moment during the stance phase which

can be presented as real-time feedback. Compared to other in-house methods which require extensive preparation time and multiple visits (Pizzolato et al., 2017b), this simple 3D LA method can be integrated into a simple gait protocol and model, with only the addition of two medial knee markers added to the widely used Helen Hayes model. The 3D LA method also considers the 3D moment without adding constraints to the model in the frontal and transverse planes unlike the HBM (Glitsch and Baumann, 1997), this ensures important 3D data is not missed or overlooked. The 3D lever arm approach slightly underestimates the moment impulse, due to the mathematical differences between the two methods. Despite this there were strong positive correlations and moderate to good agreements when comparing the 3D lever arm method to the 'Gold Standard' inverse dynamics method. Most importantly, when gait modifications were implemented, the 3D lever arm approach was also able to detect the changes in the 3D knee moment. The use of a 3D moment as opposed to just the frontal plane moment ensures no loss of information in the sagittal and transverse planes. The 3D moment also eliminates differences due to the reference frame that the moment is expressed in. This new method will be used in subsequent chapters as a training tool for gait modification interventions to reduce the 3D knee moment impulse.

Chapter 6: Six previously studied gait modifications: The ability to reduce the total 3D knee moment impulse and a description of each gait modification

6.1. Introduction

A systematic review by Simic et al. (2011) identified 14 possible gait modifications within the literature that aim to reduce the KAM. The most frequently researched were in toeing, out toeing, walking cane use, increased step width, medial knee thrust, reduced step length and lateral trunk sway. The descriptions and mechanisms for each modification are detailed in chapter 2.6.3.

There are large variations within the literature regarding the effectiveness of each modification, and little agreement on the most appropriate gait modification to reduce the knee moment. These differences are likely due to large variations in the methodologies throughout the literature. Firstly, the outcome measure used, the majority of the literature use discrete KAM parameters such as the 1st and 2nd peaks (Lynn, Kajaks and Costigan, 2008; Gerbrands et al., 2017; Lindsey et al., 2020). The association of these parameters with disease severity are outlined in chapter 2.6.1. Overall, it was found that changes in KAM parameters do not always represent the changes in the knee joint contact forces (Walter et al., 2010), likely due to increases in the sagittal and transverse planes during gait (Erhart-Hledik, Favre and Andriacchi, 2015; Roberts et al., 2018). The previous chapter overcomes this issue by creating a tool which represents the 3D knee moment impulse which is hoped to better represent the total knee loading environment. As this is the first study to use the total 3D knee moment impulse as an outcome measure for a gait modification intervention, it is also important to understand how the components of the 3D moment are distributed within the joint.

Another explanation for the variation within the literature is the individual responses to each gait modification. When healthy participants were prescribed gait modifications in a previous study, they reported a large variation in individual responses (Lindsey et al., 2020). Therefore, there should be an understanding of the individual response to each gait modification within healthy controls, as any variability is likely to increase within patient populations. Additionally, only a few studies have reported the effects of gait modifications on other joint moments (Richards et al., 2018). Alkaptonuria affects multiple joints, most prominently the large weight bearing joints, therefore, it is extremely important to identify and eliminate any gait modifications that are potentially harmful, by evaluating any increased moments in adjacent lower limb joints. Finally, it has been previously shown that some gait modifications do not occur in isolation, and it is often a combination of kinematic

movements (Favre et al., 2016; Anderson et al., 2018; Tokuda et al., 2018). An in-depth description of each gait modification is needed to assess the kinematic demand of each modification. The literature also suggests that the most effective way of reducing the knee moment is to present direct feedback (Wheeler, Shull and Besier, 2011; van den Noort et al., 2015). The direct feedback approach displays the outcome variable that is wished to be changed as opposed to an indirect feedback such as a kinematic change. The tool developed in the previous chapter will allow for direct feedback on the 3D knee moment impulse. The effectiveness of gait modification interventions is further improved if the participants or patients have prior understanding of gait modifications and some short training on specific gait modifications (Richards et al., 2018). To understand which gait modifications to use as guidance for patients and to plan an effective gait modification intervention, an in-depth understanding is needed of previously studied gait modifications. The gait modifications that will be evaluated within this chapter are: toes in, toes out, short strides, lateral trunk sway, medial knee thrust and increased step width. These gait modifications were chosen based on their biomechanical mechanisms which aim to reduce the frontal plane knee moment, these are also the most commonly reported in the literature (Simic et al. 2011). Finally, these six gait modifications are those that are feasible within the context of this protocol and are likely to still be achievable even when presented with the direct knee moment impulse feedback. Walking aids were excluded to ensure safety when walking on the treadmill and due to the complication of force plate data.

Overall, to decide which of the previously studied gait modifications to use as guidance to patients in future interventions should be based on their ability to reduce the total 3D moment impulse, the variability of individual responses to the gait modification, their effects on other joint moments, and how they are achieved kinematically. To assess the previously studied gait modifications safely, asymptomatic pain free healthy controls should be used in a proof-of-concept study.

The aim of the study reported in this chapter was to establish through a feasibility study whether previously reported gait modifications which are designed to reduce the KAM, are effective at reducing the total 3D joint moment impulse when using a novel real-time biofeedback tool. Effective and non-harmful gait modifications can then be used to inform the planning of future gait modification interventions for alkaptonuria patients.

6.1.1. Objectives

1. To evaluate the effectiveness of well-known gait modifications on reducing the knee moment in healthy controls

The six modifications that will be assessed are: out toeing, in toeing, short strides, lateral trunk sway, medial knee thrust and wide base. The modifications were chosen based on

the most common findings within the Simic et al. (2011) systematic review and are feasible within this protocol. The evaluation of the effectiveness of each modification will be realised through the following tasks:

a) To assess the effects of six gait modifications on the total 3D knee joint moment impulse.
b) To assess the individual responses to the six gait modifications on the 3D knee joint moment impulse.
c) To assess the effects of six gait modifications on the adjacent lower limb joint moment profiles.
d) To describe the temporal-spatial and kinematic changes during each gait modification.

It is hypothesised that the six gait modifications may not reduce the 3D knee joint moment, and that reduction in one plane may increase the moment in another plane as well as changing the moment in the adjacent joints.

6.2. Methods

The data collected from the previous chapter was analysed in further detail for this chapter to investigate the effectiveness of each gait modification. Sixteen healthy participants completed seven gait trials whilst walking at 1.2 m/s on a split belt treadmill (M-GAIT, Motek Medical, Amsterdam, The Netherlands). A normal walking trial was recorded followed by six gait modification trials: in toeing, out toeing, short strides, lateral trunk sway, medial knee thrust and wide base. The 3D moment impulse was visually provided as real-time feedback with a 10% reduction target line whilst participants tried to modify their gait in the prescribed way. For detailed participant, protocol and gait modification information see the previous chapter 5.3.1.1, 5.3.1.2 and 5.3.1.3.

6.2.1. Data processing

All marker positions and force data were exported directly from Nexus to a .c3d file. All data were filtered using a 6 Hz Butterworth low pass filter in Visual 3D (V6, Visual3D, C-Motion, Germantown, USA).

The real-time biofeedback of the 3D knee moment impulse was provided using the 3D lever arm method described in the previous chapter. However, for the full offline analysis of all lower limb joint moments and kinematics the results were calculated using inverse dynamics and both kinematics and kinetics were expressed in the proximal reference frame. All joint moments were normalised to body mass. The impulse of the stance phase, which was defined with a force threshold of > 20 N, was calculated for each 30 second trial and divided by the number of steps taken within that trial. The 3D knee moment was

calculated as the vector sum of its three components and the impulse over time was calculated. All joint angle data were calculated in Visual 3D, these were normalised to 101 points to represent % of gait cycle. The mean curve and SD for each gait modification were graphed using Matlab (MATLAB R2017a, Mathworks, MA, USA).

6.2.2. Data Analysis

Traditional gait analysis interpretation of the kinematic profiles was used to evaluate whole body movement during each gait modifications.

Temporal and spatial parameters; stride length, step width and cadence's mean and SD's were calculated in Visual 3D. To test the distribution of the data for normality a Shapiro-Wilk test was conducted ($p > 0.05$), the results showed that the 3D knee moment impulse was normally distributed for the normal, in, out, short and wide gait trials. On visual inspection of the histogram, normal Q-Q plots and box plots, Sway and Thrust showed outliers, however upon inspection of the data, these outliers were deemed true and the histograms were symmetrical. Therefore a paired sample t-tests compared the six modifications to normal gait using (SPSS, IBM, USA) for the 3D knee moment impulse, the three components of the knee moment, the three components of the hip moment and the sagittal plane ankle moment, alpha was set at 0.05. For the moment impulses, raincloud plots were used to show the mean and SD but also to visualise the spread and distribution of the data (Allen et al., 2019), these plots were created in R Studio (RStudio Inc, Version 1.2.5042, Boston, USA).

6.3. Results

6.3.1. The 3D knee moment impulse

Four out of the six gait modification trials significantly reduced the 3D knee moment impulse (Table 12). There was a significant decrease of the 3D knee moment impulse during the in toeing, out toeing, short strides and wide base gait trials compared to normal gait. The trunk sway and medial knee thrust gait trials did not significantly reduce the 3D knee moment impulse. The short strides gait trial demonstrated the largest reduction from normal (0.073 ± 0.045 Nm/kg.s).

Table 12: The 3D knee moment impulse for all six gait modifications compared to the normal gait trial, (*) and bold represent a significant difference compared to normal along with the direction of change (↓) represents a decrease in 3D knee moment impulse and (↑) an increase in 3D knee moment impulse.

Gait Trial	3D Knee Moment Impulse (Nm/kg.s)							
	Mean ± SD	**Absolute difference from normal Mean ± SD**	95% CI of the Difference Lower	95% CI of the Difference Upper	t	df	Sig. (2-tailed) *P* – value	Direction
Normal	0.309 ± 0.064	-	-	-	-	-	-	-
In	0.267 ± 0.052	**0.041 ± 0.051**	0.022	0.060	4.435	30	**0.000 ***	↓
Out	0.263 ± 0.044	**0.045 ± 0.038**	0.031	0.059	6.602	30	**0.000 ***	↓
Short	0.236 ± 0.047	**0.073 ± 0.045**	0.056	0.089	9.008	30	**0.000 ***	↓
Sway	0.291 ± 0.070	0.016 ± 0.047	-0.001	0.033	1.925	30	0.064	↓
Thrust	0.278 ± 0.089	0.031 ± 0.058	-0.001	0.063	1.974	28	0.058	↓
Wide	0.253 ± 0.048	**0.055 ± 0.057**	0.034	0.077	5.384	30	**0.000 ***	↓

The mean ± SD and the distribution of the 3D knee moment impulse for each of the gait trials is visualised in Figure 28, the short strides and wide base trial's SD does not go above the mean impulse of the normal gait trial.

When calculating the mean % difference between normal and each gait modification all show a reduction of < 0% indicating a positive response (i.e. a decrease in 3D knee moment) (Figure 28b). Based on the original 10% target threshold only in toeing, out toeing short stride and wide based gait showed a mean % difference below -10% (12%, -13%, -23% and 16% respectively. The trunk sway and medial knee thrust mean reduction was -5% and -9% respectively. However, from Figure 28b there are individual responses that showed no positive response 0% difference and some that were there was an increase in 3D knee moment >0%. For the in toeing, trunk sway and medial knee thrust there were even % differences from normal >10% which would be considered a negative effect i.e. an increase in the 3D knee moment.

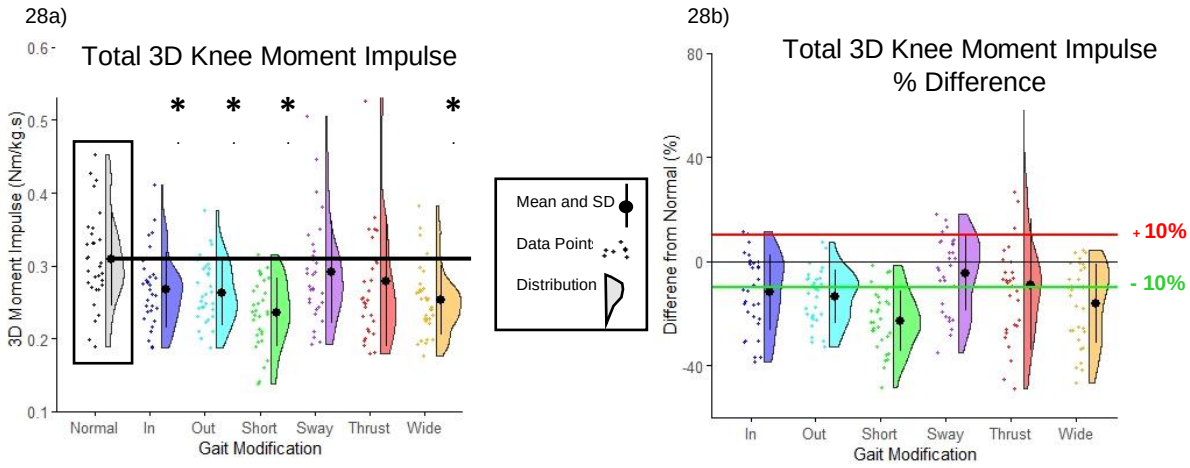

Figure 28: The 3D knee moment impulse during six gait modifications (medial knee thrust red, toe in: blue, toe out: cyan, short strides: green, trunk sway: purple, wide base: yellow). 28a) the total 3D knee moment impulse mean and SD, (*) indicates significant differences in the mean compared to normal. 28b) the mean % difference from normal for each of the six gait modifications.

6.3.2. The impulse of the three knee moment components

There were significant decreases in the sagittal plane knee moment impulse for the in toeing, out toeing and short strides gait trials compared to normal. There were significant increases in the sagittal plane knee moment impulse for the trunk sway and the wide base gait trials compared to normal, the medial knee thrust also showed increased sagittal plane knee moment impulse, however this was not significant. There were significant decreases in the frontal and transverse plane knee moment impulse for all six of the gait modifications trials (Table 13).

The mean ± SD and the distribution of the knee moment impulse in all three planes for each of the gait trials are visualised in Figure 29a, c and c, only the short stride trial's SD does not go above the mean impulse of the normal gait trial in all three planes of motion.

Table 13: The knee moment impulse in all three planes for all six gait modifications compared to the normal gait trial, (*) and bold represent a significant difference compared to normal along with the direction of change (↓) represents a decrease in the knee moment impulse and (↑) an increase in the knee moment impulse.

Gait Trial	Sagittal Plane Knee Moment Impulse (Nm/kg.s)							
	Mean ± SD	**Absolute difference from normal Mean ± SD**	95% CI of the Difference Lower	95% CI of the Difference Upper	*t*	df	Sig. (2-tailed) *P* – value	Direction
Normal	0.160 ± 0.037	-	-	-	-	-	-	-
In	0.145 ± 0.036	**0.014 ± 0.030**	0.004	0.025	2.733	30	**0.010 ***	↓
Out	0.146 ± 0.034	**0.014 ± 0.028**	0.003	0.024	2.686	30	**0.012 ***	↓
Short	0.125 ± 0.028	**0.035 ± 0.036**	0.022	0.048	5.359	30	**0.000 ***	↓
Sway	0.195 ± 0.051	**-0.036 ± 0.042**	-0.051	-0.020	-4.694	30	**0.000 ***	↑
Thrust	0.179 ± 0.104	-0.021 ± 0.094	-0.057	0.015	-1.207	28	0.238	↑
Wide	0.175 ± 0.041	**-0.015 ± 0.033**	-0.028	-0.003	-2.563	30	**0.016 ***	↑
	Frontal Plane Knee Moment Impulse (Nm/kg.s)							
	Mean ± SD	**Absolute difference from normal Mean ± SD**	95% CI of the Difference Lower	95% CI of the Difference Upper	*t*	df	Sig. (2-tailed) *P* – value	Direction
Normal	0.236 ± 0.060	-	-	-	-	-	-	-
In	0.197 ± 0.051	**0.039 ± 0.050**	0.021	0.058	4.383	30	**0.000 ***	↓
Out	0.186 ± 0.048	**0.050 ± 0.037**	0.036	0.063	7.557	30	**0.000 ***	↓
Short	0.175 ± 0.047	**0.061 ± 0.044**	0.045	0.077	7.777	30	**0.000 ***	↓
Sway	0.181 ± 0.063	**0.055 ± 0.037**	0.041	0.068	8.183	30	**0.000 ***	↓
Thrust	0.172 ± 0.067	**0.065 ± 0.067**	0.040	0.090	5.243	28	**0.000 ***	↓
Wide	0.147 ± 0.050	**0.089 ± 0.059**	0.067	0.110	8.388	30	**0.000 ***	↓
	Transverse Plane Knee Moment Impulse (Nm/kg.s)							
	Mean ± SD	**Absolute difference from normal Mean ± SD**	95% CI of the Difference Lower	95% CI of the Difference Upper	*t*	df	Sig. (2-tailed) *P* – value	Direction
Normal	0.050 ± 0.011							-
In	0.040 ± 0.011	**0.010 ± 0.012**	0.005	0.014	4.530	30	**0.000 ***	↓
Out	0.038 ± 0.010	**0.012 ± 0.007**	0.009	0.014	9.835	30	**0.000 ***	↓
Short	0.036 ± 0.009	**0.014 ± 0.007**	0.011	0.016	10.206	30	**0.000 ***	↓
Sway	0.046 ± 0.013	**0.004 ± 0.010**	0.000	0.007	2.057	30	**0.048 ***	↓
Thrust	0.041 ± 0.014	**0.009 ± 0.013**	0.004	0.014	3.778	28	**0.001 ***	↓
Wide	0.035 ± 0.012	**0.014 ± 0.011**	0.010	0.018	7.288	30	**0.000 ***	↓

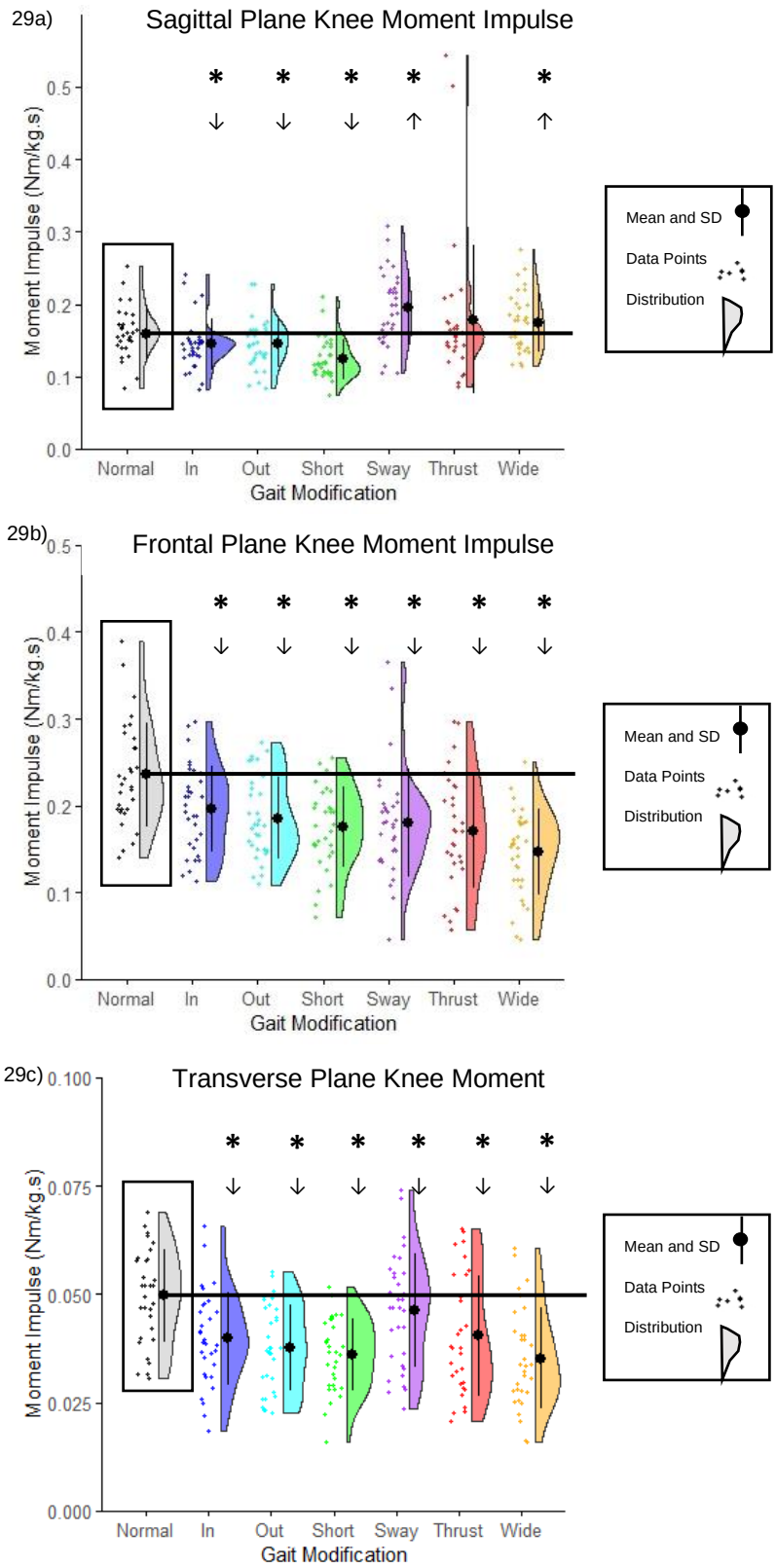

Figure 29: The knee moment impulse in all three planes of motion during six gait modifications (medial knee thrust: red, toe in: blue, toes out: cyan, short strides: green, trunk sway: purple, wide base: yellow) (*) indicates significant differences in the mean compared to normal. 29a) the sagittal plane knee moment impulse, 29b) the frontal plane knee moment impulse and 29c) the transverse plane knee moment impulse.

6.3.3. Individual responses

Despite a significant overall reduction in the mean 3D knee moment impulse for in toeing, out toeing, short strides and wide base gait trials, it is clear from Figure 28b that there is a large variation in the individual responses for the 3D knee moment impulse for each gait modification. This variation suggests that participants respond differently to each modification and may have a better response to one modification over another. Figure 30 presents the individual responses to each of the modifications. The left and right side were averaged to provide each participant a mean response to the gait modifications. Some participants were able to achieve a reduced 3D knee moment impulse (positive response) during some gait modifications but increased the 3D knee moment impulse (negative response) during other gait modifications. Based on the 10% target reduction, a positive response was defined by a reduction in the 3D knee moment impulse by more than 10% (≤ -10%), a minimal response was defined at a reduction between 0 and 10% (0 to -10%) and a negative response was an increase in the 3D knee moment impulse (> 0%).

The short gait modification saw no increases in the 3D knee moment impulse above 0% (all positive responses) and 13 out of the 16 participants saw a decrease of 10% or more. Conversely, the trunk sway saw 3 participants have an increase in the 3D knee moment above 10% and the medial knee thrust saw 2 participants, indicating negative responses. However, there were large variations in the individual responses from each participant. Figure 30 reports that some participants saw a positive response to some modifications, but not from others and the magnitude of response differed for each participant.

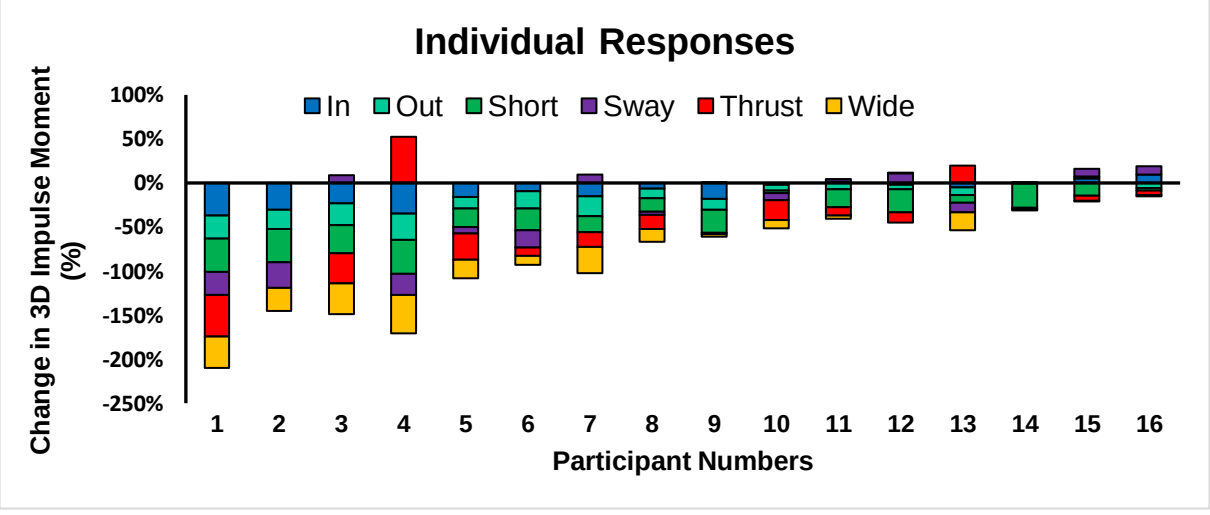

Figure 30: The individual percentage change in the 3D knee moment impulse for all gait modification trials. The participant numbers are ranked in ascending order along the horizontal axis according to the average percent reduction. A negative percent indicates a positive response (a reduction in 3D moment impulse), a positive percent indicates a negative response (an increase in 3D moment impulse).

6.3.4. Moment impulse in adjacent joints

6.3.4.1. Ankle moment impulse

There were significant increases in the sagittal plane ankle moment impulse during the trunk sway gait trial compared to normal. Figure 31 shows the sagittal plane ankle moment impulse for all gait trials. The in toeing and the medial knee thrust also resulted in some increased moment impulse compared to normal, however these were not significant. There were significant decreases in the sagittal plane ankle moment impulse during out toeing, short stride and wide base gait trials compared to normal (Table 14).

Table 14: The sagittal plane ankle moment impulse for all six gait modifications compared to the normal gait trial, (*) and bold represent a significant difference compared to normal along with the direction of change (↓) represents a decrease in sagittal plane ankle moment impulse and (↑) an increase in sagittal plane ankle moment impulse.

	Sagittal Plane Ankle Moment Impulse (Nm/kg.s)							
Gait Trial	**Mean ± SD**	**Absolute difference from normal Mean ± SD**	95% CI of the Difference Lower	95% CI of the Difference Upper	t	df	Sig. (2-tailed) *P* – value	Direction
Normal	0.541 ± 0.067	-	-	-	-	-	-	-
In	0.557 ± 0.081	-0.016 ± 0.057	-0.037	0.005	-1.542	30	0.134	↑
Out	0.482 ± 0.066	**0.059 ± 0.043**	0.043	0.075	7.569	30	**0.000** *	↓
Short	0.454 ± 0.065	**0.087 ± 0.065**	0.064	0.111	7.507	30	**0.000** *	↓
Sway	0.590 ± 0.081	**-0.048 ± 0.080**	-0.077	-0.019	-3.362	30	**0.002** *	↑
Thrust	0.556 ± 0.086	-0.016 ± 0.069	-0.042	0.010	-1.244	28	0.224	↑
Wide	0.559 ± 0.069	**-0.036 ± 0.061**	0.014	0.058	3.310	31	**0.002** *	↑

The mean ± SD and the distribution of the sagittal plane ankle moment impulse for each of the gait trials is visualised in Figure 31, the short strides SD does not go above the mean impulse of the normal gait trial.

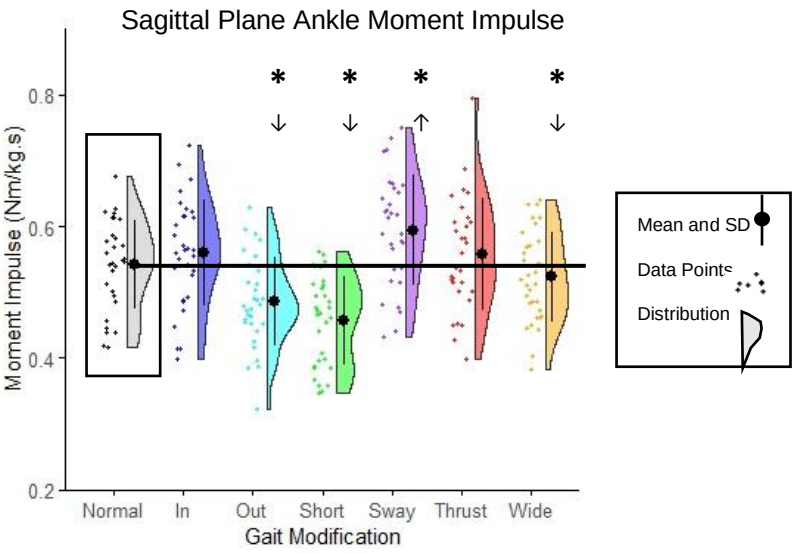

Figure 31: The sagittal plane ankle moment impulse during six gait modifications (medial knee thrust red, toe in: blue, toe out: cyan, short strides: green, trunk sway: purple, wide base: yellow) (*) indicates significant differences in the mean compared to normal.

6.3.4.2. Hip moment impulse

Figure 32 shows the hip moment impulse in all three planes for all gait trials. There were no increases in the sagittal and frontal plane hip moment impulses during any of the gait trials. There were significant decreases in the sagittal plane hip moment impulse during the in toeing, short strides, medial knee thrust and wide base gait trials compared to normal. There were significant decreases in the frontal plane hip moment impulse during all gait trials compared to normal. There were significant increases in the transverse plane hip moment impulse during the in toeing and medial knee thrust compared to normal. There were significant decreases in the transverse plane hip moment impulse during the out toeing and the short strides gait trials compared to normal (Table 15).

Table 15: The hip moment impulse in all three planes for all six gait modifications compared to the normal gait trial, (*) and bold represent a significant difference compared to normal along with the direction of change (↓) represents a decrease in the hip moment impulse and (↑) an increase in the hip moment impulse.

Gait Trial	Sagittal Plane Hip Moment Impulse (Nm/kg.s)							
	Mean ± SD	**Absolute difference from normal Mean ± SD**	95% CI of the Difference Lower	95% CI of the Difference Upper	*t*	df	Sig. (2-tailed) *P* – value	Direction
Normal	0.280 ± 0.058	-	-	-	-	-	-	-
In	0.233 ± 0.432	**0.047 ± 0.063**	0.024	0.070	4.157	30	**0.000 ***	↓
Out	0.263 ± 0.035	0.017 ± 0.053	-0.002	0.037	1.819	30	0.079	↓
Short	0.257 ± 0.042	**0.024 ± 0.050**	0.005	0.042	2.624	30	**0.014 ***	↓
Sway	0.269 ± 0.045	0.012 ± 0.050	-0.007	0.030	1.279	30	0.211	↓
Thrust	0.252 ± 0.058	**0.028 ± 0.059**	0.005	0.050	2.527	28	**0.017 ***	↓
Wide	0.233 ± 0.041	**0.047 ± 0.057**	0.026	0.068	4.628	30	**0.000 ***	↓
	Frontal Plane Knee Moment Impulse (Nm/kg.s)							
	Mean ± SD	**Absolute difference from normal Mean ± SD**	95% CI of the Difference Lower	95% CI of the Difference Upper	*t*	df	Sig. (2-tailed) *P* – value	Direction
Normal	0.323 ± 0.073	-	-	-	-	-	-	-
In	0.269 ± 0.084	**0.055 ± 0.054**	0.035	0.075	5.604	30	**0.000 ***	↓
Out	0.269 ± 0.080	**0.055 ± 0.044**	0.038	0.071	6.925	30	**0.000 ***	↓
Short	0.261 ± 0.073	**0.062 ± 0.040**	0.047	0.077	8.641	30	**0.000 ***	↓
Sway	0.253 ± 0.091	**0.070 ± 0.052**	0.051	0.089	7.576	30	**0.000 ***	↓
Thrust	0.272 ± 0.083	**0.054 ± 0.058**	0.032	0.076	5.018	28	**0.000 ***	↓
Wide	0.220 ± 0.093	**0.104 ± 0.076**	0.076	0.132	7.616	30	**0.000 ***	↓
	Transverse Plane Knee Moment Impulse (Nm/kg.s)							
	Mean ± SD	**Absolute difference from normal Mean ± SD**	95% CI of the Difference Lower	95% CI of the Difference Upper	*t*	df	Sig. (2-tailed) *P* – value	Direction
Normal	0.074 ± 0.029	-	-	-	-	-	-	-
In	0.079 ± 0.027	**-0.005 ± 0.013**	-0.010	-0.008	-2.373	30	**0.024 ***	↑
Out	0.068 ± 0.026	**0.006 ± 0.012**	0.002	0.011	2.852	30	**0.008 ***	↓
Short	0.063 ± 0.029	**0.011 ± 0.013**	0.006	0.015	4.596	30	**0.000 ***	↓
Sway	0.072 ± 0.030	0.002 ± 0.015	-0.004	0.007	0.657	30	0.516	↓
Thrust	0.085 ± 0.036	**-0.010 ± 0.014**	-0.016	-0.005	-3.789	28	**0.001 ***	↑
Wide	0.069 ± 0.023	0.005 ± 0.018	-0.002	0.011	1.536	30	0.135	↓

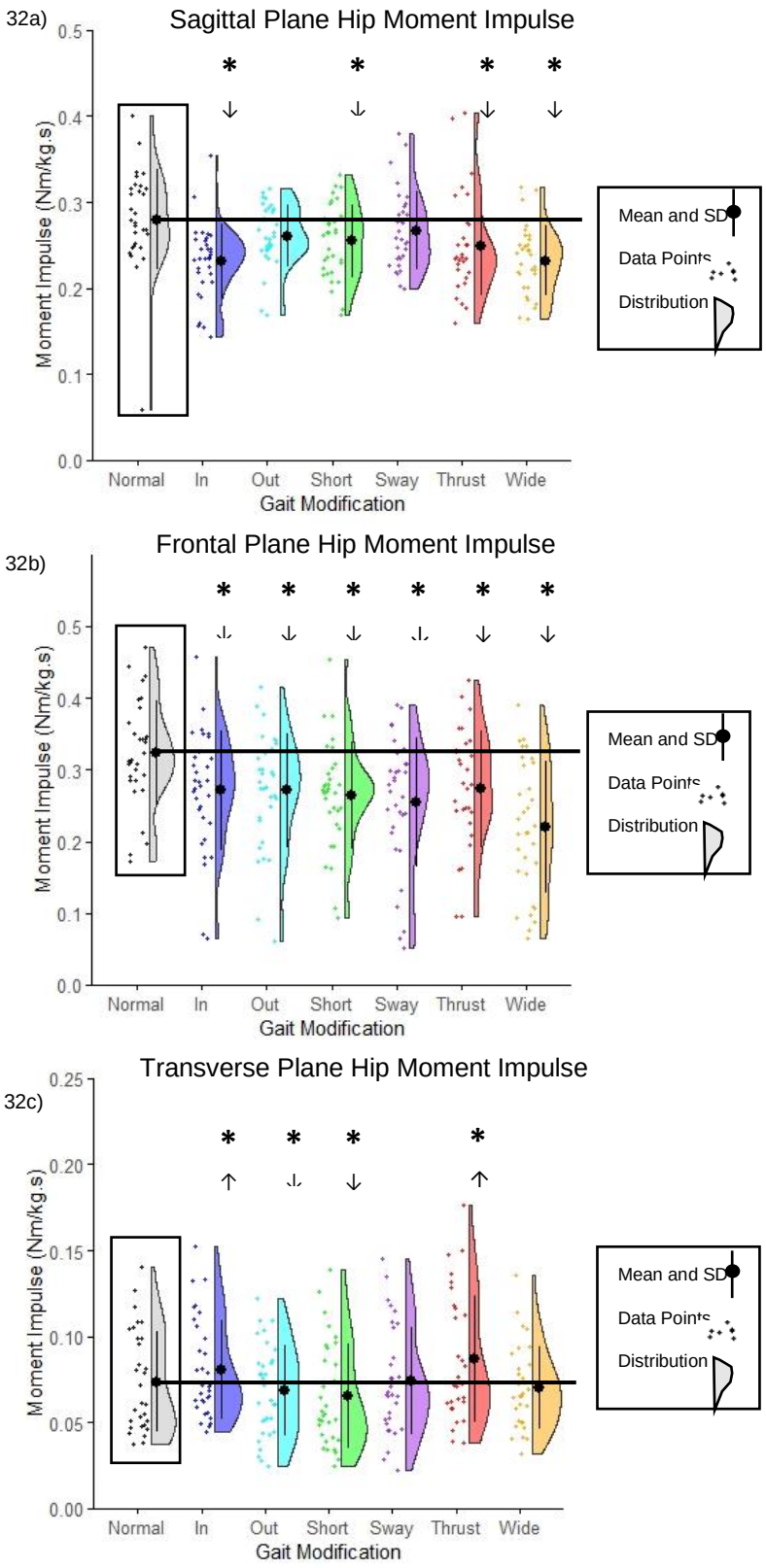

Figure 32: The hip moment impulse in all three planes of motion during six gait modifications (medial knee thrust red, toe in: blue, toes out: cyan, short strides: green, trunk sway: purple, wide base: yellow). (*) indicates significant differences in the mean compared to normal. 32a) the sagittal plane hip moment impulse, 32b) the frontal plane hip moment impulse and 32c) the transverse plane hip moment impulse.

6.3.5. Temporal-spatial and kinematic descriptions of each gait modification

The kinematic mean and SDs for each of the six gait modifications were compared to normal. The curves are presented in Figures 33-38. The ankle, knee, hip, pelvis and trunk angles in the three planes of motion were descriptively analysed. The focus in the chapter was the effect of the gait modification on moments and the kinematic descriptions are secondary, therefore, due to the large amounts of comparisons the kinematics were analysed descriptively. Any differences that were observed between the two means were marked with arrows to indicate the direction of the difference, definitions are outlined in Table 16, this method is based on the gait interpretation symbols advocated by Richard Baker (Baker and Hart, 2013). Each marked difference was given a number which is referred to in the description.

Table 16: Definitions of the arrows used to describe the differences compared to normal in the kinematic curves.

Arrow	Description
	An increase compared to normal. One arrow describes an increase over a short period of the gait cycle. Two describes an increase throughout the stance phase of the gait cycle, and three describes an increased offset throughout the gait cycle.
	A decrease compared to normal. One arrow describes a decrease over a short period of the gait cycle. Two describes a decrease throughout the stance phase of the gait cycle, and three describes a decreased offset throughout the gait cycle.
	An increased range of motion compared to normal.
	A delayed timing in the movement compared to normal.

6.3.5.1. Gait modification in toeing

Table 17 shows the mean temporal and spatial parameters of the normal and in toeing gait trials. The step width was significantly increased during the in toeing gait trial (0.27 ± 0.09 m) compared to normal (0.15 ± 0.05 m), (t_{15} = -5.941, p < 0.001). The stride length was significantly decreased during the in toeing gait trial (1.27 ± 0.07 m) compared to normal (1.34 ± 0.06 m), (t_{15} = 4.635, p = 0.002). The cadence was significantly increased during the in toeing gait trial (114 ± 7 steps/min) compared to normal (108 ± 5 steps/min), (t_{31} = -6.403, p < 0.001). Table 18 describes the differences between the normal trial and the in toeing trial which are highlighted in the kinematic profiles shown in Figure 33.

Table 17: Temporal and spatial parameter means and SD's for the normal and in toeing gait trials. Bold and * indicates where there is a significant difference between the normal and in toeing means $p < 0.05$.

	Normal (Mean ± SD)	In (Mean ± SD)	Absolute difference (Normal – In)	Direction ↑ = increase ↓ = decrease	*T*-test *P* value
Step Width (m)	0.15 ± 0.05	0.27 ± 0.09	-0.12	↑	**<0.001 ***
Stride Length (m)	1.34 ± 0.06	1.27 ± 0.07	0.07	↓	**<0.001 ***
Cadence (steps per minute)	108 ± 5	114 ± 7	-6	↑	**<0.001 ***

Table 18: Description of each kinematic difference observed during the in toeing gait trial.

Reference	Description
(1)	An increased dorsiflexion during loading response
(2)	In toeing throughout the gait cycle by ~15 ° (from normal out toeing - 5° to in toeing + 10 °)
(3)	Increased knee flexion during the stance phase
(4)	Internal rotation of the knee throughout the gait cycle by ~ 5 °
(5)	Increased hip flexion during the stance phase
(6)	Internal rotation of the hip throughout the gait cycle by ~ 5 °
(7)	Increased anterior pelvic tilt throughout the gait cycle by ~ 4 °

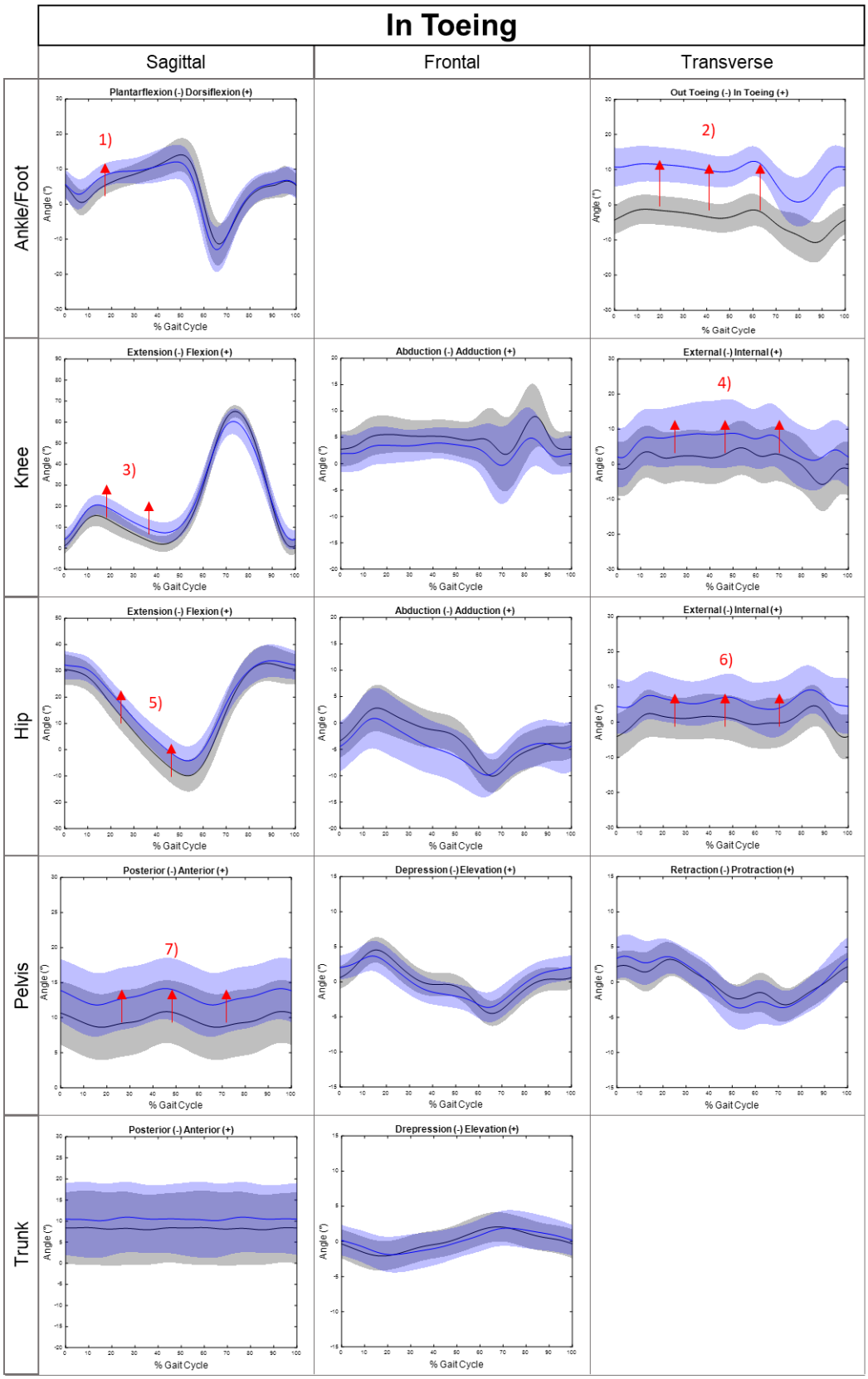

Figure 33: Kinematic gait profiles displaying the mean (line) and SD (shaded) for the in toeing gait trial (blue) and the normal gait trial (black).

6.3.5.2. Gait modification out toeing

Table 19 shows the mean temporal and spatial parameters of the normal and out toeing gait trials. There was no significant difference in step width during the out toeing gait trial. The stride length was significantly decreased during the out toeing gait trial (1.30 ± 0.06 m) compared to normal (1.34 ± 0.06 m), (t_{15} = 3.783, p < 0.001). The cadence was significantly increased during the out toeing gait trial (111 ± 5 steps/min) compared to normal (108 ± 5 steps/min), (t_{31} = -5.649, p < 0.001). Table 20 describes the differences between the normal trial and the out toeing trial which are highlighted in the kinematic profiles shown in Figure 34.

Table 19: Temporal and spatial parameter means and SD's for the normal and out toeing gait trials. Bold and * indicates where there is a significant difference between the normal and out toeing means $p < 0.05$.

	Normal (Mean ± SD)	Out (Mean ± SD)	Absolute difference (Normal – Out)	Direction ↑ = increase ↓ = decrease	*T*-test *P* value
Step Width (m)	0.15 ± 0.05	0.16 ± 0.06	-0.01	↑	0.668
Stride Length (m)	1.34 ± 0.06	1.30 ± 0.06	0.04	↓	**0.002 ***
Cadence (steps per minute)	108 ± 5	111 ± 5	-3	↑	**<0.001 ***

Table 20: Description of each kinematic difference observed during the out toeing gait trial.

Reference	Description
(1)	A decreased plantarflexion during push off
(2)	Increased out toeing throughout the gait cycle by ~12 °
(3)	External rotation of the hip by ~ 5°

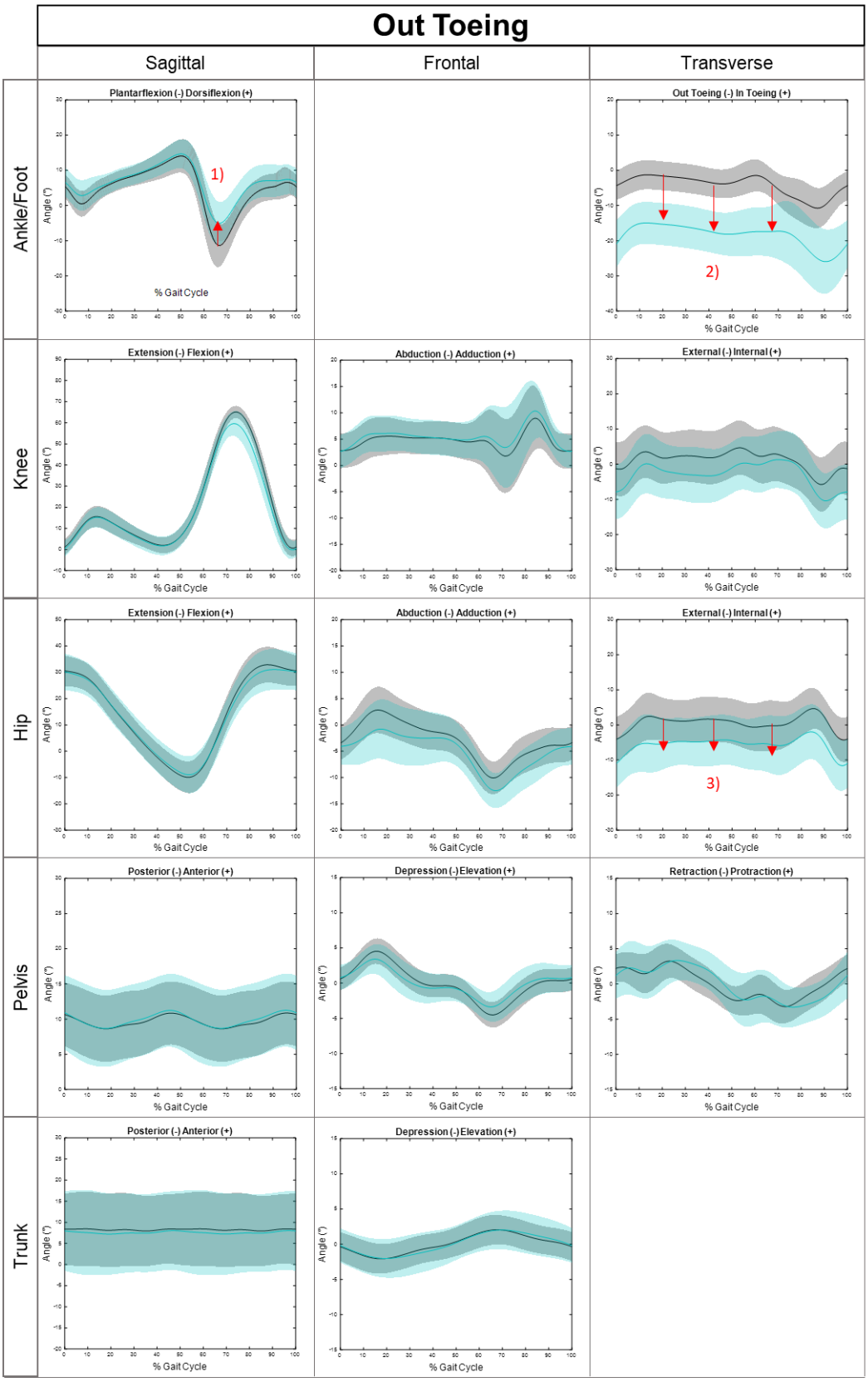

Figure 34: Kinematic gait profiles displaying the mean (line) and SD (shaded) for the out toeing gait trial (cyan) and the normal gait trial (black).

6.3.5.3. Gait Modification short strides

Table 21 shows the mean temporal and spatial parameters of the normal and short strides gait trials. There was no significant difference in step width during the short strides gait trial. The stride length was significantly decreased during the short strides gait trial (1.16 ± 0.07 m) compared to normal (1.34 ± 0.06 m), (t_{15} = 9.997, p < 0.001). The cadence was significantly increased during the short strides gait trial (125 ± 8 steps/min) compared to normal (108 ± 5 steps/min), (t_{31} = -13.826, p < 0.001). Table 22 describes the differences between the normal trial and the short strides trial which are highlighted in the kinematic profiles shown in Figure 35.

Table 21: Temporal and spatial parameter means and SD's for the normal and short strides gait trials. Bold and * indicates where there is a significant difference between the normal and short stride means $p < 0.05$.

	Normal (Mean ± SD)	Short (Mean ± SD)	Absolute difference (Normal – Short)	Direction ↑ = increase ↓ = decrease	*T*-test *P* value
Step Width (m)	0.15 ± 0.05	0.14 ± 0.03	0.01	↓	0.350
Stride Length (m)	1.34 ± 0.06	1.16 ± 0.07	0.18	↓	**<0.001 ***
Cadence (steps per minute)	108 ± 5	125 ± 8	-17	↑	**<0.001 ***

Table 22: Description of each kinematic difference observed during the short strides gait trial.

Reference	Description
(1)	A decreased plantarflexion during push off
(2)	A reduced knee extension during mid stance
(3)	A reduced hip extension during mid stance

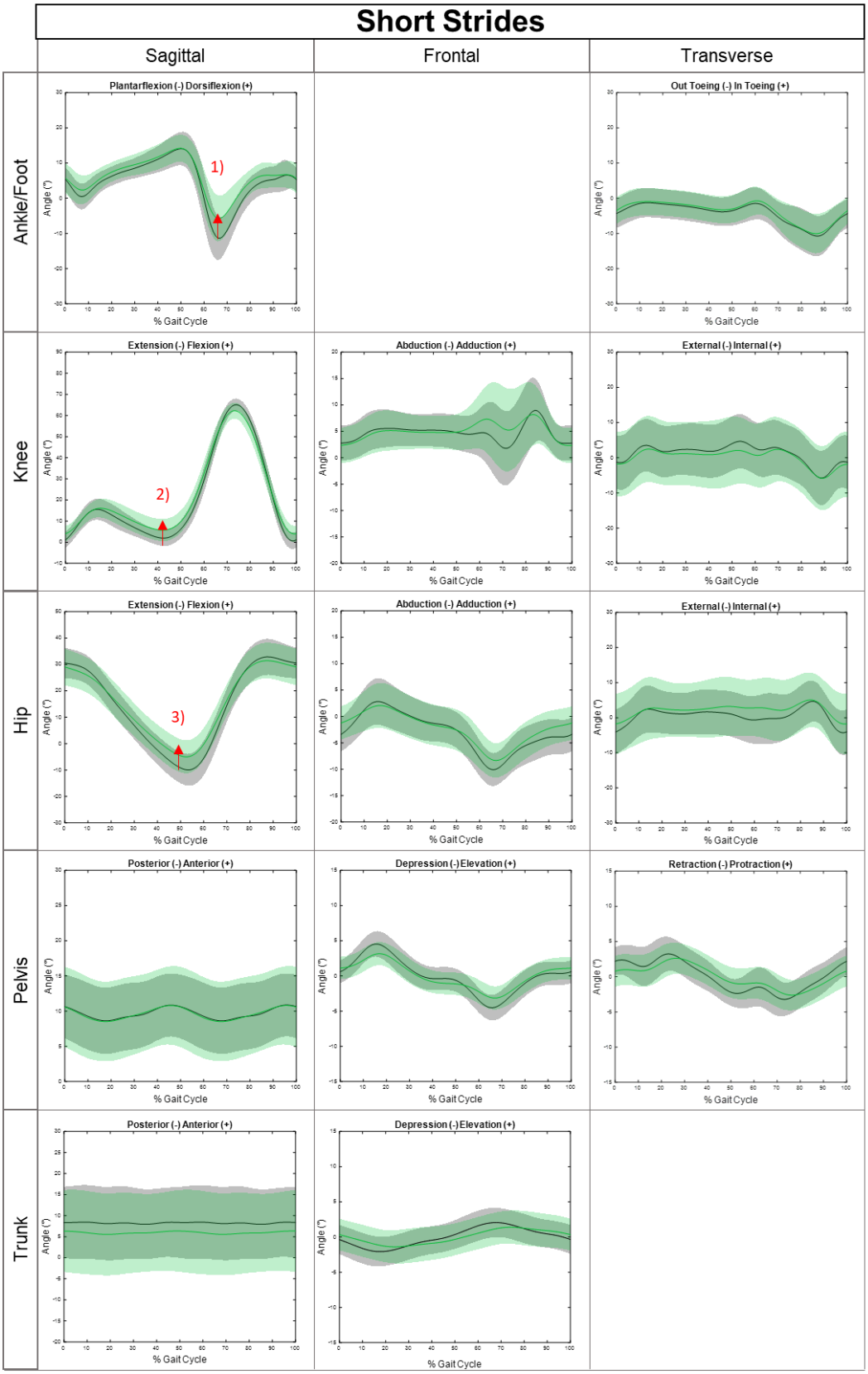

Figure 35: Kinematic gait profiles displaying the mean (line) and SD (shaded) for the short strides gait trial (green) and the normal gait trial (black).

6.3.5.4. Gait modification lateral trunk sway

Table 23 shows the mean temporal and spatial parameters of the normal and trunk sway gait trials. The step width was significantly increased during the trunk sway gait trial (0.20 ± 0.07 m) compared to normal (0.15 ± 0.05 m), (t_{15} = -2.744, p = 0.015). The stride length was significantly decreased during the trunk sway gait trial (1.16 ± 0.07 m) compared to normal (1.34 ± 0.06 m), (t_{15} = -2.746, p = 0.015). The cadence was significantly decreased during the trunk sway gait trial (103 ± 8 steps/min) compared to normal (108 ± 5 steps/min), (t_{31} = 3.549, p = 0.001). Table 24 describes the differences between the normal trial and the lateral trunk sway trial which are highlighted in the kinematic profiles shown in Figure 36.

Table 23: Temporal and spatial parameter means and SD's for the normal and trunk sway gait trials. Bold and * indicates where there is a significant difference between the normal and trunk sway means $p < 0.05$.

	Normal (Mean ± SD)	Sway (Mean ± SD)	Absolute difference (Normal – Sway)	Direction ↑ = increase ↓ = decrease	*T*-test *P* value
Step Width (m)	0.15 ± 0.05	0.20 ± 0.07	-0.05	↑	**0.015 ***
Stride Length (m)	1.34 ± 0.06	1.41 ± 0.11	-0.08	↑	**0.015 ***
Cadence (steps per minute)	108 ± 5	103 ± 8	5	↓	**0.001 ***

Table 24: Description of each kinematic difference observed during the trunk sway gait trial.

Reference	Description
(1)	An increased dorsiflexion during loading response
(2)	An increased knee flexion during loading response
(3)	An increased hip flexion during loading response
(4)	A reduced hip abduction during the stance phase
(5)	An increased anterior pelvic title by ~ 3 °
(6)	A reduced pelvic obliquity range of motion
(7)	An increased lateral trunk range of motion (~ 10 ° peak lateral trunk angle)

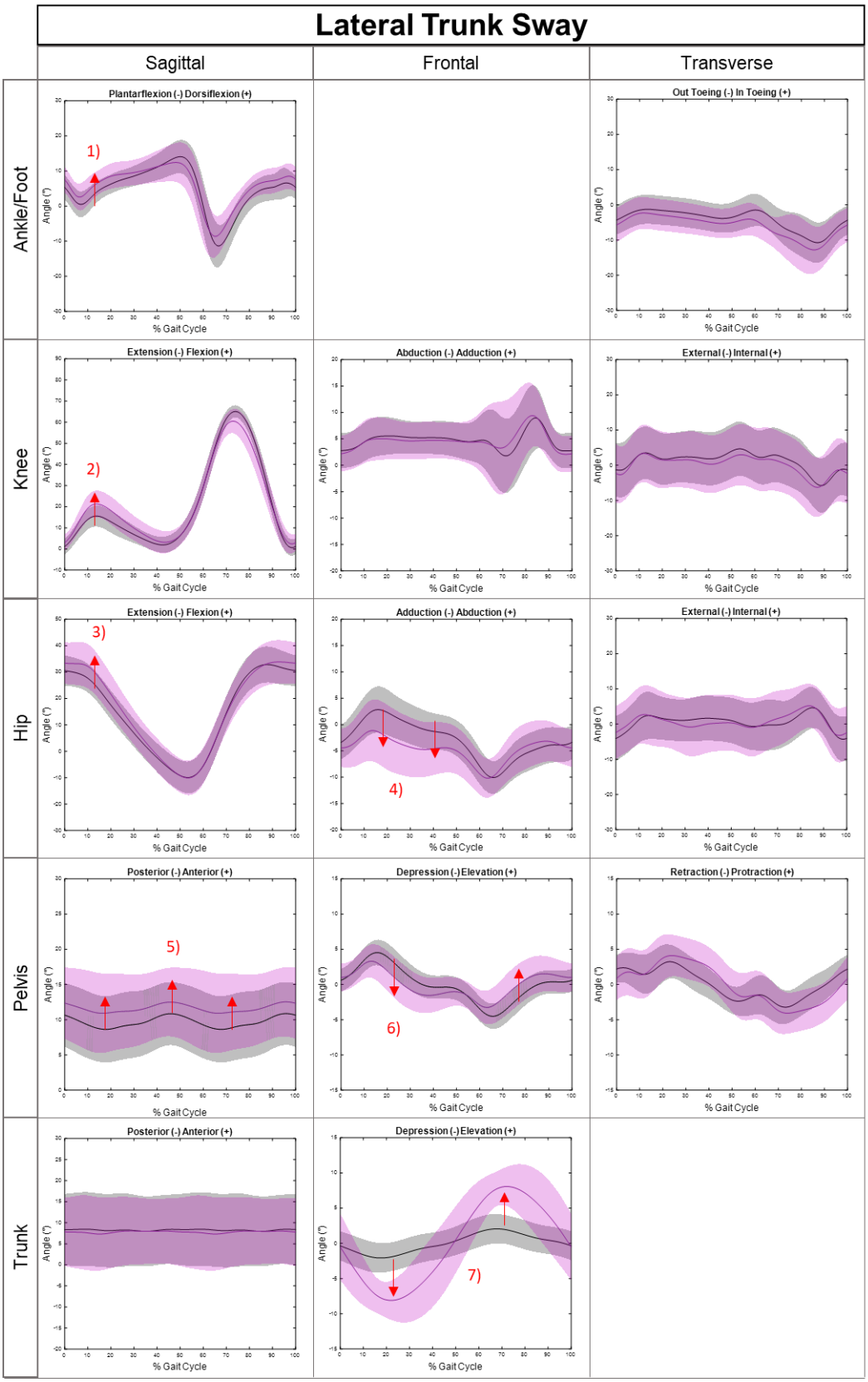

Figure 36: Kinematic gait profiles displaying the mean (line) and SD (shaded) for the trunk sway gait trial (purple) and the normal gait trial (black).

6.3.5.5. Gait modification medial knee thrust

Table 25 shows the mean temporal and spatial parameters of the normal and medial knee thrust gait trials. The step width was significantly increased during the medial knee thrust gait trial (0.26 ± 0.08 m) compared to normal (0.15 ± 0.05 m), (t_{14} = -5.999, p < 0.001). The stride length was significantly decreased during the medial knee thrust gait trial (1.26 ± 0.09 m) compared to normal (1.34 ± 0.06 m), (t_{15} = 3.252, p = 0.005). The cadence was significantly increased during the medial knee thrust gait trial (115 ± 8 steps/min) compared to normal (108 ± 5 steps/min), (t_{29} = -4.480, p < 0.001). Table 26 describes the differences between the normal trial and the medial knee trust trial which are highlighted in the kinematic profiles shown in Figure 37.

Table 25: Temporal and spatial parameter means and SD's for the normal and medial knee thrust gait trials. Bold and * indicates where there is a significant difference between the normal and the medial knee thrust means $p < 0.05$.

	Normal (Mean ± SD)	Thrust (Mean ± SD)	Absolute difference (Normal – Thrust)	Direction ↑ = increase ↓ = decrease	*T*-test *P* value
Step Width (m)	0.15 ± 0.05	0.26 ± 0.08	-0.11	↑	**<0.001 ***
Stride Length (m)	1.34 ± 0.06	1.26 ± 0.09	0.08	↓	**0.005 ***
Cadence (steps per minute)	108 ± 5	115 ± 8	-7	↑	**<0.001 ***

Table 26: Description of each kinematic difference observed during the medial knee thrust gait trial.

Reference	Description
(1)	An increased dorsiflexion during the stance phase
(2)	In toeing throughout the gait cycle by ~13 ° (from normal out toeing - 5° to in toeing + 8 °)
(3)	An increased knee flexion during the stance phase
(4)	Internal rotation of the knee throughout the gait cycle by ~ 5 °
(5)	An increased hip flexion during the stance phase
(6)	Internal rotation of the hip throughout the gait cycle by ~ 10 °
(7)	An increased anterior pelvic tilt throughout the gait cycle by ~ 5 °

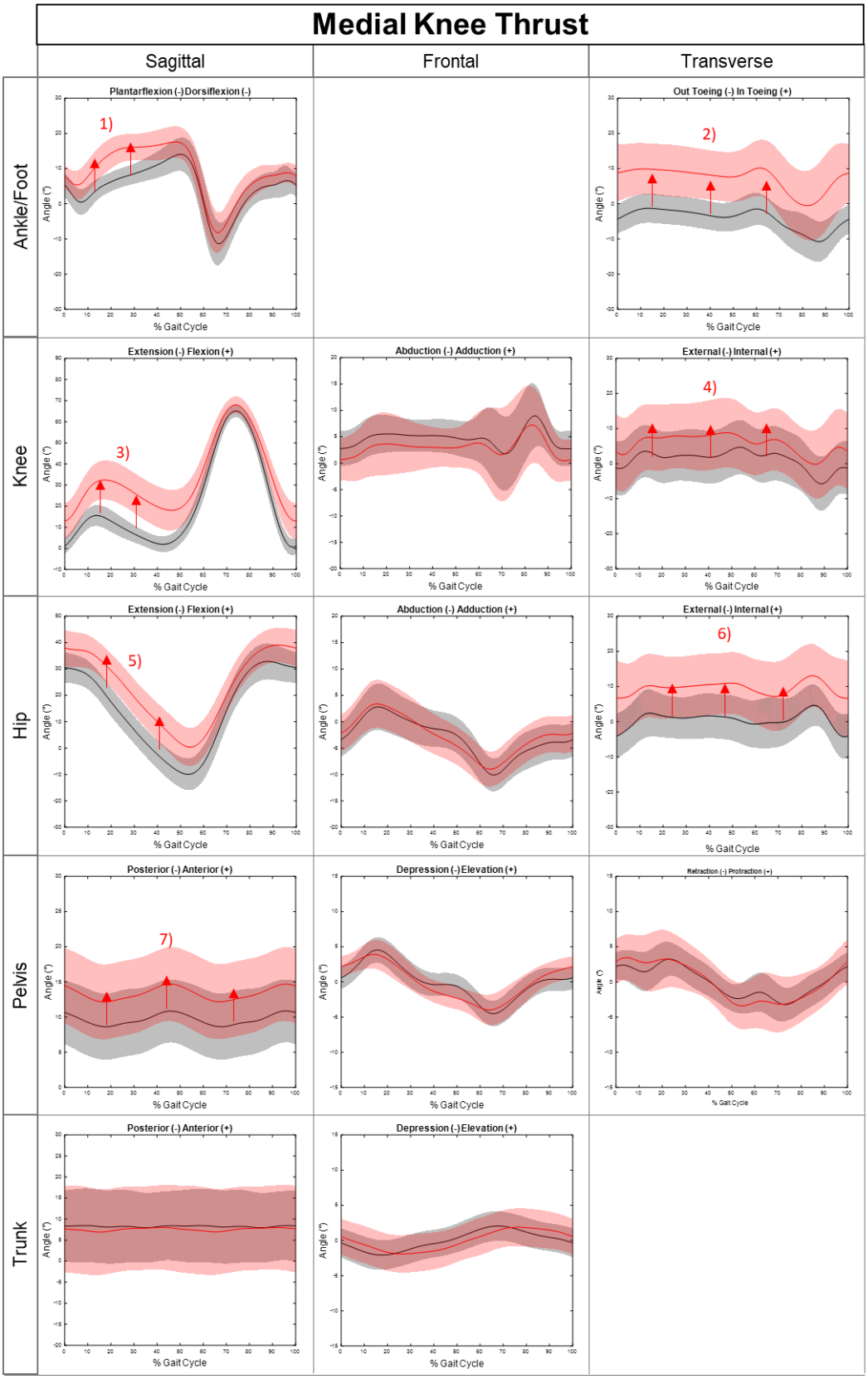

Figure 37: Kinematic gait profiles displaying the mean (line) and SD (shaded) for the medial knee thrust gait trial (red) and the normal gait trial (black).

6.3.5.6. Gait modification wide base

Table 27 shows the mean temporal and spatial parameters of the normal and wide base gait trials. The step width was significantly increased during the wide base gait trial (034 ± 0.11 m) compared to normal (0.15 ± 0.05 m), (t_{15} = -7.578, p < 0.001). The stride length was significantly decreased during the wide base gait trial (1.28 ± 0.10 m) compared to normal (1.34 ± 0.06 m), (t_{15} = 2.303, p = 0.036). The cadence was significantly increased during the wide base gait trial (113 ± 9 steps/min) compared to normal (108 ± 5 steps/min), (t_{31} = -3.567, p = 0.001). Table 28 describes the differences between the normal trial and the wide base trial which are highlighted in the kinematic profiles shown in Figure 38.

Table 27: Temporal and spatial parameter means and SD's for the normal and wide base gait trials. Bold and * indicates where there is a significant difference between the normal and the wide base means $p < 0.05$.

	Normal (Mean ± SD)	Wide (Mean ± SD)	Absolute difference (Normal – Wide)	Direction ↑ = increase ↓ = decrease	*T*-test *P* value
Step Width (m)	0.15 ± 0.05	0.34 ± 0.11	-0.19	↑	**<0.001 ***
Stride Length (m)	1.34 ± 0.06	1.28 ± 0.10	0.06	↓	**0.036 ***
Cadence (steps per minute)	108 ± 5	113 ± 9	-5	↑	**0.001 ***

Table 28: Description of each kinematic difference observed during the wide base gait trial.

Reference	Description
(1)	Increased out toeing throughout the gait cycle ~ 5 °
(2)	An increased knee flexion during loading response
(3)	A reduced hip abduction throughout the gait cycle by ~ 7 °
(4)	A reduced pelvic obliquity range of motion
(5)	A delay in trunk sway motion

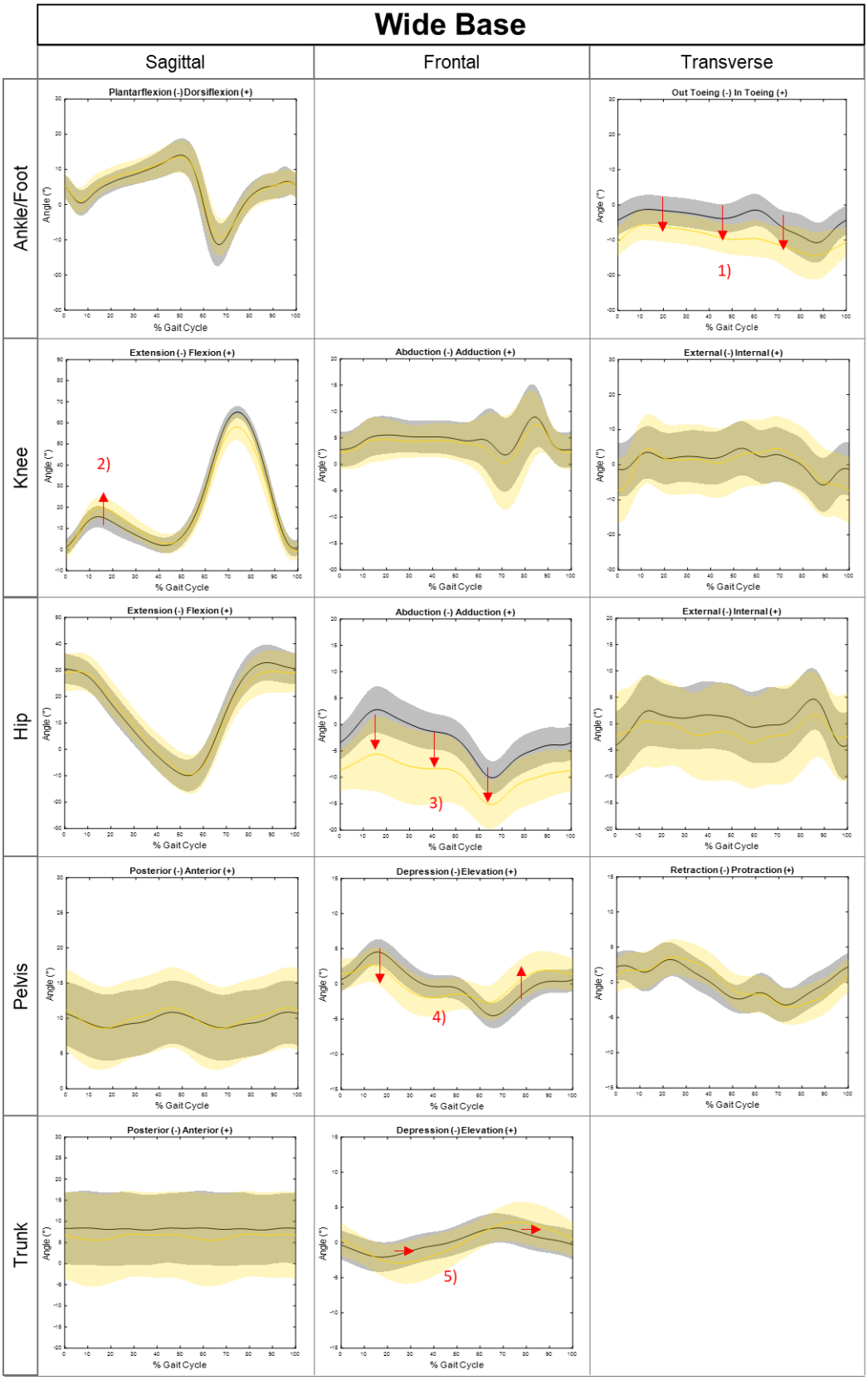

Figure 38: Kinematic gait profiles displaying the mean (line) and SD (shaded) for the wide base gait trial (yellow) and the normal gait trial (black).

6.4. Discussion

The aim of this chapter was to assess six previously studied gait modifications to decide which modifications are appropriate to take forward and use as guidance for patients during gait modification interventions. To help assess which modifications are appropriate, their ability to reduce the total 3D moment impulse, the variability of individual responses to the gait modification, their effects on adjacent joint moments, and how they are achieved kinematically were assessed.

6.4.1. 3D knee moment impulse

Based on these results four out of the six gait modifications were effective at significantly reducing the 3D knee moment impulse, these were in toeing, out toeing, short strides and wide base. Firstly, in toeing, out toeing and short strides were able to reduce the knee moment in all three planes causing the overall reduction in the 3D moment. Interestingly, the wide base gait modification showed a significant increase in the sagittal plane moment but the net effect of the large reductions in the frontal and transverse planes result in a reduction in the 3D knee moment. The change in foot progression angle during both out toeing and in toeing change the CoP position during stance phase, ultimately changing the perpendicular knee moment arm length. There have been previous inconsistencies within the research on the effect of the 1st and 2nd KAM peaks (Guo, Axe and Manal, 2007; Lynn and Costigan, 2008), however the moment impulse measured in this study sees an overall reduction in the 3D knee moment impulse. The step width gait modification reduction in the 3D knee moment impulse agrees with previous findings that show a reduction in KAM peaks during both early and late stance (Fregly, Reinbolt and Chmielewski, 2008), if decreases in the magnitude of both peaks were seen, this is likely to reduce the impulse, however impulse was not measured in the previous study, nor the effects on the moment in the other planes of motion. The short strides see the largest mean % difference in the 3D knee moment impulse (-23%). The impulse is measured as the moment over time during the stance phase. The short stride leads to less time spent in the stance phase therefore reducing the time. However, to maintain walking speed, cadence must increase, consequently if the same distance were to be covered, although the moment reduced during each step, it may be increased over time.

Although the medial knee thrust and trunk sway did reduce the 3D knee moment impulse slightly, this was not significant. To understand why these two modifications are not effective at reducing the 3D moment impulse it is important to evaluate how the moment is distributed. All six modifications are designed to reduce the frontal plane knee moment by mechanically reducing the moment arm in the frontal plane. Ultimately all six successfully reduced the frontal plane knee moment impulse significantly. However, the trunk sway

significantly increases the sagittal plane moment impulse and shows no difference in the transverse plane compared to normal. For the medial knee thrust, despite significant reductions in the frontal and transverse plane and a slight but non-significant increase in the sagittal plane compared to normal, the vectorially summed effect lead to no significant differences in the 3D moment impulse. Based on these findings the medial knee thrust and trunk sway should be used with caution, as beneficial reduction in the frontal plane moment is countered by increases in the other planes of motion.

6.4.2. Individual responses

The results from the individual responses to each gait modification on the 3D moment impulse indicate how many participants were able to achieve a positive result (a reduction in 3D moment impulse). A 10% reduction in the 3D knee moment was the target during each of the gait modifications (as calculated in chapter 5.2.3), anything greater than this was considered a positive response. Short strides saw the most positive responses, with 13 out of the 16 participants able to achieve a reduction of 10% or more, additionally short strides also saw no negative responses (increase in 3D knee moment difference above 0%). Wide base followed with 10 participants able to achieve a positive response and only 1 negative response, and out toeing showed 9 positive and 2 negative responses. Trunk sway saw the lowest number with only 5 positive responses, and 8 negative responses. Firstly, these findings help to identify which modifications may be difficult to perform, this could be due to coordination of segments, instability or fatigue. Secondly, these results demonstrate the variance in responses to each of the modifications. When gait modifications are prescribed some participants respond better to different modifications, some demonstrate no or negative effects for some modifications but large reductions in others. These results agree with Lindsey et al. (2020), who also found large variations in individual responses during medial knee thrust, in toeing and lateral trunk lean. Similar to the Lindsey et al. (2020) study the participants within this study were all healthy young adults, who do not have any current movement constraints that would limit their ability to perform each modification. All participants had the same amount of time to practice each gait modification before data was collected, the large variation in responses could be due to preference and coordination, however, these variables were not measured therefore it is difficult to conclude why the responses differ so greatly. Furthermore, the variance in response is likely to increase with AKU patients due to the large variability in gait already reported in chapter four and large variations in pain and the addition of movement constraints.

6.4.3. Adjacent joint moment impulses

Due to the nature of Alkaptonuria disease, it is paramount to monitor any negative changes to adjacent joints during a gait modification intervention. A negative change would be an increase in any of the components of the moment in the ankle and hip. Out toeing and wide base saw no negative increases in the moment impulse for the ankle and hip and short strides saw significant reductions in all the ankle and hip joint moment impulse. However, in toeing and medial knee thrust saw increases in the transverse plane hip moment impulse and the trunk sway saw increases in the sagittal plane ankle moment impulse.

6.4.4. Temporal-spatial and kinematic descriptions of each gait modification

All gait modifications resulted in significant changes in temporal-spatial parameters. All gait modifications apart from trunk sway showed a reduction in stride length and an increase in cadence. The treadmill belt velocity was set at a constant 1.2 m/s, this was to control for this variable across all gait modifications. As walking velocity is a product of stride length and stride frequency, a reduction of stride length with a constant walking velocity causes an increase in stride frequency (cadence). For the trunk sway gait trial there was an opposite result; an increase in stride length and a decrease in cadence, this may be due to increasing the stance time, a strategy which allows more time for the trunk with its large inertia to move laterally over the stance limb.

Reducing stride length was a proposed gait modification by itself, however a reduced stride length was also seen in four other gait modifications. Increasing step width also was a proposed gait modification, and a significant increase in step width was also seen during in toeing, medial knee thrust and trunk sway. For in toeing and medial knee thrust the increase may be due to the way step width is measured (the distance between the two heel markers in the medio-lateral direction). To achieve in toeing and medial knee thrust the foot's line of progression relative to the lab is changed and the forefoot is rotated inwards and the rearfoot outwards, resulting in the heel markers moving laterally and increasing the sideways distance between the two markers. For trunk sway, the trunk is shifted laterally increasing the sideways amplitude of the centre of mass bringing it close to the edge of the base of support causing instability during each step. Increasing step width may be a compensation to counteract this by increasing the base of support and maintaining stability. This mechanism was also reported in the Anderson et al. (2018) study.

There were seven kinematic changes during the in toeing gait trial. There was in toeing, which demonstrates that the participants were able to perform the gait modification. To facilitate in toeing there was internal rotation of the hip and knee. There were also four indirect differences in the sagittal plane: an increase in dorsiflexion, increased knee and hip flexion throughout stance and an increased pelvic tilt.

For out toeing, there were three kinematic changes, firstly there was an increased out toeing which demonstrates that the participants were able to perform the gait modification. To facilitate out toeing there was an external rotation of the hip. There was also an indirect change in the sagittal plane, a reduced plantarflexion at push off. This could be due to the cross-plane interaction, whereby the foot segment is now out of plane relative to the shank, affecting sagittal plane ankle angle.

For the short strides, all three kinematic differences are in the sagittal plane, these are reduced plantarflexion at push off and reduced hip and knee extension during mid-stance. These all interlink and result in a reduced range of motion as shorter ranges are required to achieve a shorter stride length.

The trunk sway gait trials showed seven kinematic differences. Firstly, the increased range of motion of the trunk demonstrated that the participants were able to perform the gait modifications. There were also increased hip adduction and reduced pelvic obliquity range of motion, these two were also a direct result of wide base gait and could therefore be a result of increasing the base of support to maintain stability. There were also increases in dorsiflexion, knee and hip flexion during loading response, in addition to an increased anterior pelvic tilt.

The medial knee thrust showed seven large kinematic differences in all planes of motion. It is impossible without structural damage for the knee joint centre to purely shift medially during gait. Therefore, to dynamically achieve medial knee thrust it is a combination of movements. This combination includes an internal rotation of the hip and increased knee flexion during stance, both of which are confirmed by the gait kinematics. As a result of the internal rotation of the hip, there is also in toeing and internal rotation of the knee. As a result of the increased knee flexion, there is increased dorsiflexion, hip flexion and anterior pelvic tilt.

The wide base gait trials showed five kinematic changes across all three planes of motion. There is increased hip adduction which is a direct result of wide base gait alongside a reduced range of pelvic obliquity. There was also increased out toeing, and increased knee flexion at loading response and a shift of trunk sway timing.

It is clear when performing a gait modification there is both direct and indirect kinematic changes and that they are non-isolated movements. It may be important to limit the kinematic demand of the modification suggested to patients. Movements that cause changes in multiple joints and multiple planes may be difficult to coordinate. They may also increase the metabolic cost of movement however this was not measured in this study.

6.4.5. Summary of each gait modification

Overall, in toeing effectively reduced the 3D knee moment impulse reducing the mean by more than 10% (-12%), seven participants were able to achieve a positive response, however four out of the16 participants increased the knee moment impulse compared to normal, there were significant increases in the transverse plane hip moment and there were seven kinematic changes to achieve this modification. Out toeing effectively reduced the 3D knee moment by reducing the mean by more than 10% (-13%), with nine participants able to achieve a positive response and only two participants increased the knee moment impulse compared to normal, there were no increases in the moment impulse at the adjacent joints and only three kinematic changes were necessary to achieve this modification. Short strides also effectively reduced the 3D knee moment by reducing the mean by more than 10% (-23%), 13 participants were able to achieve a positive response and no participants increased the knee moment impulse compared to normal, there were no increases in the moment impulse at the adjacent joints and only three kinematic changes were used to achieve this modification. Trunk sway was unable to effectively reduce the 3D knee moment mean by more than 10% (-5%) and was also not significantly reduced compared to normal, only 5 out of the 16 participants were able to achieve a positive response and 8 participants saw an increase in the knee moment impulse, there were increases in the sagittal plane moment impulse and seven kinematic changes were needed to achieve this modification. The medial knee thrust was also unable to effectively reduce the 3D knee moment mean by more than 10% (-9%) and was not significantly reduced compared to normal, nine participants were able to achieve a positive response, and only two participants increased the knee moment impulse compared to normal, there were increases in the transverse plane hip moment impulse joints and seven kinematic changes were used to achieve this modification. Wide base gait effectively reduced the 3D knee moment by reducing the mean by more than 10% (-16%), 10 participant were able to able to achieve a positive response and only one participant was unable to achieve a positive response, there were no increases in the moment impulse at the adjacent joints and five kinematic changes were made to achieve this modification.

6.4.6. Limitations

Change in walking speed has been shown to affect the knee moment and has been previously identified as a gait modification (Simic et al., 2011), to control for this factor a fixed treadmill speed was used. However, a limitation of this study was the application of a fixed treadmill speed of 1.2 m/s for all participants during all conditions. This fixed speed was based on the mean overground walking speed of the healthy control group reported in chapter 4. However, it is likely there would be some variability in the healthy control's preferred walking speed which may have affected their ability to perform a gait modification.

In addition, the preferred walking speed during treadmill walking has been found to be significantly lower than overground walking (Malatesta, Canepa and Fernandez, 2017), inducing some safety related changes such as increased stance and double support duration. To overcome this limitation by applying an individualised preferred walking speed for each participant, the self-paced treadmill function could have been used to allow participants to walk at their preferred speed whilst undertaking each trial, however familiarisation of the self-paced function may take time which would prolong protocol times and increased variability within the spatio-temporal parameters have been reported (Choi et al., 2017).

6.5. Conclusion

In conclusion, based on a comprehensive approach taking into consideration the 3D moment impulse, the effects on adjacent joints and the kinematic demand, only three out of the six gait modifications were deemed appropriate to use as guidance for AKU patients for future gait modification interventions, these were out toeing, short strides and wide base gait. These three gait modifications will be used in the gait modification information sheet given to patients as guidance on how to reduce the 3D knee moments during an individualised gait modification intervention in the next chapter.

Although the results have confirmed effective gait modifications, the findings also highlight the large variation in response to prescribed gait modifications. When participants are prescribed certain modifications, they either demonstrate a positive response (a reduction in the 3D knee moment by more than 10%), a small non-effective response (a reduction in the 3D knee moment by less than 10%) or a negative response (an increase in the 3D knee moment). These responses were shown to differ not only between participant but also between each gait modification. This suggests that there should be individualisation or subject-specific evaluations, this is particularly important when considering the AKU patient cohort. Neither of the three appropriate and safe gait modifications (out toeing, short strides and wide base) should be generalised to AKU patients nor to an individual patient without prior individual evaluation. To overcome this an individualised approach should be implemented whereby the patient is encouraged to create their own gait modification using direct feedback of the 3D knee moment and using the out toeing, short strides and wide base modifications as guidance. The patient-specific individualised gait modification should then be evaluated for effectiveness and safety to adjacent joints, these considerations will be addressed in the final chapter.

Chapter 7: An individualised gait modification intervention to reduce knee loading in AKU patients - A pilot study.

7.1. Introduction

Throughout the literature, varied individual responses to gait modifications are reported (Favre et al., 2016; Anderson et al., 2018; Lindsey et al., 2020). All three studies found large variations in the individual responses of healthy controls to various prescribed gait modifications including trunk lean, toe in, medial knee thrust and step width. Similar findings were reported in chapter 6 of this thesis, where healthy participants were prescribed six different gait modifications (out toeing, in toeing, short strides, trunk sway, medial knee thrust and wide based gait). The three modifications that were chosen for prior instructions to the patients were based on their effectiveness at reducing the 3D moment impulse, their effects to the adjacent joints and their kinematic demands. Although there was an overall reduced mean 3D moment impulse the findings also highlighted a large variation in individual responses to the six prescribed modifications, suggesting that some gait modifications may be effective for some participants and not effective for others. This variation is likely to increase when assessing the heterogenous AKU patient population, this notion is further supported by the large standard deviations in movement patterns of AKU patients seen in chapter 4. The differences in individual responses to each prescribed modification and the variability of gait within patients populations highlighted the need for an individualised approach whereby patients are not prescribed a single gait modification but instead participants are encouraged to find their own individualised gait modification with some prior instruction which could result in a combination of movements.

A study by Richards et al. (2018) used an individualised approach and provided patients with prior instructions on three gait modifications: toe in, wider steps and medialisation of the knee. They were trained on these prior to the intervention however it was not reported how long the training lasted. For the intervention they were encouraged to try different modifications (the ones they have had prior knowledge on, or to make up their own) to achieve a 10% target reduction of the 1st peak KAM which was visualised on the screen. During the intervention the knee OA patients significantly reduced the 1st peak KAM by 14% compared to baseline, KAM impulse was also significantly reduced, however the peak external flexor moment was increased, confirming the importance of considering all three components of the moment.

As well as an individualised approach, the gait modification must also be retained to achieve a successful intervention. Richards et al. (2018) continued their study by assessing the short-term retention by removing the visual feedback and continuing the gait

modification after a 10-15 minute break. The results showed that the knee OA participants retained a significant reduction of the 1st peak KAM by 9% compared to baseline. There was also a reduction in the KAM impulse however the reduction was no longer significant during the retention period.

Treadmill-based interventions are extremely useful for their repetitive feedback as it allows the collection of consecutive strides and large amounts of data. However, to achieve a reproducible and potentially long-term gait modification change, the gait modification established during treadmill walking must be transferrable to overground walking. The differences between treadmill gait and overground gait have been evaluated, results have shown kinematic differences between overground and treadmill walking such as increased hip flexion in females and increased cadence and maximum knee flexion in males on the treadmill (Altman et al., 2012). However, other studies found gait measures such as knee kinematics and temporal-spatial parameters highly correlated and not significantly different to overground walking after a 6 min familiarisation period (Matsas, Taylor and McBurney, 2000). In the Matsas, Taylor and McBurney (2000) study, 12 out of 22 kinematic parameters were significantly different however the differences were < 2°, for the kinetics 15 out of 18 moments and 3 out of 6 power parameters were significantly different but similarly, the magnitude of the differences were within the ranges of repeatability and comparable to the variability within normal gait parameters (Riley et al., 2007). When considering gait variability Van de Putte et al. (2006) found that 10 minutes of treadmill walking were needed to stabilize the kinematic and spatio-temporal parameters variability. Based on these findings a small number of UK gait labs including Stanmore Orthopaedic Hospital in London are confident to perform clinical gait assessments using the treadmill. The split belt treadmill such as the M-Gait treadmill (M-GAIT, Motek Medical, Amsterdam, The Netherlands) allows the collection of ground reaction forces of each side, which is vital for the calculation of the joint moment either through inverse dynamics or through the 3D lever arm approach. The split belt means there is a small gap between the two belts, typically between 5 to 20 mm which may induce some changes or increase variability of gait parameters. A study by Zeni and Higginson (2010) found that step width showed a change in the mean value across 9 min trials but stabilised after 5 mins, they reported a step width decrease from 17.2 to 16.0 cm after 5 minutes. Additionally, this study found that the variability of the ground reaction forces and sagittal plane kinematics also stabilized after 5 minutes. Lansink et al. (2017) noted a familiarisation period of two minutes was needed to normalise the step width and variation was stabilised after 1 minute. However, these studies did not directly compare the split-belt treadmill gait parameters to single belt treadmill or overground gait parameters. When comparing to a single belt treadmill Altman et al. (2012) found an increase in step width by of 3.7 cm during split-belt treadmill walking, however there were no significant differences in the mean lower limb kinematics. Although

there appears to be a difference in step width during split belt treadmill walking, kinematic variability shows to be stabilised after adequate familiarisation periods. All these studies assessed normal 'non-modified' gait. Modified gait requires some conscious thinking and altered coordination which when trained on a treadmill may not be transferable back to overground walking.

7.1.1. Coronavirus disruption to research

NHS ethical approval was granted by the NRES Committee (19/LO/1730) and data collection was due to begin on the first AKU patients during the NAC annual visits in April 2020. However, on March 20th 2020 a UK lockdown was implemented due to the Coronavirus (COVID-19) outbreak, this meant that the NAC service and all non-COVID-19 research was adjourned. In light of this the study was suspended. Due to the time restrictions of the PhD and uncertainty of the resumption of NHS services, the final intervention study using AKU patients will not fall within the scope of this PhD. Therefore, this chapter outlines the intervention protocol intended for the AKU patients but gives the results of a single healthy participant during a pilot study collected prior to the COVID-19 lockdown. The study will be continued with AKU patients, when it is safe to resume NAC services most likely in the autumn of 2020.

The participants were to be identified and recruited through the NAC and the intervention study would form part of their annual gait visit. The exclusion criteria for the study included those that were unable to walk without the reliance on or use of a walking aid, previous lower limb joint replacements, currently has any severe pain or unable to walk comfortably for 30 minutes consecutively. All of these exclusions were likely to lead to the inclusion of patients in the younger to middle age groups (<50 years old) rather than the older group (>50 years old). It has been found that older adults are less able to acquire a new locomotor task on the treadmill when vision is restricted compared to younger adults, this may be due to the impaired proprioception feedback mechanisms (van Hedel and Dietz 2004). These criteria were also based on the findings in chapter three, whereby we aimed to introduce potential gait modifications to the younger and middle aged AKU patients in the hope to delay the progression of the disease. The older adults had more complex gait mechanisms including significantly reduced knee abduction moments, either through compensation mechanisms in response to pain, or as a secondary outcome to other abnormalities (out toeing and valgus knees). The decision to evaluate gait modifications in the young and middle groups also coincided with the safety of the intervention. No walking aids could be used on the treadmill and those who were in a considerable amount of pain could not participate in the study. Although the patients were instructed to create their own modification and are likely to avoid painful gait modifications, the effects to adjacent joints are still unknown at this point. Pain scores were also part of the AKU patient group

protocol, using the KOOS score (Knee Injury and Osteoarthritis Outcome Score, (Roos et al., 1998)) to investigate any patterns or associations between knee pain and type of modification adopted during the intervention.

Although the participant is given prior instructions/guidance on three gait modifications identified in the previous chapter, their gait modification pattern is ultimately determined by the participant, this makes it a directed but ultimately individualised gait modification approach. To identify the gait modification pattern the participant has performed, the typical clinical gait analysis variables such as kinematics and temporal-spatial parameters will be assessed semi-quantitatively.

7.1.2. Objectives and hypothesis

1. To determine if an individualised gait modification strategy using a treadmill-based intervention and the 3D lever arm feedback method can reduce the 3D knee moment.
2. To identify how the individualised gait modification pattern is achieved through an analysis of temporal-spatial and kinematic parameters.

It is hypothesised that the individualised gait modification achieved on the treadmill using direct feedback of the 3D knee moment impulse will effectively reduce the 3D knee moment impulse, this reduction will also be retained without feedback and during overground walking.

7.2. Methods

7.2.1. Participant

One female participant volunteered for this pilot study and was recruited from Liverpool John Moores University (age: 27 years, height: 156 cm, body mass: 70.7 kg). The participant had no previous or current injuries that may have affected gait. The participant made a single visit to the Movement Function Research Laboratory at Liverpool John Moores University.

The participant was given the gait modification information sheet (Appendix 14) a few days prior to their visit to the lab. The sheet describes, in lay terms the three effective gait modifications of out toeing, shorter stride lengths, and increasing step width. These modifications were based on the results from the previous chapter.

One limitation is that the participant had participated in the previous study, therefore had some prior training and exposure to the gait modifications. This means that training times and exposure to the gait re-training should be interpreted with caution.

7.2.2. Protocol

The five gait conditions are outlined in Table 29. The participant wore their own comfortable footwear for all conditions. Ten trials were collected for the baseline overground across a seven-metre walkway. The average walking speed was calculated and this speed was used for all of the subsequent treadmill trials. The system was then switched over to the treadmill settings and calibrated.

The participant was then placed on the treadmill and fall arrest body harness was attached for safety. The participant then acclimatised treadmill walking for 3 minutes, continuously followed by a further 30 seconds of data collection for the baseline treadmill condition. The average 3D moment impulse of the final 10 strides of this condition was used to calculate a 10% reduction of this baseline value; this value was then used as the target value during the intervention treadmill condition. The participant then had time to re-read the gait modification information sheet outlining the three gait modifications (out toeing, short strides and wide base).

Approximately 2 metres in front of the treadmill there is a screen (2 m x 3 m) upon which the visual biofeedback is displayed. The feedback is visualised by two stepwise graphs displaying the stance phase 3D moment impulse given at toe off. The white line represents the 10% target reduction (as detailed in chapter 5.2.3). The participant was encouraged to try one or any combination of these gait modifications, or to develop their own modification. The participant was given 7 minutes to establish a comfortable and effective gait modification pattern, this was based on a study by Wheeler, Shull and Besier (2011) where they found on average it took healthy controls 6.5 minutes to successfully establish a reduced knee loading gait pattern, additionally step width has also been found to stabilise after 5 minutes when treadmill walking (Zeni and Higginson, 2010). The 7 minutes was followed by a further 30 seconds of data collection.

Immediately after the intervention treadmill condition the visual biofeedback was removed by switching off the projection screen. The participant then continued with their gait modification pattern for 2 minutes followed by a further 30 seconds of data collection. This concluded the treadmill conditions.

There was a 5-minute break between the retention treadmill and the retention overground conditions, during this time the participant was removed from the treadmill and the motion capture system was switched back to the overground settings and recalibrated. The

participant then performed a final ten overground walking trials with their gait modification pattern.

Standardised verbal instructions were given to the participant prior to each gait condition and no other types of verbal feedback was given throughout the conditions.

Table 29: A description of the five gait conditions.

Condition	Instruction to participant	Type of feedback	Description of trial
Baseline overground	Walk comfortably and at your typical walking speed.	No feedback.	Normal overground gait pattern without any modification to compare with other trials and to calculate the normal walking speed for the treadmill.
Baseline treadmill	Walk comfortably.	No feedback.	Normal treadmill gait pattern without any modification to compare with other trials and to calculate the 10% 3D moment impulse reduction target for the intervention treadmill trial.
Intervention treadmill	Walk in a way that the blue (right) and red (left) curves fall below or as close to the white line (10% target reduction), you may try one, or any combination of the gait modifications shown to you in the information sheet or by creating your own modification.	Visual direct feedback of the 3D moment impulse with target reduction of 10% below 3D moment impulse of baseline treadmill level (calculated over the final ten steps).	Trial used to assess the participant's response to the direct visual feedback.
Retention treadmill	The visual feedback will now be removed, try to continue the learnt gait modification from the previous trial whilst you are walking.	No feedback.	Trial to assess how well the gait modification is retained when the feedback is removed.
Retention overground	Try to continue to walk with the learnt gait modification from the intervention trials whilst you are walking overground without feedback.	No feedback.	Trial to assess how well the gait modification is retained when walking overground and without any feedback.

7.2.3. Data Processing

All overground kinematic and kinetic data were collected within Vicon Nexus (version 2.5, Vicon Motion Analysis Inc., Oxford, UK) using 11 Vicon cameras (MT10 and MT160) and two Kistler force platforms (Kistler 9281B; Kistler Instruments Ltd., Winterthur, Switzerland)

located in the centre of the walkway. All treadmill trials were performed on the M-Gait split belt treadmill (M-GAIT, Motek Medical, Amsterdam, The Netherlands) and kinematic and kinetic data were collected within Vicon Nexus (v2.5) using 15 Vicon cameras (12 Vero, and 3 MT160). All force plate data were collected at 1000 Hz and kinematic data were collected at 120 Hz for both overground and treadmill systems.

All data were labelled in Vicon and exported to .c3d files. Target and analogue data were filtered using a low pass 6 Hz Butterworth filter and joint kinematics and kinetics were calculated offline in Visual 3D (V6, Visual3D, C-Motion, Germantown, USA) using inverse dynamics with moments expressed in the proximal reference frame. Automatic gait events were calculated with a force plate threshold of 20 N. Kinematic data were normalised to 101 points to represent 100% gait cycle. The knee moments were calculated using inverse dynamics and were exported from Visual 3D to an ASCII file and opened in Excel, here the 3D knee moment impulse was calculated as detailed in 5.3.1.4.

7.2.4. Data Analysis

Due to only one participant, descriptive analysis was used for all comparisons. The mean and SDs of the 3D knee moment impulse was calculated for all five conditions to assess the effectiveness of the intervention. The moment impulse was calculated for the three knee components to assess how the load was oriented within the joints. To assess the safety of the individualised gait modification, the moment impulse in the adjacent joints was also calculated. Both the right and left leg were assessed to monitor any asymmetries.

Finally, to evaluate how the gait modification pattern was achieved, the mean and SD of the temporal-spatial parameters were calculated for all five conditions. The mean curve and SD for both baseline overground and retention overground were graphed using Matlab (MATLAB R2017a, Mathworks, MA, USA). These two conditions were prioritised to show the effect of the intervention on overground walking. The changes during overground walking are important as the modified gait that is established here is what the patient will potentially take away from the laboratory environment, as opposed to any changes established during controlled laboratory treadmill walking. Additionally, to monitor the interim steps that have led to the overground retention condition, the mean curve for all five conditions were also graphed using Matlab. A traditional gait analysis interpretation of the kinematic profiles was used to evaluate whole body movement during each gait condition.

7.3. Results

7.3.1. 3D knee moment impulse

There was a reduction of the average 3D knee moment from baseline overground (0.22 ± 0.01 Nm/kg.s) to retention overground (0.12 ± 0.01 Nm/kg.s) with an absolute difference of

0.11 ± 0.01 Nm/kg.s and a percentage difference of -48 ± 4 %. The absolute and percentage difference for all moment impulse variables are reported in Table 30. There was a small reduction of the average 3D knee moment from baseline overground to baseline treadmill (0.02 Nm/kg.s). There is a reduction of the average 3D knee moment from baseline treadmill to intervention treadmill (0.08 Nm/kg.s), this is then retained for the retention treadmill (0.14 Nm/kg.s), and the retention overground (0.12 Nm/kg.s) conditions. The asymmetry between the two limbs is larger during the treadmill trials compared to the overground trials (Figure 39).

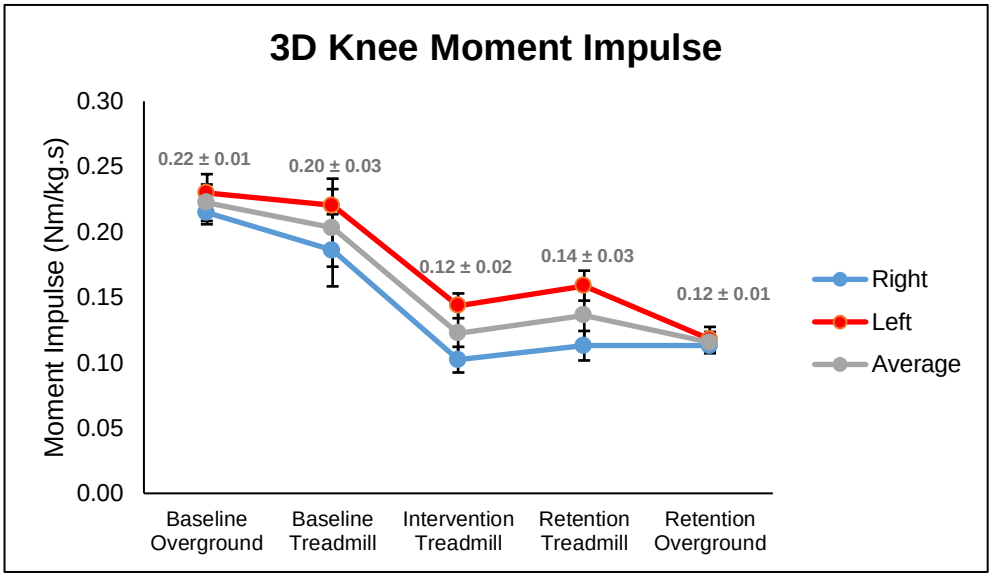

Figure 39: The 3D knee moment impulse mean and SD during all five gait conditions of the right limb (blue) left limb (red) and average (grey).

7.3.2. Knee moment components

All three components of the knee moment follow a similar profile as the 3D knee moment Figure 40. There are small differences between the baseline overground and baseline treadmill conditions, there is reductions in the moment impulse during the intervention which is then retained during the retention treadmill and retention overground, and this pattern is more pronounced in the frontal and transverse planes with some variation in the sagittal plane. For the sagittal plane there is a 23 ± 17 % reduction of the average knee moment from baseline overground to retention overground. In the frontal plane there is a 61 ± 5 % reduction, and in the transverse plane there is a 48 ± 14 % reduction (Table 30).

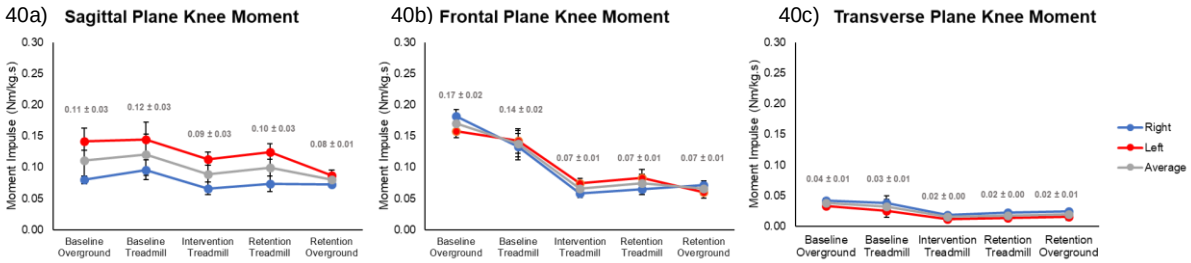

Figure 40: The knee moment impulse mean and SD of the three components of the knee a) sagittal plane, b) frontal plane and c) transverse plane during all five gait conditions of the right limb (blue) left limb (red) and average (grey). The y axis is scaled to the 3D knee moment (Figure 39) to highlight the proportion of the three components to the 3D vectoral sum.

Table 30: The baseline overground and retention overground mean and SD impulse, absolute difference and percentage difference for all joint moment variables.

Variable (Moment Impulse)	Baseline Overground (Nm/kg.s)	Retention Overground (Nm/kg.s)	Absolute Difference (Nm/kg.s)	Percentage Difference (%)
3D Knee	**0.22 ± 0.01**	**0.12 ± 0.01**	**0.11 ± 0.01**	**-48 ± 4**
Sagittal Knee	0.11 ± 0.03	0.08 ± 0.01	0.03 ± 0.03	-23 ± 17
Frontal Knee	0.17 ± 0.02	0.07 ± 0.01	0.10 ± 0.01	-61 ± 5
Transverse Knee	0.04 ± 0.01	0.02 ± 0.01	0.02 ± 0.00	-48 ± 13
Sagittal Ankle	0.32 ± 0.02	0.22 ± 0.01	0.09 ± 0.02	-30 ± 5
Sagittal Hip	0.21 ± 0.01	0.19 ± 0.02	0.03 ± 0.02	-12 ± 9
Frontal Hip	0.24 ± 0.05	0.13 ± 0.04	0.11 ± 0.02	-45 ± 6
Transverse Hip	0.08 ± 0.01	0.05 ± 0.01	0.03 ± 0.01	-39 ± 12

7.3.3. Adjacent joint moments

There was a decrease in the average sagittal plane ankle moment impulse by 30 ± 5 %. For the hip there was a decrease in the average sagittal plane hip moment impulse by 12 ± 9 % from baseline overground to retention overground. In the frontal plane there was a 45 ± 6 % reduction, and in the transverse plane there was a 39 ± 12 % reduction (Table 30). All four adjacent joint curves show a similar profile between conditions, there was an increase in the moment impulse between baseline overground and baseline treadmill, this was then reduced during the intervention condition and retained on the treadmill, the moment impulse was then further reduced during the retention overground trial (Figure 41).

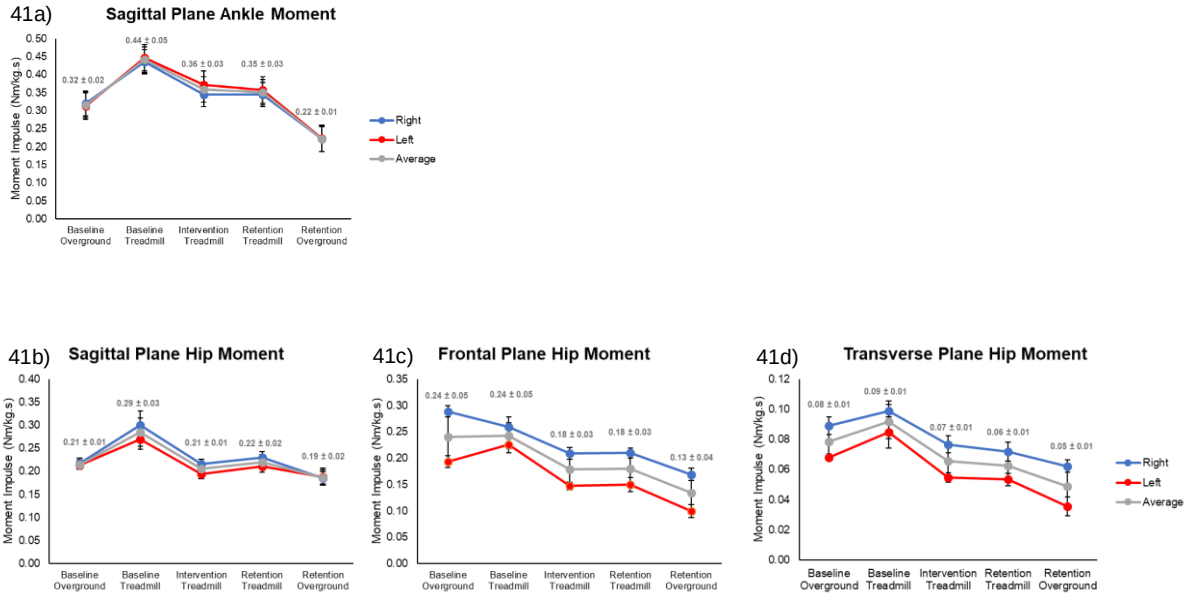

Figure 41: The ankle and hip moment impulse mean and SD 41a) sagittal plane ankle, 41b) sagittal plane hip, 41c) frontal plane hip and d) transverse plane hip during all five gait conditions of the right limb (blue) left limb (red) and average (grey).

7.3.4. Temporal-spatial parameters

Figure 42 reports the mean and SD of the temporal and spatial parameters of all the gait conditions. For the stride length and cadence mean and SD was taken from the average of both sides. There was a decrease in stride length between the baseline overground (1.26 ± 0.02 m) to the retention overground (1.20 ± 0.04 m). There was a decrease during the intervention trial (1.03 ± 0.04 m) which was retained during the retention treadmill (1.04 ± 0.05 m) before increasing during the retention overground. Step width decreased from baseline overground (0.08 ± 0.01 m) to retention overground (0.03 ± 0.01 m), step width also increased during all three of the treadmill trials compared to the overground trials. Cadence increased from baseline overground (115 ± 3 steps/min) to retention overground (155 ± 9 steps/min). Cadence increased during all three treadmill conditions compared to the baseline conditions.

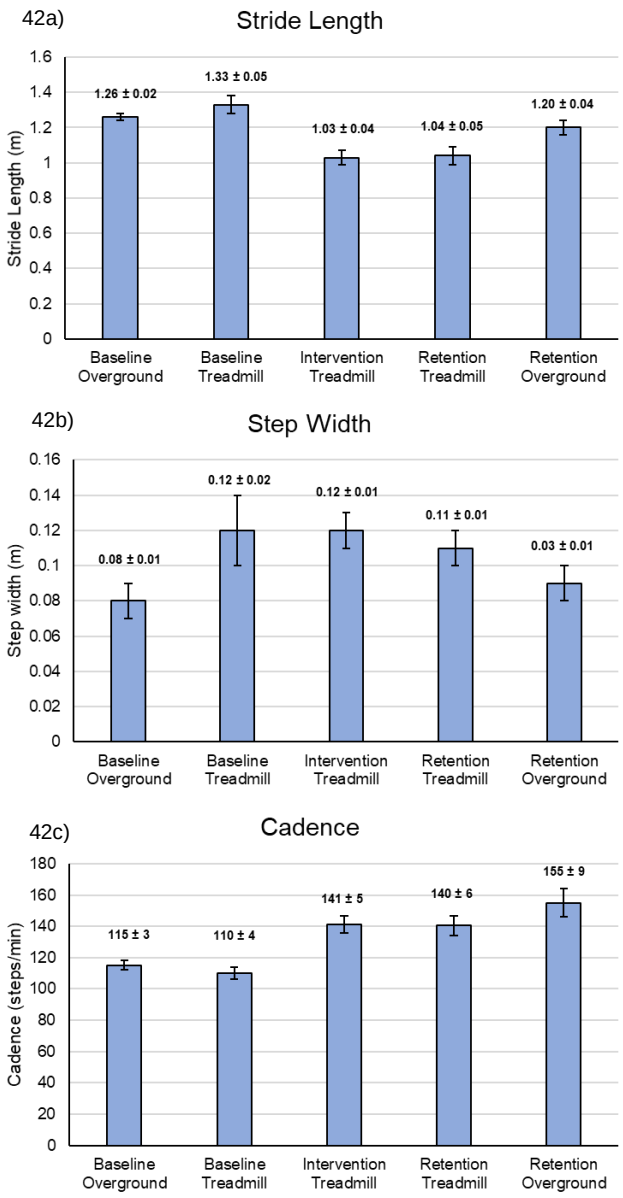

Figure 42: The mean and SD of the temporal-spatial parameters for all gait conditions, a) stride length, b) step width and c) cadence.

7.3.5. Kinematics: baseline overground vs. retention overground

Similar to chapter six, the kinematic mean and SDs were compared between the baseline overground and retention overground. The ankle, knee, hip, pelvis and trunk in the three planes of motion are descriptively analysed. Any differences that were observed between the two means were marked with arrows to indicate the direction of the difference; definitions are outlined in Table 31. Each marked difference was given a number which is referred to in the description.

Table 31: Definitions of the arrows used to describe the differences in the kinematic curves.

Arrow	Description
	An increase compared to normal. One arrow describes an increase over a short period of the gait cycle. Two describes an increase throughout the stance phase of the gait cycle, and three describes an increased offset throughout the gait cycle.
	A decrease compared to normal. One arrow describes a decrease over a short period of the gait cycle. Two describes a decrease throughout the stance phase of the gait cycle, and three describes a decreased offset throughout the gait cycle.
	An increased range of motion compared to normal.
	A delayed timing in the movement compared to normal.

Table 32 describes the differences between the baseline overground and retention overground conditions that are highlighted in Figure 43.

Table 32: Description of each kinematic difference observed between the baseline overground and retention overground conditions.

Reference	Description
(1)	A reduced first rocker
(2)	An early pre-swing plantarflexion
(3)	An early pre-swing knee flexion
(4)	An increase knee abduction during the stance phase ~ 5 °
(5)	A reduced hip flexion during mid stance ~ 5 °
(6)	An increased anterior pelvic tilt range of motion
(7)	A reduced pelvic obliquity range of motion
(8)	A posterior trunk lean

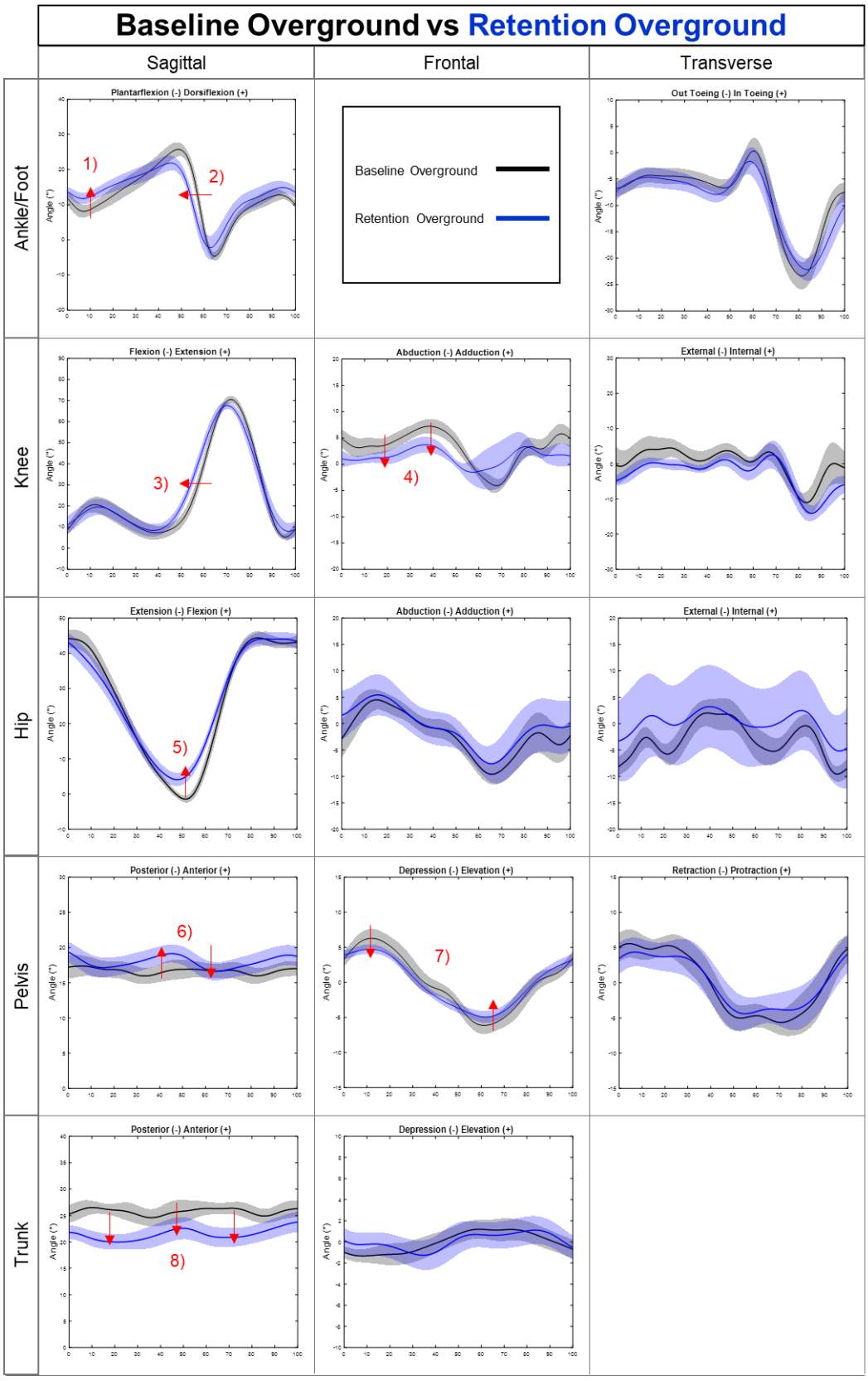

Figure 43: Kinematic gait profiles displaying the mean (line) and SD (shaded) for the overground baseline condition (black) and the overground retention condition (blue).

7.3.6. Kinematics: all conditions descriptive analysis

Table 33 describes the differences between the all gait conditions that are highlighted in Figure 44.

Table 33: Description of each kinematic difference observed between the baseline overground and retention overground conditions.

Differences between baseline conditions and intervention conditions *(the kinematic effect of the intervention)*	
Reference	Description
(4)	An increase knee abduction during the stance phase ~ 5 °
(5)	A reduced hip flexion during mid stance ~ 5 °
(6)	An increased anterior pelvic tilt range of motion
(7)	A reduced pelvic obliquity range of motion
(8)	A posterior trunk lean
Differences between treadmill conditions and baseline conditions *(the kinematic effect of the treadmill)*	
Reference	Description
(1)	A reduced plantarflexion during push-off
(2)	An increased out toeing ~ 5 °
(3)	A reduced knee extension during the stance phase

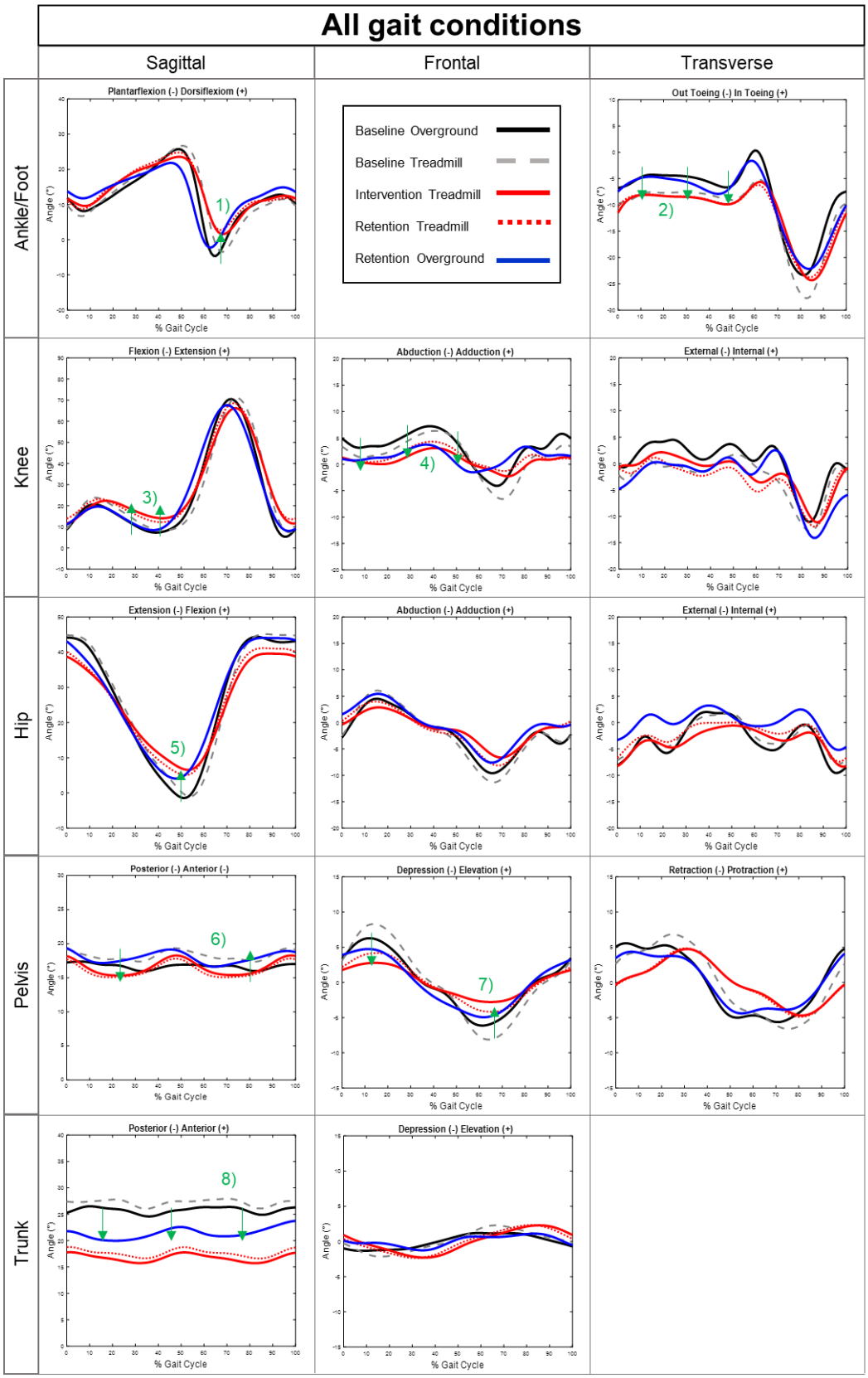

Figure 44: Kinematic gait profiles displaying the mean (line) for the baseline overground (black), baseline treadmill (grey dashed), intervention treadmill (red), retention treadmill (red dotted) and the retention overground (blue).

7.4. Discussion

Gait modification interventions are a conservative approach which aim to reduce knee loading. The primary objective of this chapter was to determine if the 3D knee moment could be reduced after an individualised gait modification intervention using direct feedback. In agreement with the hypothesis the 3D knee moment impulse was reduced during the intervention and retained without feedback and during overground walking. The second aim was to assess how the modification had been achieved by describing the temporal-spatial and kinematic patterns.

7.4.1. 3D knee moment impulse

The results showed that the 3D knee moment reduced by almost half (48% reduction) between baseline overground and retention overground in response to the individualised biofeedback intervention. This indicates that the intervention was effective at reducing the 3D knee moment and that it can be retained overground and without feedback.

As this is the first known study to use the 3D knee moment impulse as an outcome measure, it is difficult to compare to other literature. However, after specific instructions and training on three gait modifications, Richards et al. (2018) reported a reduction of the first peak KAM by 14% when using direct feedback. Interestingly, the KAM impulse was significantly reduced by 19.81% during their feedback trial, but this difference was not maintained during the treadmill retention trial where the feedback was removed. The results from this study showed a 61% reduction in the KAM impulse between baseline overground and retention treadmill showing that the reduction is maintained not only without feedback but also overground. Differences between the studies could be due to the sample used in each study, Richards et al. (2018) investigated knee OA patients aged between 51-72 years, where the single healthy participant within this study was aged 27 years. Research has indicated that older adults are less able to acquire a new locomotor task when vision is restricted potentially due to impairments to the proprioception feedback mechanisms (Van Hedel and Dietz, 2004).

There was a reduction of 0.02 Nm/kg.s of the 3D knee moment impulse between the baseline overground and baseline treadmill conditions (9% reduction). The pattern of change is similar for the moments in the three components of the knee moment in particular the frontal and transverse plane moments. One reason for the reduction in 3D knee moment from baseline overground to baseline treadmill is the change in step width and out toeing during the treadmill conditions which were not seen in the overground conditions. These changes are likely due to the split belt on the treadmill where there is a small gap between the two belts which may cause participants to walk with an increased step width, this was also reported in previous studies (Zeni and Higginson, 2010; Lansink et

al., 2017), both studies showed that the mean value and variation stabilised between 2-5 mins of treadmill walking, however neither studies compared the step width to an overground baseline value. As seen in the previous chapter both increased step width and out toeing are modifications that are effective at significantly reducing the 3D knee moment.

To ensure the safety on the individualised modification that the participant had adopted to reduce the 3D knee moment, the moment impulse was also calculated at the ankle and hip joint. There were no negative effects i.e. increases in the moment impulse at the sagittal plane ankle and sagittal, frontal and transverse hip joint, with a reduction greater than 10% in all. This is important when considering AKU patients, any increase of loading in adjacent joints as a result of their modified gait would be detrimental to their joint health and the modification would have to be re-assessed. Alternatively, if the modified gait resulted in a reduced moment as seen for this participant, it would be an added benefit to the health of the adjacent joints in AKU patients.

7.4.2. Kinematics: baseline overground versus retention overground

The mechanisms behind the reduced 3D knee moment between baseline overground and retention overground can be described by both the temporal-spatial and kinematic parameters. Firstly, there is an increased knee abduction during stance ~5°, this brings the knee joint closer to the midline of the body resulting in a reduced moment arm in the frontal plane. However, there is no other kinematic evidence of medial knee thrust (internal rotation of the hip and in toeing). The increased knee abduction would reduce the internal knee abduction moment and ultimately the 3D knee moment. The increased abduction by ~5° could be due to marker placement error causing a valgus artefact however, there were no signs of a displacement of the thigh wand (an increased external rotation) between conditions, which would cause a change in the knee axis of rotation and cause an increased knee abduction. Other changes were the early pre-swing plantarflexion and knee flexion and the reduced maximal hip extension, these smaller ranges indicate a smaller stance phase which would reduce the time spent in stance and therefore reduce the moment impulse calculation during each gait cycle, the overall stride length between baseline overground and retention overground was a reduction of 0.06 m. Finally, there was an increased posterior trunk lean during retention overground compared to baseline overground, this shifts the GRF vector posteriorly, which may be beneficial mid-terminal stance as this could reduce the moment arm in the sagittal plane.

7.4.3. Kinematics: all conditions

When comparing all five gait conditions, there are some kinematic differences between the modified gait treadmill conditions (intervention treadmill and retention treadmill) and the modified gait overground condition (retention overground). Firstly, there was a reduced

plantarflexion during push off and reduced knee extension during mid-stance in the treadmill conditions, these two modifications suggest a short step length (as described in the previous chapter six), and this is also confirmed with a reduced stride length compared to the overground conditions. These kinematic changes were not retained during overground walking. Additionally, there is an increased out toeing throughout stance by ~ 5° for all three treadmill conditions along with an increased step width as mentioned earlier. These former two changes are likely due to the split belt treadmill, and the results reverted back to those similar to baseline overground values during the modified overground retention condition.

The kinematic changes that were present in both the modified treadmill conditions and the modified overground condition were the increased knee abduction, reduced maximal hip extension range, increased sagittal plane pelvic range of motion and a reduced frontal plane pelvic range of motion. The posterior trunk lean was seen in both modified treadmill and modified overground but was more pronounced during the modified treadmill conditions. The differences and similarities suggest that although the overall 3D knee moment is reduced during the intervention, retained on the treadmill and retained overground, there are some kinematic differences that occur which may be due to walking on the treadmill. When a participant returns to overground walking, within their natural/typical walking environment and without any form of feedback, some inherent walking patterns may revert back, even when consciously thinking about the recently learned modified gait. This may also be due to the time spent training the modification, one study found that co-contractions of quadriceps-hamstring initially increased during their learned new gait pattern but decreased after 20 minutes of training (Uhlrich et al., 2018). Removing the visual feedback is important in the learning process as participants have to rely on internal cues and proprioception to continue to perform the correct gait pattern (Winstein, 1991). There were minimal differences between intervention treadmill and retention treadmill, this is likely due to the short time passed between the two conditions (participant was asked to continue with the gait modification whilst the feedback was switched off), the temporary learning effects from the biofeedback were probably still present and are likely to affect the results. Further studies should investigate the optimal time needed to learn a new gait pattern which also considers the pain and gait constraints in AKU patients, this may be motivated more so if the patients receive further positive outcomes such as a reduction in pain. However, effectiveness and safety were the main aims of this proof-of-concept study.

7.4.4. Limitations

The major limitation to the study was the lack of access to AKU patients due to unforeseen circumstances and so the data of a single participant was used to demonstrate the

intended protocol. A single study design limits any robust statistical analysis that can be performed on the data and the lack of AKU patients means that the results are not generalisable to the patient population. However, due to the heterogenous nature of the AKU sample and the individualised intervention approach, the methodology in this chapter outlines how each AKU patient and their modified gait would be assessed. Any grouping of the patient cohort data may miss the effectiveness of each individual response, the individual gait pattern characteristics and the safety to the adjacent joints.

Further investigation of AKU patients is needed to ensure the results are generalised to the patient population and most importantly is achievable for AKU patients who have pain and movement constraints. For clinical implementation, AKU patients are needed to assess if they can also achieve and retain an individualised gait modification. A systematic review showed that the reductions in KAM for patients with knee OA was smaller than that of the healthy control subjects (Richards et al., 2017), although the amount of comparable studies were limited within the systematic review. However, the results suggest that the effect of the intervention may not be transferable to patient populations, this could be due to the initial larger gait variability seen in patient populations compared to healthy controls, pain experiences and mobility constraints prior to the modification.

Another limitation of this study is the unknown clinical relevance of the change in the 3D knee moment. The 10% target reduction is based upon previous studies using the KAM as an outcome measure in knee OA patients (Shull et al., 2013; Hunt and Takacs, 2014; Richards et al., 2018). The results demonstrated a large magnitude of change in the 3D knee moment (48% reduction), such a large change is likely to lead to a clinically relevant difference. However, further studies would need to clarify the threshold for clinical relevance when using the 3D knee moment in AKU patients.

7.5. Conclusion

The participant successfully reduced the 3D knee moment impulse by almost half (48%) by creating their own individualised gait modification. This was achieved by adopting an increased knee abduction angle, reducing the maximal hip extension range, which is likely to reduce the step length and therefore shorten the time spent in the stance phase. The modified gait had no detrimental increases to the adjacent joint moments and was retained both without feedback and during overground walking. If these results are transferable to AKU patients then this novel biofeedback method could reduce the knee loading environment in AKU patients, and with further evaluation has the potential to be implemented into clinical practice by creating a personalised gait handbook detailing each individual's gait modification for them to continue, with additional follow-up testing. Through continued monitoring, this intervention may delay the progression of the disease, delay the

need for highly invasive joint replacement surgeries and improve pain and quality of life in AKU patients.

Chapter 8: General Discussion

8.1. Overview

Alkaptonuria is a painful and highly debilitating progressive disease (Keller et al., 2005). The irreversible joint damage caused by ochronosis and mechanical loading leads to disability, premature osteoarthritis and multiple costly joint replacements. However, there was little evidence describing gait patterns in AKU and no literature exploring alternative non-invasive gait modifying treatments in AKU patients.

The first aim of this research was to characterise and describe gait in AKU using novel and robust methods. Monitoring the natural progression of gait deviations would help to inform nitisinone treatment plans and joint specific gait abnormalities would help to identify important mechanisms and problematic joints which would influence the development of a real-time biofeedback intervention tool. The second aim was to develop a novel real-time biofeedback gait modification intervention tool. The knee joint loading was focused on, based on the findings within section one, alongside previous evidence that joint damage occurs within the large weight bearing joints and is influenced by mechanical loading (Taylor et al., 2011). The new method was designed to allow an individualised gait modification intervention protocol which aims to delay the progression of the disease in AKU patients.

8.2. Characterising and describing gait in AKU patients

The findings in chapter three reported no definitive clusters between AKU and controls, this indicates that there were no distinct differences between AKU and control gait. These results differ from other pathologies such as cerebral palsy (Carriero et al., 2009), where distinct clusters between gait patterns have been reported. The lack of distinct clusters could be due to subtler differences in AKU gait compared to larger movement amplitudes seen in pathologies such as cerebral palsy, furthermore the SOM has ordered complex gait patterns in one dimension reducing the dimensionality as well as some potential loss of detail. Additionally, this study used the marker coordinates as opposed to pre-determined discrete gait variables. The results also suggest that there were no distinct similarities within AKU patients' gait. This is likely due to a heterogenous AKU population sample and various gait patterns to compensate for the individual disease progression and large variations in pain experienced by each patient.

The results in chapter three also reported that gait deviations increase with age with a sharp rise at around 50 years. The sharp increase coincides with the evidence that 50% of patients above 50 years have joint replacements. A joint replacement is required when total joint failure occurs, therefore deviations are likely to occur as compensatory mechanisms

when the joint is close to failure and to avoid pain. The results also found that joint replacements contribute to higher MDP_{mean} scores, which supports the evidence that gait parameters do not return to normal following joint replacements (Sosdian et al., 2014). However, more age-matched patients with and without joint replacements were needed to conclude this this statement. Another important finding from chapter three was the increase in the MDP_{mean} in the younger AKU group (<29 years old) particularly in the youngest three patients at 16 years old. The new finding challenges the original assumption that AKU symptoms do not appear until 30 years (Introne and Gahl, 1993; Ranganath and Cox, 2011). Findings from the study by Cox et al. (2019) with the same subset of patients used within chapter three of this thesis also found other clinical symptoms in the younger AKU patients such as ochronosis, qAKUSKI scores and circulating serum HGA, which were all elevated in the youngest patients at 16 years old. These new combined findings help to further develop the understanding of AKU and may contribute to the reassessment of patient treatment plans particularly in the younger patients, and the future decision-making process on nitisinone usage and initiation.

The results within chapter four built upon the findings in chapter three by assessing the joint level kinematic and kinetic profiles. The findings confirmed the age-related patterns seen in chapter three and identified the gait mechanisms that were possibly contributing to the high MDP_{mean} across three age groups. Deviations in the younger group were found in the knee joint, occurring in the sagittal plane, specifically the abnormal loading and movement patterns could have potential negative effects to the posterior passive structure of the knee. In the middle group there were an increased number of significant differences compared to the speed matched controls, these differences were found in the knee and hip and were also seen in the sagittal plane. Finally, the oldest group saw the largest amount of significant differences compared to normal, the abnormalities were seen in all the lower limb joints, and in all three planes of motion. The increase in the amount of differences was to be expected based on the increased MDP_{mean} in chapter three in the >50 years age group. The amount of structural joint damage, spinal degradation and pain also increase with age (Cox et al., 2019), as the joint tissues have had more exposure to the circulating HGA with age. Interestingly, there were several kinematic mechanisms identified that reduce the frontal plane knee moment in the older group. These mechanisms included out toeing with related external hip rotation and valgus knee alignment with related hip adduction. Out toeing could be a subconscious movement pattern to avoid loading and reduce pain in the knee. Out toeing could also be a result of natural ageing as our controls ranged from 20-60 years and were speed-matched with the AKU patients as opposed to age matched. However, the out toeing could also be a consequence of the disease, and it is difficult to conclude whether this is a primary problem or a secondary compensation. The

second mechanism identified was the valgus alignment of the knee, this is likely due to the structural joint damage but ultimately has a beneficial effect on the knee joint loading.

Although two mechanisms were clearly identified, there were large standard deviations suggesting variation in the AKU patients' gait throughout all three age groups. The variation coincides with the lack of distinct clusters in chapter three. The variation may also mean that other mechanisms may have been missed in this cohort analysis. Drawing from the experience gained at the NAC interpreting gait data over the past four years also revealed large variation in the disease progression and the effects to gait and mobility. The results here emphasise the need for individual approaches when dealing with heterogenous populations. Overall, there were significant differences in the knee joint seen in all age groups of AKU compared to normal, this suggests that the knee is a potential problematic joint which contributes to the movement deviations seen in AKU. The characteristics and mechanism of AKU gait described in chapter four had not been previously documented and the results contributed to the development and design of a targeted gait modification intervention protocol in the remainder of this thesis.

8.2.1. Clinical implications of section one

One clinical implication that has arisen from section one of this thesis (chapters three and four), is that gait in Alkaptonuria is variable with no distinct gait mechanisms belonging to the AKU cohort that differs largely from control gait. Although some mechanisms were established when the AKU patients were split into age groups, there was still large variability particularly in the older group. This variations and lack of distinct gait patterns is likely multifactorial and gait analyst and practitioners should focus on an individualised approach to provide care and symptom management within AKU patients. The large increase in the MDP_{mean} seen in patients as young as 16 suggests that symptoms begin early and that it is important that the paediatric AKU group is monitored along with the adult population. By researching and investigating the paediatric AKU group with all sub clinical measures, a more confident and research driven decision on the most efficient time to initiate nitisinone treatment can be made. Finally from the results in chapter four, it is clear that AKU affects multiple joints in all three planes across the lifespan of an AKU patient, this information should influence future intervention protocols that aim to reduce joint loading, ensuring that a desired reduction does not come at the expense of an increase in another plane or another joint.

8.3. Development of a bio-feedback gait intervention tool for AKU patients

Real-time biofeedback gait retraining interventions to reduce the knee loading are widely used in osteoarthritis research (Wheeler, Shull and Besier, 2011; Gerbrands et al., 2017;

Richards et al., 2018), and there have been several proposed gait modification strategies that mechanically reduce the knee joint moment (Simic et al., 2011). However, there is no consensus within the literature on their effectiveness to reduce the knee loading. The reason for the disparity within the literature is likely due to the methodological designs. Firstly, the outcome variables used in the interventions within the literature are not consistent, those that have used discrete variables such as the 1st or 2nd peak KAM do not represent the whole loading environment. Some findings show a decreased frontal plane moment but increases in sagittal and transverse planes (Erhart-Hledik, Favre and Andriacchi, 2015; Richards et al., 2018; Roberts et al., 2018). Secondly, the reference frame that the moment is expressed in often vary and are not always reported which have shown to cause variation in the joint moment (Manal et al., 2002; Schache and Baker, 2007), and finally differences in the delivery of the intervention, when prescribing gait modifications there has shown to be large individual responses in both healthy controls and patient populations (Anderson et al., 2018; Lindsey et al., 2020).

These previous methodological issues were considered during the development of a new biofeedback tool in chapter five of this thesis. To achieve real-time feedback, the tool needed to accomplish a fast computation of a single variable that incorporates the whole stance phase. The method used the 3D knee moment impulse as an outcome measure, the impulse incorporates the magnitude and duration of the moment throughout the stance phase. The method also uses the 3D knee moment vector without breaking it down into its planar components, this avoids any large increases in other planes of motion at the expense of a reduced frontal plane moment. Although the frontal plane moment has been seen to be strongly associated with knee OA, the findings in chapter three suggest that AKU sees abnormal loading in the sagittal plane knee moment, additionally, AKU differs from OA in that all joint tissues are affected. However, the direct effect of the 3D knee moment impulse on disease progression remains unknown in AKU, this is further discussed in 8.5.3.

To achieve fast computation the method used a simplified 3D Lever Arm method, chapter five compared the 3D lever arm method to the ‘Gold Standard’ inverse dynamics calculation. The findings demonstrated good agreement and reported significant strong and positive correlations during normal walking. The mathematical differences between the two methods meant that the 3D lever arm method underestimated the 3D knee moment compared to the inverse dynamics, however, when six gait modifications were performed by the participants the 3D lever arm method was able to detect the changes from normal gait. These findings are contrary to previous findings by Lewinson, Worobets and Stefanyshyn (2015) who demonstrated poor agreement between the two methods during normal walking however, the study only used the frontal plane, therefore differences

between the two methods may be due to the reference frame the frontal plane moment is expressed in as opposed to the inertial properties contributing to the moment. The underestimation during the lever arm calculation could be corrected for using further mathematical methods, however this was not carried out within this thesis, due to its ability to detect change. Additionally, the method was designed to be used as a gait re-training tool only, clinical outcome measures would still be computed offline using the 'Gold Standard' method to clinically assess gait and its changes pre- and post-intervention when the computational time is no longer a confounding factor. One other positive aspect of the 3D lever arm method, is that it only requires four markers to be seen at all times for the computation of the 3D knee moment during the intervention training stage, as opposed to the full body marker set when using other systems such as the Human Body Model (HBM) which may cause drop-outs of data if all markers are not seen. The ease of application and detection of the four markers allows current clinical marker sets to be used. The seven-year repeated visits AKU NAC database uses the same Helen Hayes model (Davis et al., 1991), this method only needs the addition of two extra markers which allows for easy comparisons without the time-consuming changes to the clinical protocol.

There are some limitation of the 3D lever arm method and the approach should be used with caution. The aforementioned calculation of the knee moment is mathematically incomplete as explained by Winter (2009), with errors likely to increase with the progression up the body. Although it showed good agreement within the knee joint it has not been tested at other joints particularly the hip where the errors are likely to increase (Wells, 1981).

Based on the findings in chapters three and four, which showed large variation in gait mechanisms and a heterogenous sample, the 3D lever arm method was designed to implement an individualised gait modification intervention. This meant the direct feedback on the 3D knee moment was provided to allow patients to develop their own individualised gait modification. However, previous literature has also suggested that some prior knowledge or training of potential gait modification strategies produced a more effective result in reducing the knee moments (Richards et al., 2018). To investigate which gait modification should be used as guidance for patients, chapter six investigated the effectiveness of six previously researched gait modifications (in toeing, out toeing, short strides, lateral trunk sway, medial knee thrust and wide base) on the 3D knee moment impulse. The results found that four out of the six significantly reduced the 3D knee moment impulse, these were in toeing, out toeing, short strides and wide base. The other two, trunk sway and medial knee thrust were ineffective at significantly reducing the 3D knee moment impulse. To explain this, further analysis of the three planar components demonstrated that although all six gait modifications were able to significantly reduce the

frontal plane moment, as designed, there were increases in sagittal and transverse plane moment impulses for the trunk sway and medial knee thrust resulting in a non-significant reduction of the net 3D effect. These findings support the study by Walter et al. (2010) who found that reductions in the frontal plane 1st peak KAM did not coincide with any significant reductions in the 1st peak medial contact force, which was likely due to the increases found in the external knee flexion moment. Additionally, Roberts et al. (2018) found that the peak external rotation moment was strongly associated with the 3D architectural parameters such as the bone volume fraction and the structure model index score of the knee joint, particularly in the anterior/medial regions. These findings support the importance of considering the net sum of the three components of the knee moments, particularly when implementing lateral trunk sway and medial knee thrust as gait modifications.

Additionally, chapter six identified which of the six gait modifications do not increase the moment in the adjacent joints (ankle and hip) and these were out toeing, short strides, and wide base gait. The medial knee thrust and in toeing increased the impulse in the transverse hip moment and trunk sway increased the sagittal ankle moment. These gait modifications should be implemented with caution in future research designs, the effect on adjacent joints is often not reported but essential to understand to avoid negative consequences to other joints, particularly in AKU where there is multiple joint involvement and damage.

Chapter six also highlighted the large individual variations of responses when the six gait modifications are prescribed, even in healthy controls, although overall reduction in the mean 3D knee moment impulse for in toeing, out toeing and wide base gait there were still some individuals that increased the 3D knee moment impulse. A study by Lindsey et al. (2020) found a similar finding when assessing the KAM during three gait modifications. This thesis only investigated 16 healthy participants, the variation in individual responses is likely to increase when investigating pathological conditions particularly in heterogenous patient populations. These findings suggest that an intervention protocol should incorporate individualised approaches. Finally, chapter six saw evidence of non-isolated movement patterns when each gait modification was prescribed. Reduced stride length and wide based gait are considered gait modifications which reduce the knee moment, however, a significantly reduced stride length was also seen during in toeing, out toeing, medial knee thrust and wide based, and a significantly increased step width was also seen in in toeing, trunk sway, and medial knee thrust. Additionally, there were several kinematic changes in all three planes of motion seen for each prescribed modification. These findings suggest that each modification is a non-isolated movement strategy and the reduction in the moment is not just the effect of the one prescribed (i.e. trunk sway) but the net effect of the whole-body movement. These findings may explain the variation of individual responses

and the disparity of the literature when prescribing specific gait modifications. After the extensive assessment of each of the six modifications, chapter six concluded that only three of the gait modifications were effective at reducing the 3D knee moment impulse, did not elicit increased moments in adjacent joints, did not produce large variations in individual responses and did not require several coordinated kinematical changes. These modifications were out toeing, short strides and wide based gait and should be used as guidance in future AKU gait modification interventions. Conversely, based on the findings, in toeing, trunk sway and medial knee thrust should be used with caution in gait modification interventions.

The final chapter's objective was to design a gait intervention protocol built upon the findings throughout the thesis. The study hoped to evaluate the young-middle aged AKU patient population to potentially delay the disease progression by reducing the mechanical loading within the knee joint prior to any self-selected gait modifications or compensation mechanisms which were seen in the older group. Secondly, the 3D knee moment impulse would be used as the outcome measure to ensure no negative increases in other planes of motion and it is assumed a better indication of total joint load. Thirdly direct feedback of the 3D knee moment impulse was used, supported by previous evidence that direct feedback is more effective, but also to promote an individualised response and encourage patients to find their own gait modifications based on their movement restrictions and individual pain. To add to the previous knowledge the intervention protocol was also designed to assess the retention of the individualised gait modification without feedback and during overground walking.

Unfortunately, due to unforeseen circumstances AKU patients were not able to attend laboratory testing to carry out this final intervention study, therefore the results were from a single healthy control participant (limitations are further discussed in section 8.4). The results from chapter seven demonstrated positive response. Firstly the participant was able to reduce the 3D knee moment during the gait modification intervention by almost half (48% reduction), this was then maintained when the feedback was removed and most importantly during overground walking, with a mean reduction of 0.1 Nm/kg.s between baseline overground walking and post-intervention overground walking. Temporospatial and kinematic parameters were evaluated to identify and describe the individualised gait modification that was performed by the participant to achieve the reduction in the 3D knee moment. It was suggested that there was reduction in stride length which was also confirmed by the reduction in joint ranges of motion seen in the sagittal plane angles and an increased knee abduction angle.

Overall, the protocol appeared to be successful, however there were limitations to this study in that a single healthy participant was used who had previously carried out the

protocol for chapter five (had 1 session prior training), for AKU patients it may take more gait training sessions. The original inclusion /exclusion criteria included a pain scale, however AKU patients may be compensating already for pain which may limit their ability to successfully reduce their 3D knee moment.

8.3.1. Clinical implications of section two

Section two of this thesis provided results that can be applied to both AKU and knee OA. Firstly, the 3D LA method could be used in interventions that aim to reduce the knee loading. Due to the method's simplicity, providing direct feedback of the knee moment only requires 4 markers to be seen at all times (medial and lateral knee markers), in comparison to large marker sets such as the HBM, whereby ~36 markers are needed to be seen, this could be beneficial for labs with a limited number of mocap cameras and space. Secondly the addition of two medial knee markers to the widely used Helen Hayes model means that this can be incorporated quickly into protocols without extended preparation time, particularly for those practitioners who would provide this as an addition to their regular gait analysis service such as at the National Alkaptonuria Centre.

The introduction of the 3D knee moment impulse as an outcome measure, firstly removes the technical problem of the reference frames which would allow unambiguous comparisons across data sets and within the literature. This outcome measure also considers the joint moments in 3D without disregarding the other planes of motion, and also across the whole stance phase, which is likely to provide a better representation of the loading environment and may help clinicians and future researchers track the progression of the disease and pain, this is discussed further in 8.5.2.

Finally, the results from chapter six provides an in-depth analysis of six well known gait modifications and analyses their effect on adjacent joints and their kinematic demand, these results can be used by researchers to help decide which gait modification may be applicable to their patient groups. Additionally, the clear individual response to various gait modification seen within healthy controls in chapter six reinforces the message that gait modifications should be implemented using an individualised approach.

8.4. Limitations

Although AKU is an ultra-rare disease, with only 1233 AKU patients recorded worldwide (Zatkova, Ranganath and Kadasi, 2020), the sample sizes were low within section one. The study aimed to monitor the natural progression of the disease therefore patients that were taking nitisinone treatment were excluded, this limited the recruitment from within the UK as most UK patients have access to nitisinone through the NAC. With all these constraints, 36 patients were recruited for chapter three and four. Such low numbers made grouping and

comparisons within the cohort difficult. Comparisons between males and females, and those with joint replacement and non-joint replacements were difficult to conclude due to the lack of age-matched patients.

As with all laboratory-based gait analysis methods, the results in this thesis were affected by soft tissue artefacts and marker placement errors. To try to reduce this as much as possible, annual marker placement repeatability testing was undertaken throughout this thesis with kinematic measurements maintaining below 5° difference between repeated sessions. The Helen Hayes model is subject to errors but long existing database and marker placement time for older less mobile AKU patients means it is used within clinical practice and to make comparisons this model was used within this thesis.

Unfortunately, due to the COVID-19 outbreak the final study was not conducted. Chapter seven followed the protocol for the proposed patient intervention but reported results from a single healthy participant. These findings showed positive results, indicating that the participant was able to adopt an individualised gait modification which reduced the 3D knee moment impulse, and the effect was retained without feedback and during overground walking. Although the intervention is designed to be individualised, the results from chapter seven cannot be generalised to the AKU patient population. Finally, although the 3D knee moment impulse appeared to be a good outcome measure which overcomes many shortcomings, its clinical relevance to AKU is unknown.

8.5. Recommendations for future research

Based on the findings presented in this thesis, there are a number of future research recommendations to build upon the current understanding of gait and gait modification interventions in AKU.

8.5.1. Describe and monitor gait in AKU children

Nitisinone for children is typically only used in children with type I tyrosinemia, because if this condition is left untreated then it becomes fatal. If nitisinone is used earlier in AKU children, it could delay the progression and disease implications later in life. However, there remains concerns over the safety of elevated tyrosine levels and adverse/unknown side effects in long-term use (Suwannarat et al., 2005; Khedr et al., 2018). As AKU is a progressive but not fatal disease, it leads to the ethical decision when is the best time to begin nitisinone treatment for AKU patients. The decision must be based on when debilitative symptoms begin, the adverse side effects of long-term use and disruption to life/adherence to the drug. The results in chapter three found gait deviations in even the youngest patients at 16 years old, this coincided with the study by Cox et al. (2019) who reported signs of early ochronosis. To help distinguish the magnitude and severity of

symptoms and at what age they begin, gait deviations alongside other sub-clinical measures should be assessed in children. Alkaptonuria gait should be compared to typically developing age-matched children. The results from an AKU children study alongside the evidence reported in this thesis would provide a complete map of the natural progression of gait in AKU across the full lifespan.

8.5.2. Investigate correlations between gait variables and other variables

Ochronosis typically increases with age, as the affected joint tissues have had longer exposure to the circulating HGA (Introne and Gahl, 1993; Taylor et al., 2011). The consequence of increased ochronosis is increased joint damage, pain and disability which have also been reported to increase with age (Taylor et al., 2011; Rudebeck et al., 2020). Chapter three of this thesis, along with Barton et al. (2015) and King et al. (2017) support this pattern with results indicating that gait deviations also increase with age. However, direct correlations between these sub clinical measures would provide a more robust description of the disease.

Chapter four of this thesis saw various gait mechanisms in the older group. However, it is difficult to conclude if the mechanisms were a compensation to avoid joint pain due to joint damage, or as a natural effect of aging. Additionally, gait abnormalities were seen in the younger group, where joint damage is assumed to be less. This questions whether these gait abnormalities could contribute to the joint damage, cartilage degeneration and increased ochronosis. This is particularly important to the younger patients as gait modification interventions can be put in place earlier to prevent further damage. To further asses this, repeated visit gait measures, pain scores, and joint damage indicators such as MRI results or PET scans should be correlated and analysed together. The NAC gait analysis service provides annual visits repeated over several years. Based on the experience of interpreting this data, there seems to be a large variation in patients' mobility. There is no clear set age at which a decline in gait occur. Therefore, the correlations between gait and joint damage indictors may help to identify individual treatment plans.

8.5.3. The relationship between the 3D knee moment impulse and joint damage

Chapter five used the 3D knee moment impulse as the outcome measure to overcome some of the shortcomings and potential disparities seen in the previous literature. However, direct relationship between the 3D knee moment impulse with joint contact forces should be investigated. If the 3D knee moment impulse is confirmed to be a better predictor of the joint contact forces than the peak values in one plane, the easily implemented outcome measure should be used in future gait modification interventions, not only for AKU but it could also be used for knee osteoarthritis interventions. Additionally, the relationship

between the 3D knee moment impulse and disease severity, using magnetic resonance imaging measures of cartilage damage/thickness and sites of ochronosis in the knee joint should be analysed. However, ochronosis at the knee joint is difficult to measure without *in vivo* studies. Assessing these relationships would help to identify the clinical significance of gait modification interventions using the 3D knee moment impulse as an outcome measure.

8.5.4. Gait modification intervention in Alkaptonuria patients

Unfortunately, due to unforeseen circumstances chapter seven only used one healthy control participant in the final intervention, this intervention was successful however results are not generalisable to AKU patients. Therefore, future studies with Alkaptonuria patients during the gait modification interventions is paramount. The gait modification intervention protocol was designed to promote individualised responses which suits the heterogenous AKU population. However, pain and constraints may mean that AKU patients simply are not able to reduce the 3D knee moment impulse. If the intervention were to be successful in AKU patients, safe and effective individualised gait modifications could be identified for each patient and prescribed as part of a long-term treatment plan.

8.5.5. Gait modification intervention in AKU - A longitudinal study

The purpose of a gait modification intervention is to promote the learning of a long term meaningful and permanent gait pattern. For the gait modification intervention to be an effective, the modified gait which delays the progression of the disease and reduces joint pain it must be retained long-term. It is unknown whether immediate reductions of the 3D knee moment seen in the laboratory are transferrable to long term clinically relevant changes. Therefore, follow-up testing should be completed, one study assessed the retention of a foot progression angle gait modification after six weeks training with one month follow up (Shull et al., 2013). Results showed that the changes in KAM, foot progression angle and pain scores were retained after one month, however longer term would have to be assessed. A systematic review also revealed that biofeedback in gait retraining for knee OA patients provided medium to large treatment effects in the short-term, but long-term results were inconclusive (Tate and Milner, 2010). It is also important to consider the metabolic cost of a modified gait. One study found the metabolic requirements of treadmill walking were 23% higher than overground walking in older adults (50-73 years) despite temporal-spatial parameters and kinematics being similar (Parvataneni et al., 2009). This is then further increased during a gait modification whereby Caldwell, Laubach and Barrios (2013) found an increased perceived workload of 1178 % during a variety of gait modifications compared to normal walking in healthy controls. The metabolic demand of a gait modification may affect ability to perform the modification and the compliance

during long-term use. In addition to long term follow ups, randomised control trials (RCTs) should also be used to truly assess the effect the intervention on AKU.

The NAC sees all UK AKU patients and so a long-term study evaluating the intervention could be integrated into their clinical service. This study would involve evaluating if AKU patients are able to produce an effective individualised gait modification strategy, ensure no harmful load increases to other joints, and assess how they have achieved their individualised modification. A description of their modification could be prescribed with training and follow up analyses.

8.5.6. Wearable non-laboratory-based intervention technology.

Finally, the development of wearable sensors to provide feedback of individual gait modifications would be ideal to provide real-time feedback for gait training outside of the laboratory during daily living. This would enable the treatment and gait retraining without being confined to the laboratory and could provide valuable objective feedback directly to both patients and the researchers.

8.6. General conclusions

Alkaptonuria was the first genetic disease to be described back in 1902 by Archibald Garrod. However, there is very limited description of gait in AKU within the literature. The findings from section one provides the first joint level description of gait using robust and novel methods and therefore provide a novel insight to gait mechanisms in AKU and contribute to the understanding of the natural progression of the disease. The results from chapter three suggest that gait deviations begin as young as 16 years, and show a sharp increase at 50 years, these findings contribute to the decision of when to begin nitisinone treatment. The results from chapter four suggest gait mechanisms change with age, and deviations were found in the knee joint across all age groups, this suggests that the knee joint should be targeted within future interventions.

The results of section two build upon previous knee osteoarthritis research and the developments of real-time biofeedback intervention tools. Chapter five showed that the new method provided a new way to present the knee moment in a way that might better represent to total knee loading environment. The new method brought together components of total stance phase, the three knee moment components and was designed to provide an individualised approach. The results from chapter five showed good agreement with the ‘Gold Standard’ approaches and demonstrated the ability to detect gait modifications. The results from chapter six suggest that an individualised approach would be beneficial in future intervention designs. Finally results from chapter seven used a single healthy participant so generalisation cannot be made however, the promising results

suggest that the individualised gait modification intervention tool has the potential to be applied in future AKU interventions to reduce the knee loading and potentially slow the progression of joint damage in AKU patients.

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Appendices

Appendix 1

Gait & Posture 57 (2017) 149–150

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O86

A protective effect in females with alkaptonuria: Relationships between gait deviations and ochronosis

Stephanie King[b], Malcolm Hawken[a], Hannah Shepherd[a], James Gallagher[c], Lakshminarayan Ranganath[d], Gabor Barton[a,*]

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[b] University of Hull, Hull, UK
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[d] National Alkaptonuria Centre, Liverpool, UK

1. Introduction

Alkaptonuria (AKU) is a genetic metabolic disease resulting in elevated levels of homogentisic acid. When oxidised, ochronosis develops in connective tissues, including cartilage, resulting in a gradual tissue deterioration over time. Subsequently, gait becomes altered, with deviations from normality increasing with advancing age and disease, in parallel with deterioration of typical clinical outcome measures [1]. Qualitative investigations into disease progression suggests apparent gender differences with symptoms developing earlier in males, indicating females are somehow protected from the effects of the disease [2].

2. Research question

Is there a relationship between gender, ochronosis and gait deviations in patients with AKU?

3. Methods

3D gait analysis was performed on a total of 34 patients (age range; 19–72 years, 14 females) with AKU as part of their standard clinical assessments. Reflective markers were affixed to the lower limbs according to the Helen-Hayes model and patients were asked to walk at a self-selected pace along a 10 m walkway. The Movement Deviation Profile (MDP) [3] quantified the deviation of AKU patients' gait from normality by passing mean-corrected marker coordinate data normalised to unit standard deviation of both AKU patients and 10 healthy controls to the self-organising neural network. MDP_{mean} values were then derived for each patient and used for further analysis.

4. Results

To visualise changes over age, data were median filtered with windows ranging between 5 and 9 samples. Ochronosis levels in ear cartilage showed broadly similar disease progression in males and females. In contrast, the increase of MDP_{mean} was slow in females between the 3rd and 5th decades, and accelerated mid-way through the 6th decade. Males demonstrated a more continuous increase in MDP_{mean} throughout the lifespan.

5. Discussion

Deviation of gait from normality, as measured by the MDP_{mean}, provides a more faithful measure of movement function than ochronosis level on its own. Our findings provide some functional evidence to support previous qualitative reports of a protective effect in females with AKU [2]. Gait deviation from normality was minimal until ~55 years, coinciding with the typical onset of menopause although it is unclear how the onset of menopause affects gait mechanics in healthy females. However, it could be suggested that the subsequent effects on bone mineral density and bone loading, particularly in those with AKU, would also impact joint loading and lead to altered walking patterns. Total joint arthroplasties have been reported to occur in more than 50% of patients around 50 years of age [4] and the present findings indicate that females experience a greater and, more importantly, rapid change in gait mechanics between the ages of 50–60 years. Hormonal status was not investigated as part of this study, but the data suggests that therapies aiming to prolong the seemingly protective effect of oestrogen might be advocated. Certainly, female patients in particular must be closely monitored during this 6th decade for signs of sudden functional impairments.

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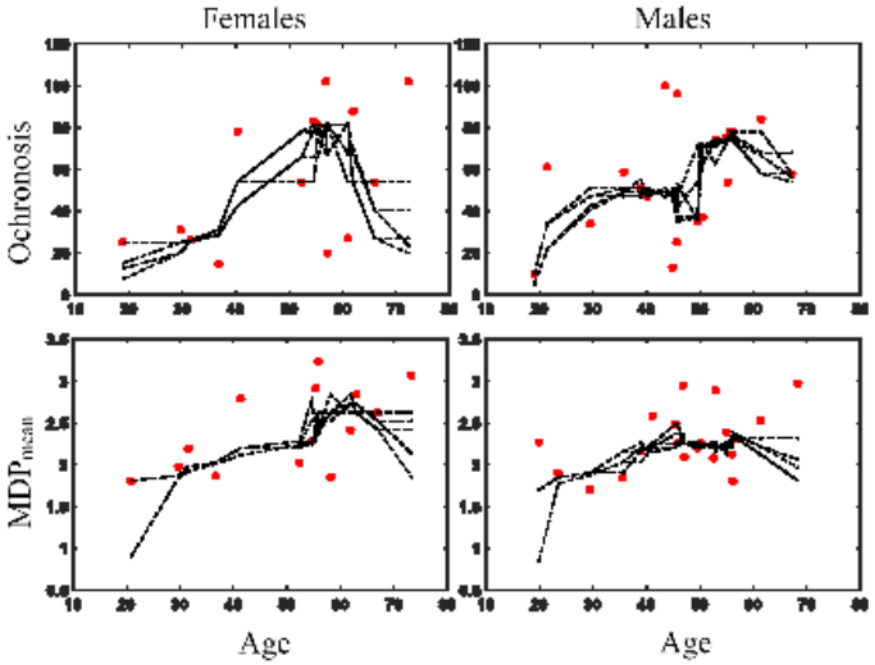

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Appendix 2

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Subclinical ochronosis features in alkaptonuria: a cross-sectional study

Trevor Cox[1], Eftychia Eirini Psarelli[2], Sophie Taylor[3], Hannah Rose Shepherd[4], Mark Robinson[5], Gabor Barton[5], Alpesh Mistry[6], Federica Genovese[7], Daniela Braconi[8], Daniela Giustarini[9], Ranieri Rossi[9], Annalisa Santucci[8], Milad Khedr[10], Andrew Hughes[11], Anna Milan[11], Leah Frances Taylor[12], Elizabeth West[13], Nicolas Sireau[14], Jane Patricia Dillon[15], Nicholas Rhodes[16], James Anthony Gallagher[15], Lakshminarayan Ranganath[17]

Author affiliations +

Abstract

Background Alkaptonuria (AKU) is present from birth, yet clinical effects are considered to appear later in life. Morbidity of AKU, considered irreversible, is secondary to ochronosis. Age of ochronosis onset is not clearly known. Nitisinone profoundly lowers homogentisic acid (HGA), the metabolic defect in AKU. Nitisinone also arrests ochronosis and slows progression of AKU. However, tyrosinaemia post-nitisinone has been associated with corneal keratopathy, rash and cognitive impairment in HT 1. The optimal time to start nitisinone in AKU is unknown.

Methods In an open, cross-sectional, single-site study, 32 patients with AKU were to be recruited. The primary outcome was presence of ochronosis in an ear biopsy. Secondary outcomes included analysis of photographs of eyes/ears, serum/urine HGA, markers of tissue damage/inflammation/oxidation, MRI imaging, gait, quality of life and Alkaptonuria Severity Score Index (qAKUSSI).

Results Thirty patients, with mean age (SD) 38 (14) years, were recruited. Percentage pigmentation within ear biopsies increased with age. Ear pigmentation was detected in a 20-year-old woman implying ochronosis can start in patients before the age of 20. Gait and qAKUSSI were outside the normal range in all the patients with AKU.

Conclusions Ochronosis can be present before age 20 years.

View Full Text

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Appendix 3

Gait deviations in a European cohort with Alkaptonuria

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Introduction: Alkaptonuria (AKU) is an ultra-rare inherited autosomal recessive metabolic disorder [1]. The defected copy of the HGD gene results in a build-up of homogentisic acid (HGA). After the oxidation of HGA, a melanin-like polymer is produced which binds to effectively all fibrous connective tissues and cartilage leading to joint ochronosis [1]. There appears to be a rapid increase of symptoms including ochronosis levels, joint pain [1, 2] and a subsequent decline in gait [3] at the age of ~30 years.

Research Question: How do gait deviations from normality change as a function of age in Alkaptonuria when evaluating a European group of patients?

Methods: A 3D gait analysis using motion capture (Vicon Oxford, UK) was performed on 36 AKU patients (age range: 16 – 70 years, 16 females, 21 males). At the time of testing patients were not taking nitisinone treatment which might have had an effect on their gait. Reflective markers were placed on the lower limbs in accordance with the Helen Hayes model [5]. Patients were asked to walk at a self-selected speed across a 10m walkway. Data were analysed using the Movement Deviation Profile (MDP) [6], by processing each patient's mean corrected marker coordinate data through a self-organising neural network which gave the deviation of gait from normality derived from 10 healthy controls. The MDP_{mean} was used to represent each patient's overall deviation from normality. MDP_{mean} values of the 36 patients were median filtered with a sliding window size of 7 samples.

Results: All but one AKU patients had higher gait deviations from normality than the mean of controls (1.63) and most of them were outside the mean+SD of controls. While the MDP_{mean} values are noisy, the median filtered curve shows an incline of gait deviation around 50 years of age (Figure 1).

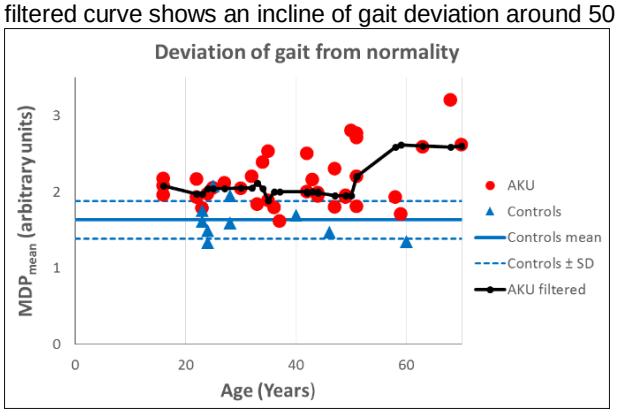

Figure 1: Gait deviations (MDP_{mean}) of Alkaptonuria (AKU) patients and controls as a function of their age. The MDP_{mean} values of patients were median filtered to visualise any trends.

Discussion: Our results show a minimally elevated level of gait deviation between 16 and 50 years of age and a delayed onset of major gait deviations over 50 years. Previous results showed a similar increase of gait deviations in younger patients but an earlier major increase around 35 years of age [3]. Our explanations of the differences are speculative at this stage because only incomplete information is available about the patients to allow a blind evaluation in a larger study. One factor may be that the current cohort is from Europe and not only from the UK and so their genetic profile may be different. The level of protein intake may influence disease progression in AKU and so their dietary habits may also account for the differences. Their physical activity levels and related circulatory load are also unknown and this may also be a factor affecting the timing of symptoms' onset.

Conclusions: Minor gait deviations develop in Alkaptonuria from young age and the rapid onset of major gait deviations can vary depending on the cohort examined, given the multifactorial causation of the onset of symptoms. For a more refined analysis a joint specific deviation of gait from normality is planned.

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Appendix 4

Gait & Posture 65 (2018) 180–181

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Short communication

O 088 - Self-selected gait modifications to reduce the internal knee abduction moment in Alkaptonuria patients

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ARTICLE INFO

Keywords:
Alkaptonuria
Gait modifications
Internal knee abduction moment

1. Introduction

Alkaptonuria (AKU) is an ultra-rare inherited autosomal recessive metabolic disorder [1]. A defected copy of the HGD gene results in a melanin-like polymer being produced binding to all fibrous connective tissues and cartilage leading to joint ochronosis [1]. Evidence shows a rapid increase of symptoms ~30 years including ochronosis levels [1] and a decline in gait [2]. It is evidenced in Osteoarthritis that joint loading of the knees contributes to the degeneration of the articular cartilage [3]. Sharing similar pathologies, it is expected that increased joint loading would accelerate joint disease progression in AKU.

2. Research question

How do AKU patients naturally modify their gait with age to reduce the internal knee abduction moment (IKAM)?

3. Methods

A 3D gait analysis (Vicon Oxford, UK) was conducted on 36 AKU patients (16–70 years, 14♀/22♂) who walked at a self-selected speed across a 10 m walkway. Patients had reflective markers placed on the lower limbs in accordance with the Helen-Hayes model to allow joint angles, moments and powers to be calculated. A healthy control group of 17 (20–60 years, 10♀/ 7♂) were used, data was collected at a variety of speeds (very slow, slow, normal and fast (0.6–2 m/s)) to allow speed-matched comparisons. A 1D independent *t*-test was performed on the gait data using statistical parametric mapping to compare differences between the three age groups (Young:16–29y, Middle:30–49y and Old:50 + y) of AKU patients and their respective speed matched control group (Young to normal (1.30 m/s), Middle/Old to slow (0.96 m/s)). All SPM analyses were conducted using the open-source SPM1D package (v.M0.4, www.spm1d.org) in Matlab (R2017a, Mathworks Inc., Natick, MA, USA) corrected for nine comparisons (alpha = 0.0055).

4. Results

The SPM results from the IKAM (Fig. 1) show a significant decrease with age. The SPM results from the foot progression angle show out-toeing significantly increases with age (Fig. 2). Hip external rotation is significantly increased throughout stance in the old group ($p < 0.001$).

5. Discussion

This study identifies for the first time, an age-adaptation mechanism whereby AKU patients naturally modify their gait to reduce the IKAM which is considered as an indirect measure of joint loading [4] and ultimately joint pain. This is done by out-toeing which mechanically moves the force vector closer to the knee joint centre in the frontal plane reducing the lever arm length, resulting in a reduction of the IKAM. The external hip rotation allows for greater out-toeing seen in the old group. Previous studies focus on the global deviations from normality suggesting that gait deviations are negative outcomes however some deviations could be beneficial compensations to reduce joint loading and pain.

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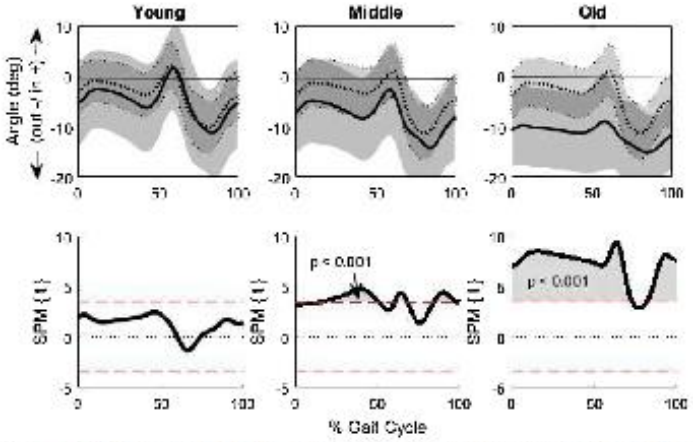

Fig. 1. Foot progression angle mean ± SD for three age groups (AKU = solid, Control = dotted). SPM t-values analysis: dashed lines show the t-thresholds, above which the grey areas indicate significant differences between the curves.

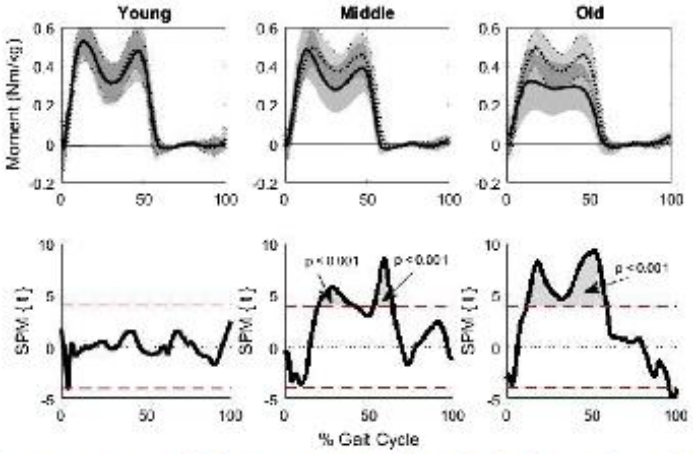

Fig. 2. Internal knee abduction moment mean ± SD for three age groups (AKU = solid, Control = dotted). SPM t-values analysis: dashed lines show the t-thresholds, above which the grey areas indicate significant differences between the curves.

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Appendix 5

Identifying joint specific gait mechanisms in alkaptonuria patients

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Introduction: Gait deviations from normality in Alkaptonuria (AKU) patients have previously been identified using the Movement Deviation Profile (MDP), a gait summary measure [1]. Whilst deviations are likely due to the disease's detrimental effects on structures in the weight bearing joints [2], gait summary measures alone are unable to identify the specific mechanisms contributing to these gait deviations.

Research Question: Can joint specific gait mechanisms in Alkaptonuria patients be identified using Statistical Parametric Mapping (SPM)?

Methods: An over ground 3D gait analysis (Vicon Oxford, UK) was conducted on 36 AKU patients (16 – 70 years, 14♀/22♂) at a self-selected speed using the Helen-Hayes marker model [3]. Joint angles, moments and powers were calculated. For speed-matched comparisons, gait data was collected from 17 healthy controls (20-60 years, 10♀/ 7♂) at 4 speeds (very slow, slow, normal and fast, 0.6-2m/s). A 1D independent t-test was performed throughout the gait cycle using SPM to compare differences within three AKU patient age groups (Young: 16-29y, Middle: 30-49y and Old: 50+y) and their respective speed-matched control group (Young to normal (1.30m/s), Middle/Old to slow (0.96m/s)). All SPM analyses were conducted using the open-source SPM1D package [4] (v.M0.4, www.spm1d.org) in Matlab (R2017a, Mathworks Inc., Natick, MA, USA) correcting for 60 comparisons (alpha=0.00083). The SPM analysis identified significant differences throughout the gait cycles. Neighbouring areas of difference formed significant clusters, the *p*-value of which represents the length (% gait cycle) and amplitude of the difference between healthy and AKU gait. The *p*-values were ranked for each age group and their associated motion and direction described. Any differences found in the swing phase or for <5% of the gait cycle are not reported.

Results: Results are presented in figure 1.

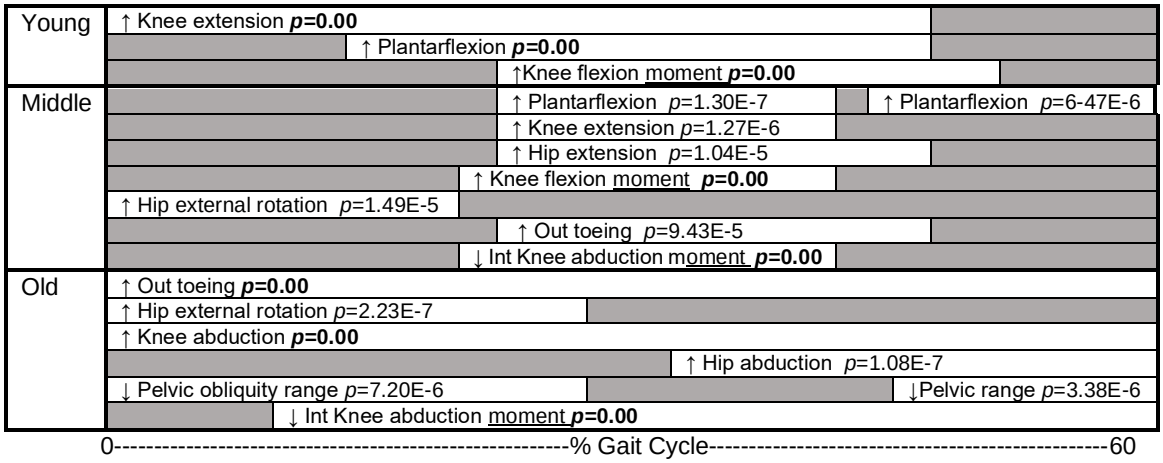

Figure 1: The gait mechanisms for each Alkaptonuria patient age group over the stance phase 0-60% of the gait cycle. In each age group the SPM p-values are ranked, those with the smallest p-value are highlighted in **bold.**

Discussion: Although previous work has shown that structural and physiological changes do not appear in AKU patients until ~30 years [5], this study showed significant gait deviations even in the young group. The joint specific gait mechanisms appeared to change with age. Initially, the young group showed sagittal plane mechanisms which increased the knee extension moment, the effects of this on AKU joint health is unknown. Kinematic mechanisms in the frontal and transverse planes were adopted by the older groups who are typically more affected by AKU. These mechanisms reduced the internal knee abduction moment, likely to avoid pain, without increasing the loading in other joints. The results from this study suggest that for AKU patients, in all age groups, the knee loading is the priority factor when considering the gait deviations from normality.

References: [1] Barton et al., JIMD Rep (2015) 24:39-44. [2] Taylor et al., Rheum (2011) 50:271-277. [3] Davis et al., Hum Mov Sci (1991) 10:575-587. [4] Pataky Comput Methods Biomech Biomed Eng (2012) 15:295-301. [5] Ranganath & Cox, JIMD (2011) 34:1141-1151.

Appendix 6

Inverse dynamics versus a simplified 3D knee joint moment: a potential method for real-time biofeedback during gait modifications.

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[2]National Alkaptonuria Centre, Royal Liverpool University Hospital, Liverpool L7 8XP.

Introduction: When presenting real-time biofeedback to patients with musculoskeletal disorders during gait modification interventions, research typically focuses on reducing the internal knee abduction moment [1]. However, presenting just one component of the knee moment may not give an indication of the total 3D joint moment. Inverse dynamics is the most commonly used and comprehensive method of calculating components of the knee joint moment during gait. However, it can be difficult to present these in real-time due to model and software constraints. Additionally, inverse dynamics has shown significant differences when expressed in various reference frames [2,3]. Alternatively, a simplified total 3D joint moment can be calculated. This can be presented in real-time and provides a single variable representing the total knee joint moment during gait.

Research Question: Does a simplified method of calculating the total 3D knee joint moment compare well to the typically used inverse dynamics method?

Methods: A 3D gait analysis (Vicon, Oxford, UK) was conducted on five healthy adults (age:24±3years, mass:74.0±9.1kg, height:174.8±8.7cm) on the M-Gait treadmill (Motekforce Link, Netherlands) at three speeds (Normal:1.2m/s, Fast:1.6m/s and Slow:0.8m/s). A modified Helen-Hayes model with the addition of medial knee markers was applied. For the simplified method the 3D joint moment was calculated in D-Flow (Motekforce Link, Netherlands) from the positions of medial and lateral knee markers and the force vector by multiplying the distance from the knee joint centre to the force vector (moment arm length) by the magnitude of the 3D force vector. For comparison, inverse dynamics (Visual3D, C-Motion, Germantown, USA) was used to calculate the 3D knee joint moment. All moments were resampled at 300Hz and normalised to body mass. The ratio and root mean square difference between both moment impulses were calculated during stance phase.

Results: Figure 1 shows a single participant's knee joint moments during the 3 walking speeds to demonstrate the closeness of the curve profiles. The ratio between the impulses averaged over participants showed Normal 83±6.5%, Fast 85±4.7% and Slow 79±8.9%. The average absolute difference between impulses averaged across all conditions showed the simplified 3D moment calculation to underestimate by 0.24±0.08Nm.s/kg compared to the inverse dynamics method.

Discussion: The shape of both curves are closely matched. The underestimation of the simplified 3D moment method could be explained by inverse dynamics using a link chain model working algebraically from the ground up [4]. When segmental masses were removed from the inverse dynamics calculation the difference was minimal in the stance phase. The theoretical differences between the two methods should be further investigated and optimised. If the simplified 3D method continues to show good closeness during abnormal gait, it has the potential to be used as a simple variable which represents the total 3D knee joint moment during gait modification interventions.

References: [1] M. Simic, R. S. Hinman, T.V. Wrigley, K.L. Bennell, M. A. Hunt, Gait modification strategies for altering medial knee joint load: a systematic review. Arthrit. Care. Res, 63 (2011) 405-426. https://doi.org/10.1002/acr.20380| [2] J. Lui, T.E. Lockhart, Comparison of 3D joint moments using local and global inverse dynamic approaches among three different age groups, Gait. Posture, 23, (2005) 480-485. https://doi.org/10.1016/j.gaitpost.2005.06.011 [3] Schache & Baker, On the expression of joint moments during gait, Gait. Posture, 25, (2006) 440-452. https://doi.org/10.1016/j.gaitpost.2006.05.018 [4] I. Kingmade, M.P. Looze, H.M Toussaint, H.G. Klijnsma, & T.B.M. Bruijnen, Validation of a full body 3-D dynamics linked segment model. Hum. Mov. Sci, 15, (1996) 833-860. https://doi.org/10.1016/S0167-9457(96)00034-6

Appendix 7

Taking a moment to consider the medial knee thrust: Gait modifications to reduce the 3D knee moment.

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[2]National Alkaptonuria Centre, Royal Liverpool University Hospital, Liverpool, UK. Royal Liverpool University Hospital

Introduction: Gait retraining for osteoarthritis patients typically focus on reducing the frontal plane knee moment peaks by mechanically shortening the moment arm [1]. These peaks are considered a surrogate measurement for the medial compartment load, however during gait modifications, changes in all three knee moment components have been observed [2]. When exactly the frontal plane knee moment is reduced during stance (1st or 2nd peak) also remains unclear [1]. It is therefore appropriate to consider all three planes, and to monitor the changes in the moment throughout the stance phase to understand the effects of gait modifications on the 3D knee moment.**Research Question:** How do gait modifications affect the 3D knee moment throughout stance?
Methods: As a proof of concept, five healthy participants were recruited (27±2.5years, 1.72±0.1m, 76.1±9kg). The M-Gait split belt treadmill was used (Motekforce Link, Netherlands). A custom real-time biofeedback program visually displayed the 3D knee moment impulse as a stair-step plot on a screen. A target 10% reduction from their baseline impulse was also plotted. (Six gait modifications were implemented; toes in, toes out, short strides, trunk sway, medial knee thrust and wide base [1]. Lower limb moments were calculated using inverse dynamics (Visual 3D, C-Motion, Germantown, USA). The 3D knee moment was calculated as the vector sum of its three components, followed by its impulse. Paired sample t-tests compared the six gait modifications to normal gait (SPSS26, IBM, USA), alpha was corrected for multiple comparisons.
Results: Toes out, short strides and wide base significantly reduced the 3D knee moment impulse by 0.056Nm.s/kg, 0.074Nm.s/kg and 0.082Nm.s/kg respectively. No significant differences in the sagittal plane moment impulse. Medial knee thrust, toes out, short strides, trunk sway and wide base all reduced the frontal plane knee moment impulse by 0.072Nm.s/kg, 0.053Nm.s/kg**,** 0.06Nm.s/kg**,** 0.06Nm.s/kg and 0.103Nm.s/kg respectively. Toes in, toes out, short strides and wide base reduced the transverse plane moment impulse by 0.009Nm.s/kg, 0.015Nm.s/kg, 0.014Nm.s/kg and 0.019Nm.s/kg respectively.

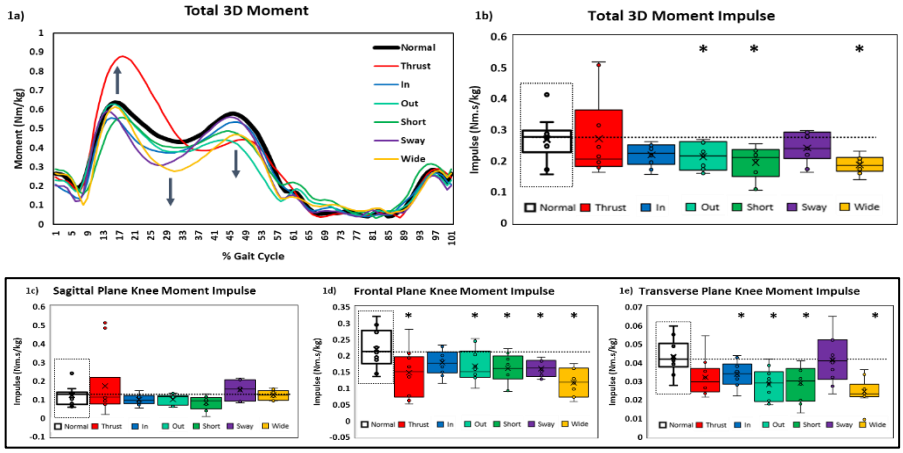

Figure 1: The knee moments during six gait modifications (medial knee thrust: red, toes in: blue, toes out: cyan, short stride: green, trunk sway: purple, wide base: yellow). 1a) shows the total 3D moment trajectory across the gait cycle. 1b) shows the total 3D moment impulse. 1c) shows the sagittal plane moment impulse. 1d) shows the frontal plane moment impulse and 1e) shows the transverse plane moment impulse.

Discussion: Using a novel biofeedback protocol based on the 3D knee moment impulse, only three of the six gait modifications significantly reduced the 3D knee moment impulse. The medial knee thrust reduces the frontal plane impulse as designed, however it does not significantly reduce the 3D moment suggesting a load redistribution. Additionally, from observing figure 1a) each gait modification showed different effects on the 3D knee moment curve at different points of the gait cycle. Compared to normal, the medial knee thrust saw large increases during the first peak, wide base and trunk sway reduced during mid-stance whereas toes out, short strides, wide base and medial thrust reduced second peaks. These results demonstrate the importance of assessing the effectiveness of gait modifications in all three components of the knee moment across the stance phase. **References:** [1] Simic et al. (2011). *Arthritis Care Res (Hoboken),* 63**,** 405-26. [2] Van den Noort et al. (2013). *Hum Mov Sci,* 32**,** 412-24.

Appendix 8 – Gait analysis information sheet for alkaptonuria patients

What are the possible benefits of taking part?

Individual evaluations of how movement is performed can be drawn for participants which can then be used to compare to others.

Will my taking part be kept confidential?

Your identity will be kept confidential using numerical codes during processing. If any photos are taken during testing, the face will be covered. Any personal information given by participants will be protected with passwords and made available only to the researchers.

Travel costs and information:

Travel to and from Liverpool John Moores University will be provided at no cost to you. Further information on this will be provided upon consent to the study.

Kit considerations:

Participants will be required to wear a tight fitted t-shirt and shorts. Participants will be asked to go barefoot during testing but have the option to wear socks if they prefer.

What will become of the results?

A full written analysis of the results will be sent to the National Alkaptonuria Centre. The results may also lead to publications in biomechanics journals and serve as a pilot study for further research.

What are the risks?

Possible risks of this test could involve tripping or falling, a reaction to the double-sided sticky tape used to apply markers and effects to circulation caused by the stretchy bandages. These will all be minimised by testing on a flat surface, using medically approved tape and not applying the bandage straps too tight.

How can I seek independent advice about participation or discuss any problems encountered during or after the test?

You may request additional information through the researchers at the Alkaptonuria Society and at Liverpool John Moores University. Details of contact information for this are given below.

Contact details:

Hannah Shepherd and Professor Gabor Barton

Liverpool John Moores University, Tom Reilly Building, Byrom Street, Liverpool, L3 3AF

Telephone: 0151 904 6263

Email: h.r.shepherd@ljmu.ac.uk

g.j.barton@ljmu.ac.uk

Prof. Lakshminarayan Ranganath

Department of Clinical Biochemistry and Metabolic Medicine, Royal Liverpool University Hospital, Prescot Street, Liverpool, L7 8XP

Telephone: 0151 706 4197

Email: lrang@liv.ac.uk

AKU Alkaptonuria Society — LIVERPOOL JOHN MOORES UNIVERSITY

Participant information sheet

Gait analysis in Alkaptonuria

Invitation to join this study

You are being invited to have a clinical gait analysis to assess how your movement function is affected by Alkaptonuria.

Before you decide, it is important for you to understand why the test is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information.

Take time to decide whether or not you wish to take part. If you decide not to take part, this will not affect the standard care you will receive.

The rest of this leaflet explains the study in more detail and describes what being in the study would mean for you.

What are the possible benefits of taking part?

Individual evaluations of how movement is performed can be drawn for participants which can then be used to compare to others.

Will my taking part be kept confidential?

Your identity will be kept confidential using numerical codes during processing. If any photos are taken during testing, the face will be covered. Any personal information given by participants will be protected with passwords and made available only to the researchers.

Travel costs and information:

Travel to and from Liverpool John Moores University will be provided at no cost to you. Further information on this will be provided upon consent to the study.

Kit considerations:

Participants will be required to wear a tight fitted t-shirt and shorts. Participants will be asked to go barefoot during testing but have the option to wear socks if they prefer.

What will become of the results?

A full written analysis of the results will be sent to the National Alkaptonuria Centre. The results may also lead to publications in biomechanics journals and serve as a pilot study for further research.

What are the risks?

Possible risks of this test could involve tripping or falling, a reaction to the double-sided sticky tape used to apply markers and effects to circulation caused by the stretchy bandages. These will all be minimised by testing on a flat surface, using medically approved tape and not applying the bandage straps too tight.

How can I seek independent advice about participation or discuss any problems encountered during or after the test?

You may request additional information through the researchers at the Alkaptonuria Society and at Liverpool John Moores University. Details of contact information for this are given below.

Contact details:

Hannah Shepherd and Professor Gabor Barton

Liverpool John Moores University, Tom Reilly Building, Byrom Street, Liverpool, L3 3AF

Telephone: 0151 904 6263

Email: h.r.shepherd@ljmu.ac.uk

g.j.barton@ljmu.ac.uk

Prof. Lakshminarayan Ranganath

Department of Clinical Biochemistry and Metabolic Medicine, Royal Liverpool University Hospital, Prescot Street, Liverpool, L7 8XP

Telephone: 0151 706 4197

Email: lrang@liv.ac.uk

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Participant information sheet

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Invitation to join this study

You are being invited to have a clinical gait analysis to assess how your movement function is affected by Alkaptonuria.

Before you decide, it is important for you to understand why the test is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information.

Take time to decide whether or not you wish to take part. If you decide not to take part, this will not affect the standard care you will receive.

The rest of this leaflet explains the study in more detail and describes what being in the study would mean for you.

Appendix 9 – Consent form for alkaptonuria patients

LIVERPOOL JOHN MOORES UNIVERSITY

PARTICIPANT CONSENT FORM

Gait analysis in Alkaptonuria: A series of case studies.

Name of researcher: Hannah Shepherd
Name of supervisor: Dr Gabor Barton

School of Sport and Exercise Sciences, Faculty of Science

1.	I confirm that I have read and understand the information provided for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason and that this will not affect my legal rights.	
3.	I understand that any personal information collected during the study will be anonymised and remain confidential	
4.	I have read, understood and accept all risks	
5.	I give consent to allow the researcher to attach markers to my trunk, hips, knees, ankles and feet	
6.	I understand that any data collected may be used for future publications and research	
7.	I understand that I will be video recorded walking and I am happy to proceed	
8.	I understand that the video recording may be used for future scientific publications or presentations but that my identity will be anonymised and disguised by blurring out my face	
9.	I understand that the video recording may be used for publicity purposes with my identity and showing my face	

I confirm that I understand the full requirements of the study and agree to take part voluntarily in testing.

Name of Participant	Date	Signature
Name of Researcher	Date	Signature

Hannah Shepherd

Name of Person taking consent *(if different from researcher)*	Date	Signature

Appendix 10 – D-Flow Script for the real-time biofeedback of the 3D knee moment impulse

LEFT Script

```
--initalise local variables
LMomImp=LMomImp or 0
LMaxMomImp = LMaxMomImp or 0
Counter = Counter or 0
LV1 = LV1 or 0
LV2 = LV2 or 0
LV3 = LV3 or 0
LV4 = LV4 or 0
LV5 = LV5 or 0
LV6 = LV6 or 0
LV7 = LV7 or 0
LV8 = LV8 or 0
LV9 = LV9 or 0
LV10 = LV10 or 0
LVmean = LVmean or 0

--All inputs from Mocap LEFT
LCoPx=inputs.get(1)
LCoPy=inputs.get(2)
LCoPz=inputs.get(3)
LFx=inputs.get(4)
LFy=inputs.get(5)
LFz=inputs.get(6)
LKneeX=inputs.get(7)
LKneeY=inputs.get(8)
LKneeZ=inputs.get(9)

LMedKneeX=inputs.get(10)
LMedKneeY=inputs.get(11)
LMedKneeZ=inputs.get(12)

--Knee joint centre
LKJCx=((LKneeX+LMedKneeX)/2)
LKJCy=((LKneeY+LMedKneeY)/2)
LKJCz=((LKneeZ+LMedKneeZ)/2)

outputs.set(19,LKJCx)
outputs.set(20,LKJCy)
outputs.set(21,LKJCz)

--Force vector inputs scaled to give position in (m)
LFx_m=LFx/1000
LFy_m=LFy/1000
LFz_m=LFz/1000
```

```
--The x,y,z end position of Force vector
LFendx=LFx_m+LCoPx
LFendy=LFy_m+LCoPy
LFendz=LFz_m+LCoPz

--Flength=math.sqrt(((Fx_m-CoPx)^2)+((Fy_m-CoPy)^2)+((Fz_m-CoPz)^2)) ****
Flength=math.sqrt(((LFx_m)^2)+((LFy_m)^2)+((LFz_m)^2))
CoP_KneeLength=math.sqrt(((LKJCx-LCoPx)^2)+((LKJCy-LCoPy)^2)+((LKJCz-LCoPz)^2))
Fend_KneeLength=math.sqrt(((LFendx-LKJCx)^2)+((LFendy-LKJCy)^2)+((LFendz-LKJCz)^2))

--Cosine rule c^2 = a^2+b^2-2abcos(O)
if Flength==0 then OriginAngle=0 else OriginAngle=math.acos((Flength^2+CoP_KneeLength^2-
Fend_KneeLength^2)/(2*Flength*CoP_KneeLength))
end

--angle in degrees
OriginAngleDeg=math.deg(OriginAngle)

--Moment arm length
MomentArmLength=CoP_KneeLength*math.sin(OriginAngle)

--Force vector length to intersect
IntForceLength=CoP_KneeLength*math.cos(OriginAngle)

--Ratio of Length to intersect on Force vector length
Ratio=IntForceLength/Flength

--Intersect coordinates
Ix=Ratio*(LFendx-LCoPx)+LCoPx
Iy=Ratio*(LFendy-LCoPy)+LCoPy
Iz=Ratio*(LFendz-LCoPz)+LCoPz


--3D GRF magnitude
GRF_mag=math.sqrt(LFx^2+LFy^2+LFz^2)
KneeMoment2=GRF_mag*MomentArmLength
if GRF_mag>30 then Ib=1 else Ib=0
end

--Moment in all 3 directions
LMx=MomentArmLength*LFx
LMy=MomentArmLength*LFy
LMz=MomentArmLength*LFz

--3DMoment
KneeMoment=math.sqrt(LMx^2+LMy^2+LMz^2)

--3DMoment Impulse
```

```
LMomImp=LMomImp+KneeMoment*framedelta()
--trigger event when moment drops to zero for Record module
if (KneeMoment==0 and LMomImp>0) then
Counter = Counter + 1 -- counter of strides
if Counter == 11 then Counter = 1 end
LMaxMomImp = LMomImp
broadcast("LKneeMomentToZero")
end

--Reset Impulse to zero at beginning of swing phase
if KneeMoment==0 then LMomImp=0 end
if Counter == 1 then LV1 = LMaxMomImp end
if Counter == 2 then LV2 = LMaxMomImp end
if Counter == 3 then LV3 = LMaxMomImp end
if Counter == 4 then LV4 = LMaxMomImp end
if Counter == 5 then LV5 = LMaxMomImp end
if Counter == 6 then LV6 = LMaxMomImp end
if Counter == 7 then LV7 = LMaxMomImp end
if Counter == 8 then LV8 = LMaxMomImp end
if Counter == 9 then LV9 = LMaxMomImp end
if Counter == 10 then LV10 = LMaxMomImp end

LVmean = (LV1 + LV2 + LV3 + LV4 + LV5 + LV6 + LV7 + LV8 + LV9 + LV10) / 10
LVmeanReduced = LVmean * .9

--Draw moment arm
-- Knee (xyz)    I (xyz)
MomentArm_RotY=-math.atan((Iz-LKJCz)/(Ix-LKJCx))
MomentArmProjXZ=(Ix-LKJCx)/math.cos(MomentArm_RotY)
MomentArm_RotZ=math.atan((Iy-LKJCy)/MomentArmProjXZ)
-- to degrees
MomentArm_RotY=math.deg(MomentArm_RotY)
MomentArm_RotZ=math.deg(MomentArm_RotZ)

--print(KneeMoment)

outputs.set(1,LFendx)
outputs.set(2,LFendy)
outputs.set(3,LFendz)

outputs.set(4,LCoPx)
outputs.set(5,LCoPy)
outputs.set(6,LCoPz)

--print(OriginAngleDeg,Flength)
--outputs.set(7,OriginAngleDeg)

outputs.set(7,MomentArmLength)
```

```
outputs.set(8,KneeMoment)
outputs.set(9,KneeMoment2)

--outputs for moment arm length visuals--
--Bead1x=KneeX(1-0.1)+Ix*0.1
--Bead1y=KneeY(1-0.1)+Iy*0.1
--Bead1z=KneeZ(1-0.1)+Iz*0.1
outputs.set(10,Ix)
outputs.set(11,Iy)
outputs.set(12,Iz)
outputs.set(13,Ib)
outputs.set(14,LKneeX)
outputs.set(15,LKneeY)
outputs.set(16,LKneeZ)
outputs.set(17,MomentArm_RotY)
outputs.set(18,MomentArm_RotZ)
outputs.set(22,LMomImp)
outputs.set(23,LMaxMomImp)
outputs.set(24,LVmean);
outputs.set(25,LVmeanReduced);
```

RIGHT Script

```
--initalise local variables
RMomImp=RMomImp or 0
RMaxMomImp = RMaxMomImp or 0
Counter = Counter or 0
RV1 = RV1 or 0
RV2 = RV2 or 0
RV3 = RV3 or 0
RV4 = RV4 or 0
RV5 = RV5 or 0
RV6 = RV6 or 0
RV7 = RV7 or 0
RV8 = RV8 or 0
RV9 = RV9 or 0
RV10 = RV10 or 0
RVmean = RVmean or 0

--All inputs from Mocap RIGHT
RCoPx=inputs.get(1)
RCoPy=inputs.get(2)
RCoPz=inputs.get(3)
RFx=inputs.get(4)
RFy=inputs.get(5)
RFz=inputs.get(6)
RKneeX=inputs.get(7)
RKneeY=inputs.get(8)
RKneeZ=inputs.get(9)
```

```
RMedKneeX=inputs.get(10)
RMedKneeY=inputs.get(11)
RMedKneeZ=inputs.get(12)

--Knee joint centre
RKJCx=((RKneeX+RMedKneeX)/2)
RKJCy=((RKneeY+RMedKneeY)/2)
RKJCz=((RKneeZ+RMedKneeZ)/2)

outputs.set(19,RKJCx)
outputs.set(20,RKJCy)
outputs.set(21,RKJCz)

--Force vector inputs scaled to give position in (m)
RFx_m=RFx/1000
RFy_m=RFy/1000
RFz_m=RFz/1000


--The x,y,z end position of Force vector
RFendx=RFx_m+RCoPx
RFendy=RFy_m+RCoPy
RFendz=RFz_m+RCoPz

--Flength=math.sqrt(((Fx_m-CoPx)^2)+((Fy_m-CoPy)^2)+((Fz_m-CoPz)^2))
Flength=math.sqrt(((RFx_m)^2)+((RFy_m)^2)+((RFz_m)^2))
CoP_KneeLength=math.sqrt(((RKJCx-RCoPx)^2)+((RKJCy-RCoPy)^2)+((RKJCz-RCoPz)^2))
Fend_KneeLength=math.sqrt(((RFendx-RKJCx)^2)+((RFendy-RKJCy)^2)+((RFendz-RKJCz)^2))

--Cosine rule c^2 = a^2+b^2-2abcos(O)
if Flength==0 then OriginAngle=0 else OriginAngle=math.acos((Flength^2+CoP_KneeLength^2-
Fend_KneeLength^2)/(2*Flength*CoP_KneeLength))
end

--angle in degrees
OriginAngleDeg=math.deg(OriginAngle)

--Moment arm length
MomentArmLength=CoP_KneeLength*math.sin(OriginAngle)

--Force vector length to intersect
IntForceLength=CoP_KneeLength*math.cos(OriginAngle)

--Ratio of Length to intersect on Force vector length
Ratio=IntForceLength/Flength

--Intersect coordinates
```

```
Ix=Ratio*(RFendx-RCoPx)+RCoPx
Iy=Ratio*(RFendy-RCoPy)+RCoPy
Iz=Ratio*(RFendz-RCoPz)+RCoPz

--3D GRF magnitude
GRF_mag=math.sqrt(RFx^2+RFy^2+RFz^2)
KneeMoment2=GRF_mag*MomentArmLength
if GRF_mag>30 then Ib=1 else Ib=0
end

--Moment in all 3 directions
RMx=MomentArmLength*RFx
RMy=MomentArmLength*RFy
RMz=MomentArmLength*RFz

--3DMoment
KneeMoment=math.sqrt(RMx^2+RMy^2+RMz^2)

--3DMoment Impulse
RMomImp=RMomImp+KneeMoment*framedelta()
--trigger event when moment drops to zero for Record module
if (KneeMoment==0 and RMomImp>0) then
Counter = Counter + 1 -- counter of strides
if Counter == 11 then Counter = 1 end
RMaxMomImp = RMomImp
broadcast("RKneeMomentToZero")
end

--Reset Impulse to zero at beginning of swing phase
if KneeMoment==0 then RMomImp=0 end
if Counter == 1 then RV1 = RMaxMomImp end
if Counter == 2 then RV2 = RMaxMomImp end
if Counter == 3 then RV3 = RMaxMomImp end
if Counter == 4 then RV4 = RMaxMomImp end
if Counter == 5 then RV5 = RMaxMomImp end
if Counter == 6 then RV6 = RMaxMomImp end
if Counter == 7 then RV7 = RMaxMomImp end
if Counter == 8 then RV8 = RMaxMomImp end
if Counter == 9 then RV9 = RMaxMomImp end
if Counter == 10 then RV10 = RMaxMomImp end

RVmean = (RV1 + RV2 + RV3 + RV4 + RV5 + RV6 + RV7 + RV8 + RV9 + RV10) / 10
RVmeanReduced = RVmean * .9

--Draw moment arm
-- Knee (xyz)    I (xyz)
MomentArm_RotY=-math.atan((Iz-RKJCz)/(Ix-RKJCx))
MomentArmProjXZ=(Ix-RKJCx)/math.cos(MomentArm_RotY)
```

```
MomentArm_RotZ=math.atan((Iy-RKJCy)/MomentArmProjXZ)
-- to degrees
MomentArm_RotY=math.deg(MomentArm_RotY)
MomentArm_RotZ=math.deg(MomentArm_RotZ)

--print(KneeMoment)

outputs.set(1,RFendx)
outputs.set(2,RFendy)
outputs.set(3,RFendz)

outputs.set(4,RCoPx)
outputs.set(5,RCoPy)
outputs.set(6,RCoPz)

--print(OriginAngleDeg,Flength)
--outputs.set(7,OriginAngleDeg)

outputs.set(7,MomentArmLength)
outputs.set(8,KneeMoment)
outputs.set(9,KneeMoment2)

--outputs for moment arm length visuals--
--Bead1x=KneeX(1-0.1)+Ix*0.1
--Bead1y=KneeY(1-0.1)+Iy*0.1
--Bead1z=KneeZ(1-0.1)+Iz*0.1
outputs.set(10,Ix)
outputs.set(11,Iy)
outputs.set(12,Iz)
outputs.set(13,Ib)
outputs.set(14,RKneeX)
outputs.set(15,RKneeY)
outputs.set(16,RKneeZ)
outputs.set(17,MomentArm_RotY)
outputs.set(18,MomentArm_RotZ)
outputs.set(22,RMomImp)
outputs.set(23,RMaxMomImp)
outputs.set(24,RVmean);
outputs.set(25,RVmeanReduced);
```

PARTICIPANT INFORMATION SHEET

LIVERPOOL JOHN MOORES UNIVERSITY
Participant Information Sheet

LJMU's Research Ethics Committee Approval Reference:

YOU WILL BE GIVEN A COPY OF THIS INFORMATION SHEET

Title of Study: Can a simplified method of measuring knee abduction moment provide data comparable to that obtained through inverse dynamics?

You are being invited to take part in a study. Before you decide it is important for you to understand why the study us being done and what participation will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for taking the time to read this.

1. Who will conduct the study?

Study Team

Principal Investigator: Miss Hannah Shepherd
Co-investigator: Professor Gabor Barton

School/Faculty within LJMU: School of Sport and Exercise Science, Faculty of Science, LJMU

2. What is the purpose of the study?

The aim of the proposed study is to investigate whether a simplified method of measuring knee moment can provide data comparable to that obtained through inverse dynamics?

3. Why have I been invited to participate?

You have been invited because you may meet the inclusion criteria of the study.
The exclusion / inclusion criteria are if you are between the ages of 18 and 30, are capable of walking unaided and are free from current lower limb injuries or have not suffered any mayor lower limb injuries in the last 12 months.

4. Do I have to take part?

No, participation is voluntary - it is up to you to decide whether or not to take part. You should read this information sheet and if you have any questions you should ask the research team. You should not agree to take part in this research until you have had all your questions answered satisfactorily. If you agree to take part, you will be given this participant information sheet and asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw will not affect your rights.

5. What will happen to me if I take part?

We will talk you through the study procedures and give you the chance to ask any questions. You will be invited to the biomechanics laboratory in LJMU Tom Reilly Building for testing during *one session lasting no longer than 120 minutes*.

1. You will be asked to sign a participant consent form.
2. The researcher will then measure your height and weight in addition to measures of your knee and ankle width.
3. You will have reflective markers attached to your lower limbs and pelvis using double-sided sticky tape with 3D motion capture cameras recording your movement and measures of the force you exert on the treadmill will also be recorded.
4. You will be asked to complete a series of walking trials on a treadmill lasting 7 minutes per condition.
5. Measures will be recorded under two separate conditions:
   A. Normal walking condition
   B. Reduced knee loading conditions:
      - Toes in
      - Toes out
      - Increased step width
      - Increased trunk sway
      - Shorter stride lengths
      - Medial knee thrust

Within each condition you will have 5 minutes to practice. You will also be given a 'Gait modification information booklet' describing each condition.

6. Are there any possible disadvantages or risks from taking part?

There are no identifiable risks to taking part in the study. However, should you get injured before any of the testing sessions then you should withdraw from the study from that point forwards.

7. What are the possible benefits of taking part?

There are no direct benefits to individual participants. However the information gathered may help the researcher identify simplified methods of calculating knee moments during gait.

8. What will happen to the data provided and how will my taking part in this project be kept confidential?

The information you provide as part of the study is the **study data**. Any study data from which you can be identified (e.g. from identifiers such as your name, date of birth, audio recording etc.), is known as **personal data**. This includes more sensitive categories of personal data (**sensitive data**) such as your race; ethnic origin; politics; religion; trade union membership; genetics; biometrics (where used for ID purposes); health; sex life; or sexual orientation.

When you agree to take part in a study, we will use your personal data in the ways needed to conduct and analyse the study and if necessary, to verify and defend, when required, the process and outcomes of the study. Personal data will be accessible to the study team. In addition, responsible members of Liverpool John Moores University may be given access to personal data for monitoring and/or audit of the study to ensure that the study is complying with applicable regulations.

When we do not need to use personal data, it will be deleted or identifiers will be removed. Personal data does not include data that cannot be identified to an individual (e.g. data collected anonymously or where identifiers have been removed). However, your consent form, contact details will be retained for 5 years.

Personal data collected from you will be recorded using a linked code – the link from the code to your identity will be stored securely and separately from the coded data. You will not be identifiable in any ensuing reports or publications.

9. Limits to confidentiality

Please note that confidentiality may not be guaranteed; for example, due to the limited size of the participant sample, the position of the participant or information included in reports, participants might be indirectly identifiable in transcripts and reports. The investigator will work with the participant in an attempt to minimise and manage the potential for indirect identification of participants.

10. What will happen to the results of the study?

The investigator intends to publish results in a PhD thesis and peer-reviewed journal articles.

11. Who is organising the study?

This study is organised by Liverpool John Moores University

12. Who has reviewed this study?

This study has been reviewed by, and received ethics clearance through, the Liverpool John Moores University Research Ethics Committee (Reference number: M20SPS001).

13. What if something goes wrong?

If you have a concern about any aspect of this study, please contact the relevant investigator who will do their best to answer your query. The investigator should acknowledge your concern within 10 working days and give you an indication of how they intend to deal with it. If you wish to make a complaint, please contact the chair of the Liverpool John Moores University Research Ethics Committee (researchethics@ljmu.ac.uk) and your communication will be re-directed to an independent person as appropriate.

14. Data Protection Notice

Liverpool John Moores University is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Liverpool John Moores University will process your personal data for the purpose of research. Research is a task that we perform in the public interest. Liverpool John

Moores University will keep identifiable information about you for 5 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the study to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information at by contacting secretariat@ljmu.ac.uk.
If you are concerned about how your personal data is being processed, please contact LJMU in the first instance at secretariat@ljmu.ac.uk. If you remain unsatisfied, you may wish to contact the Information Commissioner's Office (ICO). Contact details, and details of data subject rights, are available on the ICO website at: https://ico.org.uk/for-organisations/data-protection-reform/overview-of-the-gdpr/individuals-rights/

15. Contact for further information

Miss Hannah Shepherd
h.r.shepherd@2016.ljmu.ac.uk
Prof. Gabor Barton
G.J.Barton@ljmu.ac.uk

Thank you for reading this information sheet and for considering to take part in this study.

Note: A copy of the participant information sheet should be retained by the participant with a copy of the signed consent form.

Appendix 12 – Gait modification consent form

LIVERPOOL JOHN MOORES UNIVERSITY

CONSENT FORM

Title of Project: Can a simplified method of measuring knee moment provide data comparable to that obtained through inverse dynamics?

Name of researcher[s] (student[s]): Hannah Shepherd

Name of Research Supervisor: Gabor Barton

School of Sport and Exercise Science, Faculty of Science, LJMU.

10. I confirm that I have read and understand the information provided for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily ☐

11. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason and that this will not affect my legal rights. ☐

12. I understand that any personal information collected during the study will be anonymised and remain confidential ☐

13. I agree to take part in the above study ☐

Name of Participant Date Signature

Name of Researcher Date Signature

Appendix 13 – Gait modification information sheet

Gait Modifications Information Sheet

Can a simplified method of measuring knee abduction moment provide data comparable to that obtained through inverse dynamics?

***Name of researcher**: Hannah Shepherd*

***Name of Supervisor**: Prof. Gabor Barton*

Research Institute for Sport and Exercise Sciences

Here are examples of the 6 gait modifications you will be asked to do whilst walking on the treadmill.

1. Walking with your toes pointing inwards

Normal

In toeing

2. Walking with your toes pointing outwards

Normal

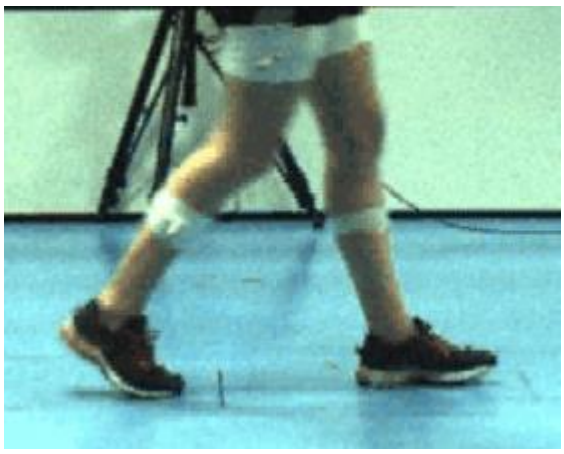
Out toeing

3. Increased side-to-side trunk sway

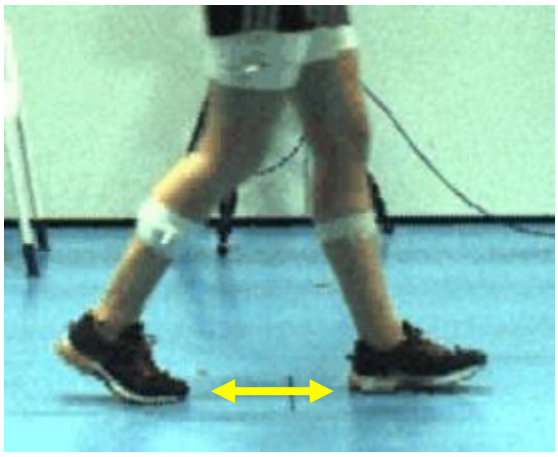
Normal

Trunk Sway

4. Taking shorter strides



Normal



Shorter

5. Changing the distance between your feet (step width)

Normal

Wider

6. Rotate the leg and knee inwards

Normal

Knee Inwards

If there are any questions please do not hesitate to ask, or if at any point of the study you would like to stop please inform the researcher (Hannah Shepherd).

Appendix 14 – Gait modification information sheet for alkaptonuria patients

Gait Modifications Information Sheet for Alkaptonuria

Individualised gait modification strategies in Alkaptonuria patients
***Name of researcher**: Hannah Shepherd*
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The main aim of this intervention is for you to try a new walking pattern that will reduce the amount of loading in your knees during walking.

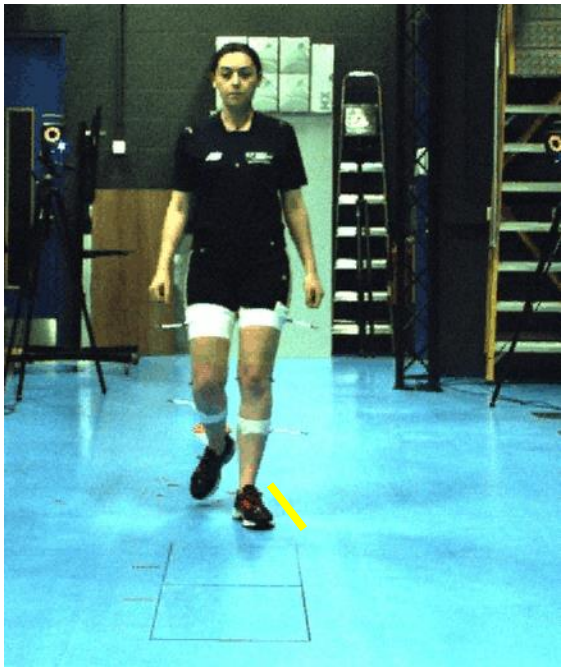
Whilst walking on the treadmill, on the screen in front of you, we will show you the amount of load on your knees during every step.

Firstly, we will record your 'usual' knee loading during walking and this will be used as your baseline score. Then, the goal is to reduce your knee loading below your baseline knee loading score or as low as possible. This can be achieved by subtly modifying the way you walk.

To start you off, here are a few different ways to walk that may help you to reduce your knee loading (Simic et al., 2011).

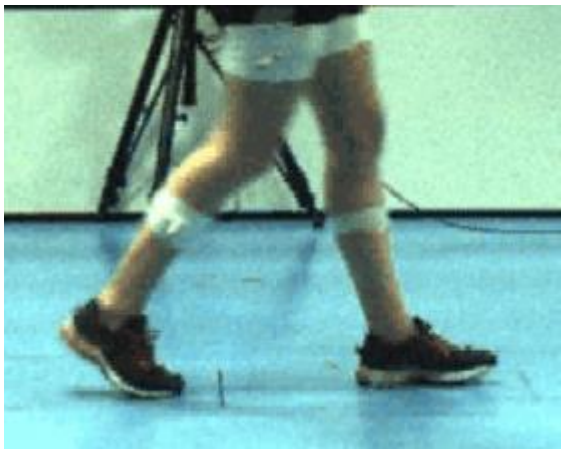
1. **Walking with your toes pointing outwards**

Normal

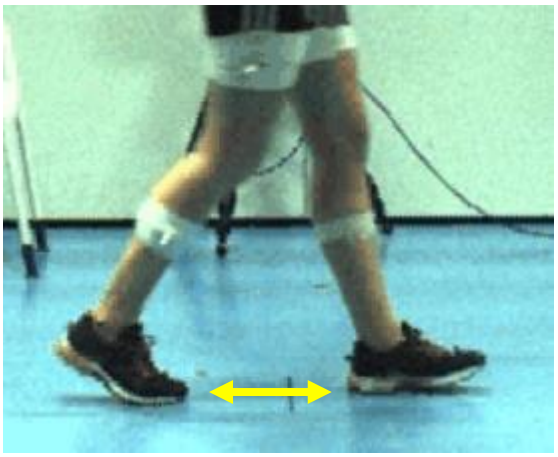


Out toeing

2. **Taking shorter strides**



Normal



Shorter

3. **Changing the distance between your feet (step width)**

Normal

Wider

Try any one, or a combination of these. You are also free to make any other modifications.

However, your new walking pattern should also be:

Symmetrical	Sustainable	Safe
Aim to keep the modification same on both sides of the body	It should be something you would consider permanently and is not too tiring	It should not cause increased pain in other joints

Please note that your individual gait modifications are still experimental at this point, please do not continue any modifications after your visit. Further investigation into the efficiency and safety of each modification will need to be carried out.

If there are any questions please do not hesitate to ask, or if at any point of the intervention you would like to stop please inform the researcher (Hannah Shepherd).