Update on the effects of physical activity on insulin sensitivity in humans

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Abstract

Purpose and Methods: This review presents established knowledge on the effects of physical activity on whole-body insulin sensitivity (SI) and summarises the findings of recent (2013 - 2016) studies.

Discussion and Conclusions: Recent studies provide further evidence to support the notion that regular physical activity reduces the risk of insulin resistance, metabolic syndrome and type 2 diabetes, and SI improves when individuals comply with exercise and/or physical activity guidelines. Many studies indicate a dose response, with higher energy expenditures and higher exercise intensities, including high intensity interval training, producing greater benefits on whole-body SI, although these findings are not unanimous. Aerobic exercise interventions can improve SI without an associated increase in cardiorespiratory fitness as measured by maximal or peak oxygen consumption. Both aerobic and resistance exercise can induce improvements in glycaemic regulation, with some suggestions that exercise regimens including both may be more efficacious than either exercise mode alone. Some studies report exercise-induced benefits to SI that are independent of habitual diet and weight loss, whilst others indicate an association with fat reduction, hence the debate over the relative importance of physical activity and weight loss continues. During exercise, muscle contraction stimulated improvements in SI are associated with increases in AMPK activity, which deactivates TCB1D1, promoting GLUT4 translocation to the cell membrane and thereby increasing glucose uptake. Post-exercise, increases in Akt deactivate TCB1D4 and thereby increase GLUT4 translocation to the cell membrane. The reduction in intramuscular saturated fatty acids (FA) and concomitant reductions in ceramides, but not diacylglycerols (DAGs), provide a potential link between intramuscular lipid content and SI. Increased skeletal muscle capillarisation provides another independent adaptation through which SI is improved, as does enhanced beta cell activity. Recent studies are combining

exercise interventions with dietary and feeding manipulations to investigate the potential for augmenting the exercise induced improvements in SI and glycaemic control.

Key words: Exercise, Physical Activity, Insulin Sensitivity (SI), Diabetes

Introduction

Individuals with poor insulin sensitivity (SI) are characterized by impaired insulin action on whole-body glucose uptake. This results in elevated blood [glucose], impaired glycaemic control, a risk of pancreatic beta cell failure and the development of type 2 diabetes (T2D). In developed countries the prevalence of this pre-diabetic state is currently reported to be 15 – 20%.[1] Furthermore, it is estimated that 366 million people, ~8% of the population are affected by diabetes wordwide,[2] hence strategies for the treatment of the prediabetic state, its prevention and preventing progression from prediabetes to T2D are an imperative. Key amongst these is the inclusion of physical activity into a healthy lifestyle, and current research in this field continues to seek to understand the behavioural and molecular aspects of exercise in preventing diabetes and poor SI, with the intent to identify efficacious exercise interventions.

The comparison of results between research studies into the effects of a physically active lifestyle and/or exercise on insulin sensitivity and glycaemic control are problematic due to differences in the methods of assessment of outcome variables. Whilst the precise protocols vary, the general methods for assessing insulin sensitivity/glycaemic control include: (i) measuring fasting insulin concentrations, with elevated fasted [insulin] >25mIU/L indicating poor insulin sensitivity, as the pancreas endeavours to compensate for the lack of peripheral insulin sensitivity by secreting greater amounts of insulin, thereby resulting in hyperinsulinaemia; (ii) Oral Glucose Tolerance Testing (OGTT), which involves the ingestion of a standard glucose bolus (75 g), followed by blood glucose monitoring for the subsequent 2 hours. Blood glucose concentrations of >7.8 and <11.0 mmol/L at 2 hours are indicative of impaired glycaemic control, and >11.0 mmol/L indicates diabetes; (iii) Hyperinsulinaemic euglycaemic clamp, in which the participant is infused with insulin at a known rate, creating a hyperinsulinaemic state (~100 μU/ml), while simultaneously blood glucose levels are monitored and adjusted by a variable-rate infusion to maintain glycemia (5.0 – 5.5 mmol/L).

A high rate of glucose infusion indicates insulin sensitivity as the glucose is being rapidly taken up by the cells of the body, whilst a low rate of glucose infusion indicates a loss of insulin sensitivity, as the glucose is remaining in the blood rather than being taken up by the cells of the body;[3] (iv) Hyperglycaemic clamp, in which plasma glucose levels are initially increased to ~125mg/dl above basal values and then maintained at this hyperglycaemic level, through the infusion of glucose. High infusion rates indicated good insulin sensitivity, whilst low infusion rates indicate insulin resistance. [3]; (vi) Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), which uses fasting [glucose] and [insulin], and is calculated as (glucose mmol/L x insulin)/ 22.5, with a relatively low score indicating well regulated fasting glucose that is being maintained through relatively low concentrations of insulin, hence good insulin sensitivity, whereas an elevated HOMA-IR value, such as >2.5 indicates insulin resistance. In the updated homeostatic model, HOMA2-IR, values >1.5 suggest insulin resistance; (vii) HOMA-β is a measure of beta-cell function derived from fasting values using the equation (20 x Insulin)/(Glucose mmol/L - 3.5) %. With this measure indicating the extent to which a deficient beta-cell function, as opposed to insulin resistance, contributes to hyperglycaemia in the fasting state; (viii) Quantitative Insulin Sensitivity Check Index (QUICKI), which is an index of insulin sensitivity, calculated as QUICKI = 1/(log (fasting plasma insulin μU/ml) + log (fasting blood glucose mg/dL)). [4]

Regardless of the methods used to assess insulin sensitivity/glycaemic control, a lifestyle incorporating regular physical activity has been identified as a key factor for maintaining and improving many aspects of health, including insulin sensitivity.[5, 6] In this context, the term physical activity covers all forms of muscular movement, including that associated with strenuous physical work, active transport (walking and cycling), household tasks (cleaning and gardening), incidental physical activity which occurs when undertaking other tasks, sport and other active leisure pursuits. Whereas the term ‘exercise’ refers specifically to the context of physical activity that is undertaken with the specific intent of improving health and/or fitness and is therefore a subset of physical activity. Hence many cross-sectional

studies investigate physical activity levels as well as specific exercise habits, but interventions tend to involve exercise, as they have the specific intent of affecting an aspect of health.

Cross-sectional studies identify an association between regular physical activity and/or aerobic fitness and superior SI.[5, 6] Adding further support to this association, studies involving exercise interventions usually report an amelioration or in some cases, complete reversal of insulin resistance.[7, 8] Assessments of the impact of a physically active lifestyle suggest a dose response with each 500 kcal/wk increase in physical activity, reducing the risk of type 2 diabetes by ~9%. [9]

Physical activity has both immediate (acute) and longer term effects on insulin sensitivity. The immediate effects are the direct result of a single exercise bout and may be evident during and/or for up to 72 hours post exercise. If repeated regularly these bouts produce additional long term chronic improvements to SI, thereby providing superior baseline glycaemic control compared to that typically seen in less active individuals. In this healthy, physically active, 'trained' condition, the effects of individual exercise bouts may then produce further acute responses from this already elevated SI state and thereby promote optimal SI and glycaemic control. Some key issues around physical activity that are considered in recent literature include: the effects of manipulating the mode of exercise; the influence of exercise intensity and exercise duration; the potential benefits of high intensity interval training; and the relative effects of the aforementioned on groups of different ages and at different levels of impaired SI. Other innovative strategies that have received recent attention include assessing whether the impact of exercise on SI is affected by whether it is undertaken in a fed or fasted state, and whether a short exercise bout (exercise snack) performed before meals is beneficial.

The purpose of this review is to provide an overview of the topic for those new to it and an update of recent developments for the established researcher.

Methods

A literature search was undertaken using PubMed in in November 2015, using search terms 'Exercise' OR 'Physical activity', AND 'Insulin sensitivity'. This resulted in 10,185 articles, which were then limited to clinical trials (n = 1,672 articles), filtered using the terms 'Human' and limited to English Language publications (n = 1,371). Reviews and key articles published in English since 2000 were used to present established knowledge and set the background context, whilst to identify recent updates the search was reduced to articles published after 2012: this resulted in 394 articles. The abstracts of these articles were then evaluated and studies included if the main focus was an exercise intervention or cross sectional study of physical activity habits and not confounded by the inclusion of other interventions, such as drugs or diseases such as cancer. Studies were excluded if SI or other measures of glycaemic control were not included as an outcome measure. Titles were manually sorted and articles rejected if primary objectives were not exercise-based. They were then divided on the basis of whether they assessed the acute responses that occur during or immediately after a bout of physical activity, or the chronic adaptations that occur over a more prolonged period of time due to repeated exercise bouts – the training effects. A further search using the same search criteria was undertaken in July 2016 when the manuscript was undergoing minor revisions. This identified a further 80 articles that met the criteria of the search terms and the aforementioned manual sorting produced the resultant total of 53 recent articles which are summarised in Tables 1 - 3.

In presenting this review, the authors acknowledge the growing evidence for the adverse effects of sedentary behaviour on diabetes risk and SI, and that this aspect of behaviour needs to be considered in the wider context of metabolic health. Likewise that exercise may benefit the SI of patients with a number of chronic disease conditions, such as cancers, but due to word limits, these scenarios were beyond the scope of this review.

Molecular mechanisms for exercise-induced changes in insulin sensitivity and glycaemic control

Glucose uptake into skeletal muscle occurs via facilitated diffusion down the diffusion gradient through the presence of the glucose transporter GLUT4 in the sarcolemma and T-tubules. A single bout of exercise promotes acute increases in glucose uptake into the skeletal muscle, both during the exercise bout and for some hours post-exercise. This increase occurs as a result of GLUT4 being translocated from intracellular sites to the sarcolemma and T-tubules, thereby increasing the sites at which glucose can diffuse into the muscle. For a detailed review of the processes resulting in increased glucose uptake during exercise, readers are directed to that by Richter and Hargreaves,[10]

In summary, During a bout of exercise the increased contraction-stimulated glucose uptake is linked to increases in AMP-activated protein kinase (AMPK), which results in the phosphorylation of the Rab-GTPase-activating protein TBC1D1.[11] This phosphorylation appears to inactivate the TBC1D1, although there is some suggestion that the TBC1D1 needs to be phosphorylated at both the AMPK and Akt sites for deactivation to occur.[12] Since active TBC1D1 has an inhibitory effect, its deactivation enables GTP to react with Rab proteins on the GLUT4 vesicles, and as a consequence there is an increase in GLUT4 vesicle translocation and glucose uptake into the cell.

It appears that a slightly different pathway is utilised to regulate glucose uptake at rest, and involves TBC1D4 (also known as AS160), the paralogue of TBC1D1. TBC1D4 is involved in the insulin stimulated regulation of GLUT4 translocation and glucose uptake in adipocytes and myocytes. Insulin promotes the phosphorylation of TBC1D4 causing its deactivation and thereby increasing GLUT4 activity. TBC1D4 is also involved in the regulation of glucose uptake post-exercise, when increases in SI are associated with elevated intracellular kinase

Akt, which results in the phosphorylation of TBC1D4.[11] TBC1D4 has similar properties to TBC1D1 and produces similar effects, in that the active form TBC1D4 promotes the hydrolysis of GTP to GDP on Rab proteins, thereby preventing the translocation of GLUT4 to the cell membrane. Whereas when TCB1D4 is phosphorylated and deactivated the GTP reaction with Rab proteins increase GLUT4 translocation to the cell membrane and T tubules, which elevates SI.[13] However, in contrast with TCB1D1, TCB1D4 appears to display a delayed response to exercise/contraction stimuli, with its deactivation exerting an effect post-exercise rather than during exercise, [11] an effect which has also been reported in rats.[14] Regular exercise training may also result in chronic improvements in TBC1D4 phosphorylation and thereby increase basal SI.[11]

Repeated exercise bouts (exercise-training) has been demonstrated to increases GLUT4 concentrations in populations with metabolic syndrome and type 2 diabetes, [15] and these increases are associated with changes in SI.[6, 16, 17] Such improvements are tissue specific, as exercise appears to improve skeletal muscle but not hepatic SI, nor insulin-stimulated glucose uptake in adipose tissue.[18, 19] In addition to which the improvements are primarily located in the muscle fibres undertaking most of the work during the exercise.[20]

Other molecules associated with the SI regulatory processes include insulin receptor substrate 1 (IRS-1) and IRS-2. Whilst the precise roles of these receptor molecules require further elucidation, it is evident that they are activated by the insulin receptor tyrosine kinase and promote the phosphorylation/activation of Akt.[21] Thereby promoting glucose uptake into the cell. Reduced p-IRS-1 (ser^{612}) phosphorylation has been reported in obese and obese insulin-resistant subjects, suggesting an association between lower concentrations of activated IRS-1 and impaired SI. Whereas acute increases in IRS-1 phosphorylation have been demonstrated following a single 60 minute bout of moderate intensity exercise (60% $VO_{2\ peak}$), suggesting an association with increased activation of IRS-1 and improved SI.[22]

Obesity, excess lipid availability and SI

It is well established that obesity and an associated excess of available lipids results in a loss of SI in skeletal muscle, and this may be linked with impaired deactivation of TCB1D4.[23] Paradoxically, whilst obesity increases intramyocellular triglycerides (IMTG) concentrations, so does endurance-exercise training.[24] Yet the skeletal muscles of obese sedentary individuals have a compromised SI, whilst those of well-trained endurance athletes are highly insulin sensitive.[24, 25] Hence there must be distinct molecular basis, other than differences in IMTG concentration to explain their contrasting SI characteristics. Diacylglycerols (DAGs) and ceramides are lipid intermediates that have been proposed to explain this apparent paradox. However, whilst some studies have demonstrated that exercise can reduce DAGs in previously inactive obese individuals, with a concomitant increases in SI,[25, 26] the causative role of DAGs has been questioned as the muscles of endurance trained athletes have been shown to have nearly twice the DAG content of obese sedentary individuals and have a 50% higher DAG content than normal weight sedentary individuals.[27, 28]

Conversely, evidence is accumulating for the view that ceramides (sphingolipid metabolites) may be the causal link between saturated fatty acid content (but not unsaturated fats) in skeletal muscle and impaired SI.[27, 28, 29] In the acute phase, exercise has been demonstrated to increase serum ceramide [30], but these returned to basal levels 2 h post-exercise, whilst the sphingolipids lipids measured in this study were not elevated during exercise but declined to below basal levels post-exercise. However, exercise training has been demonstrated to reduce plasma ceramides and these changes are negatively correlated with increased SI.[31] An explanation for the molecular link between ceramides and SI is through the presence of excess saturated FFA.[29] This explanation suggests that the excess saturated FFA and associated high ceramide content inhibits Akt/PKB

phosphorylation and activation by protein phosphatase 2A, thereby preventing the translocation of Akt/PKB from the cytoplasm to the membrane. This may then link to the aforementioned effects on the activation of other signalling molecules, leading to an impaired translocation of GLUT4 to the membrane.

Other molecular and physiological changes linked to exercise induced improvements to SI

Other molecules that may be linked to aerobic exercise induced changes in SI include intracellular adhesion molecule 1, C-reactive protein and serum amyloid A, all of which have been shown to be associated with impaired SI, but are reduced by exercise and weight loss, thereby suggesting a link with vascular inflammation.[22] Additionally, exercise stimulated increases in glycogen synthase activity, have also been proposed as a factor that increases SI.[23]

Another process through which SI may be improved is through the exercise-training stimulated increase in skeletal muscle capillarisation. Prior *et al*.,[32, 33] reported that increases in capillarisation correlated with improvements in insulin sensitivity following 6 months of aerobic exercise with weight loss in older adults with impaired glucose tolerance. This outcome was further investigated when after 6-months of training the participants followed a 2-week no aerobic exercise washout phase, in order to isolate the acute post-exercise changes in SI from the training effects. The outcome of which was that whilst many of the aforementioned molecular factors returned to baseline after the washout, capillary density and SI remained elevated by 15% and 18% respectively, providing evidence for a link between these two factors.[34]

Additionally, whilst a good level of cardiorespiratory fitness (CRF) is associated with a reduced risk of poor insulin sensitivity, exercise interventions don't always find an association between improvements in SI and CRF ($VO_{2\ max}$). This may be because

improvements in CRF are a result of a combination of both peripheral adaptations within the muscle and central cardiovascular adaptations, such as increases in cardiac output, the latter of which may not impact upon SI directly.[35]

An alternative mechanism by which exercise could improve glycaemic control, is via the enhancement of pancreatic beta cell activity, which can become compromised as a consequence of overstimulation and excessive insulin secretion in response to a loss of SI. In support of this, it has been reported that exercise training plus weight loss can increase pancreatic β-cell function in a linear dose-response manner in adults with pre-diabetes.[34] Although in this study, relatively high exercise doses of >1,900 kcal/wk were used and the exercise intensity increased from 60-65% HR_{max} during the first 4 weeks, to a relatively high 80 – 85% HR_{max} for the following 8 weeks. Hence the intervention was of relatively high volume and intensity, which may not be feasible for most of the population in question. By comparison, Madsen *et al*.,[36] reported improved beta cell function in type 2 diabetic patients following more moderate volumes of exercise training in the form of high intensity interval training (HIIT), hence the exercise intensity may be key. However, Slentz *et al.,* [37] have suggested that whilst both moderate and vigorous exercise are capable of stimulating improvements in beta-cell function as indicated by the Disposition Index (Disposition Index (DI) = Insulin Sensitivity (SI) x Acute Insulin Response to Glucose (AIRg)), they may do so via different mechanisms. Since in their 8-month intervention study, large volumes of moderate intensity exercise produced a greater DI improvement than vigorous exercise, and achieved this with an improvement in SI but virtually no change in AIRg, whilst the vigorous exercise improved SI and resulted in a compensatory reduction in AIRg.

Updates to acute SI responses to exercise

Studies assessing the acute responses during or immediately following a single bout of aerobic exercise suggest that SI is improved by more than 50% for up to 72 hours after the last exercise bout.[6] However, this acute improvement in SI is lost within 5 days after the last exercise bout, even in highly trained subjects.[6]

Table 1 summarises recent studies that assessed acute responses to exercise on SI. Rynders *et al.*'s study confirms the previously reported improvements in SI in prediabetics of around 50% one hour after aerobic exercise.[38] Likewise, Newsom *et al.* reported an increase in SI in sedentary obese adults the day after moderate intensity exercise,[39] indicating that the acute response was evident for some hours. However, whereas Rynders *et al.,*[38] reported higher intensity exercise to produce greater improvements in SI (85% following high intensity exercise vs 51% following moderate intensity exercise), Newsom *et al.,*[39] found that it did not. Indeed Newson *et al.,* reported that their lower intensity (50% $VO_{2\ peak}$) but longer duration bout of the same calorific cost was more effective as it resulted in a statistically significant 35% improvement in SI, whereas their bout at 65% $VO_{2\ peak}$ only resulted in a 20% increase that was not statistically significant. The discrepancy between these studies may at least in part be due to the differences in the 'higher' exercise intensities used in these studies, with Newsom *et al.*'s being of a more 'moderate' rather than 'high' intensity.

302 **Table 1.** Summary of recent studies assessing acute insulin sensitivity responses to exercise

Reference	Participants	Study type	Exercise type and inensity	Outcome measure	Authors conclusions and comments
de Matos *et al*., 2014 [22]	Twenty-seven obese or obese insulin-resistant patients.	Exercise intervention.	Acute 60 min of aerobic exercise on a cycle ergometer at 60 % of peak oxygen consumption.	Compared with paired eutrophic controls, obese subjects had higher basal levels of p-JNK and p-IRS-1(ser612), and reduced HSP70. Exercise reduced p-IRS-1(ser612) for both obese and obese insulin-resistant subjects. A main effect of exercise was observed for HSP70.	A single session of exercise promotes changes that are characteristic of a reduction in cellular stress. Such changes may contribute to an exercise-induced increase in SI.
Rynders *et al*., 2014 [38]	Eighteen pre-diabetic adults.	Randomised controlled trial of acute responses to exercise.	Moderate intensity exercise at Lactate threshold (LT) vs High Intensity Exercise (75% of difference between LT and peak O_2 consumption vs Control (1 hour of seated rest). One hour after exercise, subjects undertook an oral glucose tolerance test (OGTT).	SI improved by 51% following Moderate intensity exercise and 85% following High intensity exercise.	Acute exercise had an immediate and intensity-dependent effect on improving postprandial glycaemia and SI.
Newsom *et al*., 2013 [39]	Eleven sedentary, obese adults.	Randomised controlled trial.	Three experimental trials: (i) exercise at 50% $VO_{2\ peak}$ for ~70 min (expending ~ 350 Kcal); (ii) exercise at 65% $VO_{2\ peak}$ for ~55 min to expend	Seventy minutes of exercise at 50% $VO_{2\ peak}$ increased insulin sensitivity by 35% compared with control condition. Whereas the	A prolonged single session of exercise at a moderate intensity improved SI the next day in obese adults. This may be more effective than a shorter duration bout at a

			350 kcal; (iii) no exercise. Exercise was undertaken in the afternoon SI assessed the following morning.	55 min of exercise at 65% $VO_{2\ peak}$ produced average increase SI of 20% compared to control condition, this was not statistically significant.	higher intensity.
Malin *et al.*, [40],	Fifteen prediabetics aged 49.9 ± 3.6 years	Randomised, controlled, cross over trial, with control condition.	Three trial conditions: (i) 1 hr rest (control); (ii) 200 kcal cycle ergometer exercise bout at lactate threshold; and (iii) 200 kcal cycle ergometer exercise bout at 75% of difference between lactate threshold and $VO_{2\ peak}$. A 75g OGTT was undertaken 1 hr post-exercise/control.	Compared to control, exercise lowered skeletal muscle insulin resistance independently of exercise intensity, but hepatic and adipose insulin resistance was increased. Glucose-stimulated insulin secretion did not differ between conditions, but post-prandial glucose levels were lower post-exercise.	Exercise promoted insulin sensitivity in skeletal muscle post exercise. The increase in insulin resistance in adipose and hepatic tissue, may further promote glucose uptake and glycogen restoration in the muscles.
Ortega *et al*., 2015 [43]	Ten healthy young men.	Randomised cross-over trial with control condition.	Sprint Interval Training (SIT) of 4 x 30 s sprints vs continuous low intensity exercise at 46% $VO_{2\ peak}$ vs moderate intensity exercise at 77% $VO_{2\ peak}$ vs Control. Intravenous glucose tolerance tests undertaken 30 min, 24 h and 48 h post-exercise.	All exercise conditions improved SI for at least 48 h compared to the control condition. Thirty minutes post-exercise the improvements induced by SIT were greater than for either of the continuous exercise bouts.	All exercise bouts improved SI, and in the short-term (30 minutes post-exercise) SIT was more effective than low or moderate intensity continuous exercise at improving SI.
Terada *et al.*, [44],	Ten diabetics aged 45 – 75 years	Randomised, controlled, cross over trial, with control condition.	Four exercise conditions each of 60 minutes duration: (i) HIIT (repetitions of 3 minutes	HIIT reduced overnight and fasting glycemia the day after the exercise by more than moderate	HIIT resulted in acute benefits to glycemic regulation, which were further enhanced by undertaking the exercise in a

			at 40% $VO_{2\ peak}$ and x 1 minute at 100% $VO_{2\ peak}$) in fasted state; (ii) HIIT post-breakfast; (iii) Moderate intensity exercise (55% of $VO_{2\ peak}$) in fasted state; and (iv) and Moderate intensity exercise, post-breakfast; plus no exercise (control).	intensity exercise. Exercising in a fasted state rather than 'post-breakfast' attenuated post-prandial glycemic increments. Compared to the control condition, HIIT in a fasted state produced significant improvements to: 24-h mean glucose, fasting glucose, postprandial glycemic increment, glycemic variability and time spent in hyperglycemia.	fasted state.
Whyte *et al*., 2013 [45]	Ten overweight/obese men aged 26.9 ± 6.2 years.	Randomised, controlled, cross over trial.	Three trial conditions: (i) four maximal 30-s sprints, with 4.5 min recovery between each (SIT); (ii) a single maximal extended sprint (ES) matched with SIT for work done; and (iii) no exercise (CON). Oral glucose tolerance tests were undertaken on the days following each of the above.	SI Index was 44.6% higher following ES than CON, but did not differ significantly between SIT and CON. On the day following exercise, fat oxidation in the fasted state was increased by 63% and 38%, compared to CON, in SIT and ES, respectively.	A single ES, which may represent a more time-efficient alternative to SIT, can increase SI and increase fat oxidation in overweight/obese sedentary men.

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In a more recent study, Malin *et al.*,[40] sought to identify the acute impact of exercise intensity on different components of insulin sensitivity and indicators of glycaemic control, including: glucose-stimulated insulin secretion (GSIS), skeletal muscle insulin resistance (SM_{IR}), hepatic insulin resistance ($HOMA_{IR}$) and adipose insulin resistance ($ADIPOSE_{IR}$). In their study they administered a 75 g OGTT 1 hr post-exercise/control and in their analyses they assessed the relationship between the aforementioned measures and reported that exercise lowered SM_{IR} independently of exercise intensity, but that compared to controls, high intensity exercise (200 kcal cycle ergometer exercise bout at 75% of difference between lactate threshold and $VO_{2\ peak}$) increased $HOMA_{IR}$ and $ADIPOSE_{IR}$: which may initially appear contradictory. However, since GSIS was not reduced post-exercise and the disposition index (DI) of the hepatic and adipose tissues were lowered with high intensity exercise, whilst that of muscle increased, it resulted in a lower post-prandial blood glucose. Based on these findings the authors suggest that insulin secretion from the pancreas matches the combined requirements of these tissues and there is some communication between them to produce this outcome. They also suggest that the elevated $HOMA_{IR}$ and $ADIPOSE_{IR}$ may be beneficial post-exercise, as it could promote greater glucose uptake into the skeletal muscle, in which insulin resistance is lower, and thereby more effectively promote the restoration of muscle glycogen post-exercise.

The variable of exercise intensity is manipulated and taken to greater extremes through the prescription of 'high-intensity interval training' or Sprint Interval Training (SIT), in which relatively short bursts of high intensity exercise are interspersed with lower intensity activity or rest recovery.[41] Gibala *et al.,* [42] propose that the term HIIT be used when repeated short bouts of exercise at intensities of between 80 – 100% HR_{max} are used, whilst protocols that involve repeated short bouts of maximal 'all-out' exercise at intensities greater than the work rate that elicits $VO_{2\ max}$ be classified as SIT.

In the context of studies assessing the impact of short duration, high-intensity exercise, including HIIT and SIT, Ortega *et al.,* [43] found that whilst their high intensity intervals (four x thirty second sprints), continuous low intensity (46% $VO_{2\ peak}$) and moderate intensity (77% $VO_{2\ peak}$) exercise bouts all improved insulin sensitivity in healthy men for at least 48 hrs. The repeated sprints produced the greatest short term effects 30 minutes post exercise. Similarly, the study by Terada *et al.,* [44] reported that 60 minutes of HIIT (repetitions of 3 minutes at 40% $VO_{2\ peak}$ and x 1 minute at 100% $VO_{2\ peak}$), reduced overnight and fasting glycemia the day after the exercise by more than a bout of continuous moderate intensity exercise at 55% of $VO_{2\ peak}$. They also reported that exercising in a fasted state rather than 'post-breakfast' attenuated post-prandial glycemic increments; and compared to the control condition, HIIT in a fasted state produced significant improvements to: 24-h mean glucose, fasting glucose, postprandial glycemic increment, glycemic variability and time spent in hyperglycemia.

In comparison, Whyte *et al.* compared four maximal 30-s sprints with 4.5 min recovery between each (SIT) and a single maximal extended sprint matched for work done.[45] The day following exercise, the SIT session had failed to improve SI over a control (no exercise) condition, but the extended sprint had improved SI by 45%. Hence the failure of SIT to improve SI in this study contradicts the findings of Ortega *et al.,*[43] but raises the possibility of a single bout of high intensity exercise, of relatively short duration (approximately 2 – 3 minutes) being sufficient stimulus to promote the regulatory processes underlying improvements in SI, and this requires further elucidation.

Updates on the association between SI and physical activity - lifestyle studies

Table 2 summarises the results from recent studies assessing potential links between a lifestyle involving regular physical activity and SI. Uemura *et al.'s*[46] survey confirms previous work that demonstrates a link between a lifestyle involving physical activity and better glycaemic control, as did Rosenberger *et al.,*[47] who reported that a lifestyle involving regular walking and other activities reduced by 50% the odds ratio for metabolic syndrome. Similarly, Caro *et al*.,[48] reported a significantly lower (21 vs 46%) prevalence of metabolic syndrome in people who complied with the aerobic exercise guidelines of 30 – 60 minutes of moderate activity 5 days per week.

The importance of lifestyle is evident even in young people as a survey of children found that physical activity was negatively associated with markers of insulin resistance, [49] and the study by Telford *et al*., found that the prevalence of insulin resistance was reduced in primary school age children when physical activity was increased in school.[50]

364 **Table 2.** Summary of recent studies assessing the association between regular physical activity and insulin sensitivity

Reference	Participants	Study type	Physical Activity or other data collected	Outcome measure	Authors conclusions and comments
Uemura *et al*., 2013 [46]	Five hundred and eighteen eligible subjects (380 men and 138 women) who attended the Tokushima Prefectural General Health Checkup Center.	Survey.	Questionnaire on lifestyle characteristics, including leisure-time exercise and daily non-exercise activities.	Subjects with longer durations of daily non-sedentary activities had significantly lower adjusted odds ratios for metabolic syndrome. Daily non-sedentary activities were associated with lower homeostasis model of assessment-Insulin Resistance (HOMA-IR).	A lifestyle involving greater time spent in non-sedentary activities reduced the risk of insulin resistance.
Rosenberger *et al*., 2013 [47]	Three hundred and one overweight/obese pre-diabetics.	Survey of physical activity habits.	Participants reported walking and other activities, and were assessed for factors associated with metabolic syndrome (MetS). Participants were categorised as those with and those without MetS.	18% of subjects with MetS reported at least 150 minutes of activity minutes per week compared with 29.8% of those without MetS. The odds of MetS was lower with greater activity minutes.	Meeting Physical Activity goals of 150 min/wk, reduced MetS odds in overweight/obese pre-diabetic adults.
Caro *et al*., 2013 [48]	One hundred and one adults with no personal history of disease aged 30-70 years.	A cross-sectional, observational study in an adult population. Participants were age- and sex-matched for comparison.	Participants were classified into: (i) those who undertook regular exercise of 30-60 minutes of moderate physical exercise 5 days per wk, and (ii) non exercising controls who exhibited a	Indicators of fasting plasma insulin levels HOMA-IR were significantly lower in the regular physical activity group. Prevalence rates of metabolic syndrome were 20.7% and 45.8% in the regular physical activity and sedentary groups	Moderate regular physical activity is associated with higher SI.

			sedentary lifestyle.	respectively.	
Jiménez-Pavón *et al*., 2013 [49]	One thousand and fifty three boys and girls, aged 12.5 -17.5 years.	A cross-sectional study in a school setting.	Physical Activity (PA) was assessed via accelerometry; Cardio Respiratory Fitness (CRF) assessed via a 20-m shuttle run test. Fasting insulin and glucose concentrations were measured. The HOMA-IR and quantitative SI index were calculated.	In males, vigorous PA (VPA) was negatively associated with markers of resistance (IR) after adjusting for confounders including waist circumference. In females, moderate PA, moderate to vigorous PA, and average PA were negatively associated with markers of IR after adjusting for confounders. When the sample was segmented by CRF levels, all the PA intensities were significantly negatively associated with the markers of IR in females with low CRF but not in those with middle-high CRF after adjusting for confounders.	The findings suggest that PA is negatively associated with markers of IR after adjusting for confounders including total and central body fat in both sexes. This relationship is modified by the CRF levels, which are especially important in those females with low CRF. Preventive strategies should focus not only on increasing the volume of PA but also on enhancing CRF through VPA.
Telford *et al*., 2013 [50]	Seven hundred and eight primary school children, mean age 8.1 ± 0.35 years.	4-yr cluster-randomized intervention study into the effects of specialists vs non-specialists delivering physical education classes.	The intervention involved the employment of specialist Physical Education teachers to deliver PE classes (intervention) in primary schools, rather than delivery by generalist primary	The PE classes delivered by the PE specialists involved more fitness work than the control PE classes delivered by primary generalists (7 vs 1 min) and more moderate physical activity (17 vs 10 min respectively). There were no differences at	Specialist-taught primary school PE increased physical activity in PE classes, and was associated with a lower prevalence of IR in community-based children.

			teachers (control).	baseline, but by grade 6, the intervention had lowered the prevalence of insulin resistance (IR) by 14% in the boys and by 9% in the girls, also the percentage of children with insulin resistance (IR) greater than 3 (a cut off point for metabolic risk) was lower in the intervention than the control group (combined, 22% vs 31%; boys, 12% vs 21%; girls, 32% vs 40%).	

Updates from studies assessing the effects of exercise training upon SI

Exercise training studies generally report health benefits for the majority of participants, providing the exercise dose is of an appropriate intensity, frequency, duration, and undertaken for sufficient time.[7, 20] Meta-analyses and reviews indicate that regular aerobic exercise that complies with exercise prescription guidelines,[51] increases SI by ~25-50%.[6, 8] This training adaptation is likely induced by the increased activity of the muscle fibres, since low intensity aerobic activity, which primarily utilises type 1 fibres, induces changes in type 1 fibres expressing myosin heavy chain (MHC) I, but not type 2 fibres (expressing MHC IIA or MHC IIX).[12] If such adaptations are specific to the fibres that experience increased activity, then this presents the possibility of higher intensity exercise, which involves a greater recruitment of the type 2 fibres, inducing beneficial adaptations in both type 1 and type 2 fibres.

Aerobic exercise interventions, including the assessment of the influence of exercise volume and intensity

Table 3 summarises the results of recent studies assessing the effect of exercise interventions upon SI. Studies consistently show that moderate aerobic exercise for 30 minutes or more, 3 or more times a week for 8 or more weeks improves SI and other markers of glycaemic control. This has been reported in a range of populations including diabetic women,[52] diabetic and impaired glucose tolerance men and women,[53, 54] obese men,[55] obese women,[56] obese and overweight postmenopausal women,[38] obese adolescents,[57, 58] obese patients,[59] sedentary moderately overweight young men,[19, 60] subjects with metabolic syndrome,[61] older obese adults with impaired glucose tolerance,[34] obese adolescent girls,[62] and adults with T2DM and non-alcoholic fatty liver disease.[63]

390 **Table 3.** Summary of recent studies assessing exercise training effects on insulin sensitivity

Reference	Participants	Study type	Exercise mode	Outcome measure	Authors conclusions and comments
Stuart *et al*., 2013 [15]	Eleven participants with the metabolic Syndrome and seven non-diabetic, sedentary controls.	Exercise intervention. Pre-v post intervention comparison.	Eight weeks of increasing intensity stationary cycle training.	Cycle training without weight loss did not change insulin resistance in metabolic syndrome subjects or sedentary controls. Muscle insulin receptor expression increased in both metabolic syndrome and sedentary groups, while GLUT4 expression also increased in the metabolic syndrome subjects. The excess phosphorylation of insulin receptor substrate 1 (IRS-1) at Ser337 in metabolic syndrome muscle tended to increase further after training in spite of a decrease in total IRS-1.	In the absence of weight loss, the cycle training of metabolic syndrome subjects increased the expression of insulin receptors and GLUT4 in muscle but did not decrease the insulin resistance.
Malin *et al.,* 2013 [18]	Twenty four, older, obese adults with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT).	Exercise intervention.	12-wks of exercise (60 min/day, 5 days/wk at ~85% HR_{max}).	Exercise increased clamp-derived peripheral and hepatic SI more in adults with IFG or IGT alone than with IFG + IGT.	Exercise increased peripheral but not hepatic SI.
Reichkendler *et al.,* 2013	Sixty-one, healthy,	Randomised, controlled trial.	Moderate (300 kcal/day)	Aerobic exercise training increased insulin-	Aerobic exercise training enhances glucose uptake in

[19]	sedentary, moderately overweight, young men.		or high (600 kcal/day) physical exercise for 11 wks, vs sedentary living (control). Pre and post training, insulin-stimulated glucose uptake was assessed in five individual femoral muscle groups and four different adipose tissue regions.	stimulated glucose uptake in skeletal muscle but not in adipose tissue.	muscle but not adipose tissues, indicating a differential effect on these tissues.
Prior *et al.,* 2014 [32]	Sixteen, sedentary, overweight-obese, older men and women, with impaired glucose tolerance.	Pre- vs post-intervention comparison.	Six-months of aerobic exercise and weight loss. Three sessions a week progressing from 20 min at 50% heart rate reserve to 45 min at 85% of heart rate reserve.	Hyperinsulinemic-euglycemic clamp and oral glucose tolerance test (OGTT). Capillary density was measured via biopsies of the vastus lateralis.	Insulin sensitivity increased and 120-min post-prandial glucose was lower post-intervention. These changes were associated with increases in capillary density.
Malin *et al.,* 2013 [34]	Thirty five, older, obese, adults with prediabetes.	Exercise intervention.	Progressive 12-wk exercise intervention (60 min at ~85% HR_{max} 5 days/wk).	Exercise increased first- and second-phase disposition index (DI; β-cell function = glucose-stimulated insulin secretion × clamp-derived SI).	Exercise training plus weight loss increased pancreatic β-cell function in a linear dose-response manner in adults with pre-diabetes. Relatively high exercise doses (>2,000 kcal/wk) may be necessary to enhance β-cell function in adults with poor insulin secretion capacity.
Madsen *et al.,* 2015 [36]	Ten, non-active type 2 diabetic patients (56 ± 2 years) and	Pre v post intervention comparison.	Three sessions per week of HIIT (10 x 60s) for 8 weeks for both type 2 diabetics and	Type 2 diabetics displayed significant improvements in HOMA-IR and β cell function. The healthy	HIIT was effective in improving HOMA-IR and β cell function in type 2 diabetics.

	thirteen matched healthy participants.		healthy participants. Glycemic control was assessed using HOMA-IR and β cell function assessed.	group, who displayed superior HOMA-IR and β cell function results at baseline, exhibited no change in these measures, which was not unexpected given their baseline values.	
Brennan *et al.,* 2014 [37]	Seventy seven, sedentary, obese men and women.	Repeated measures, intervention vs control condition.	Three to four months of aerobic exercise vs control	Hyperinsulinemic-euglycemic clamp and $VO_{2\ peak}$.	Changes to insulin sensitivity were not associated with changes to $VO_{2\ peak}$.
de Sousa *et al*., 2014 [40]	Forty-four, type 2 diabetic patients, aged 48-68 years (27 females, 17 males).	Randomized trial: Diet vs Football training plus diet.	Football training: 3 × 40 min/week for 12 weeks.	Football training plus diet group displayed improvements in HOMA-IR, whereas diet alone did not	Football training plus diet was potentially better at preventing T2D complications than diet alone. It was also more effective than diet alone at improving other markers of metabolic and cardiovascular health, such as blood lipid profile and CRF.
Motahari-Tabari, *et al.,* 2014 [52]	Fifty-three, type 2 diabetic women.	Randomized clinical trial: exercise vs control.	Thirty minutes at a maximum intensity of 60% increase in heart rate, 3 times a week for 8 weeks.	HOMA-IR improved and fasting plasma glucose and insulin were lowered.	Exercise was effective at improving SI.
Ryan *et al*., 2014 [53]	Seventy-seven, overweight and obese, sedentary, postmenopausal, women.	Prospective controlled study.	Six months of: 'aerobic exercise (3 d/wk) + weight loss' vs 'weight loss without exercise'.	Insulin resistance decreased in both groups. Glucose utilization increased by 10% with 'aerobic exercise + weight loss' and 8% with 'weight loss without exercise'.	No statistically significant difference in changes to insulin resistance between 'aerobic exercise + weight loss' vs 'weight loss without exercise'. However, exercise benefitted other markers of metabolic health.
Mitranun *et*	43 participants	Randomised	Sedentary (control) vs	Fasting blood glucose	Both continuous and interval

al., 2014 [54]	with type 2 diabetes.	controlled trial.	continuous exercise vs interval training. For 30 and 40 min/day, 3 times/week for 12 weeks.	levels decreased in both exercise groups. Glycosylated haemoglobin levels decreased only in the interval training group.	training were effective in improving glycaemic control, but the interval training program appears to confer greater improvements.
Skleryk *et al*., 2013 [55]	Sixteen, sedentary, obese men.	Exercise intervention.	Two weeks of reduced-volume sprint interval training (SIT) (three sessions of 8-12 × 10 s sprints/wk) compared to traditional exercise recommendations (TER) (5 x 30 min sessions at 65% peak oxygen consumption/wk).	HOMA-IR, AS160 phosphorylation and COX II, COX IV, GLUT-4, Nur77 and SIRT1 protein expression assessed at baseline and approximately 72 h after the final training bout were unaltered in either group.	Two weeks of reduced-volume SIT or TER did not elicit any measurable metabolic adaptations in previously sedentary, obese men.
Trachta *et al*., 2014 [56]	Fifteen, obese women.	Intervention with comparison group comprising of 'healthy' lean subjects who did not undertake the exercise intervention.	Three-month exercise program consisting of 30 min of aerobic exercise, 3 times a week.	HOMA-IR improved in the obese group.	Three months of regular exercise improved, blood glucose and HOMA-IR, but had no significant effect on lipid profile and blood pressure.
Many *et al*., 2013 [57]	Eleven, morbidly obese minority adolescents (BMI 41.4 ± 1.8 kg/m^2)	Exercise intervention.	Eight weeks of aerobic exercise training (~180 min/wk at 40-55% $VO_{2\ peak}$). Pre- and post-intervention, SI and inflammatory markers were assessed.	Insulin action improved in response to training, as indicated by a ~37% increase in SI.	This study supports the efficacy of exercise training interventions on improving metabolic syndrome features in morbidly obese minority youth.
Racil *et al*., 2013 [58]	Thirty-four, obese,	Randomised controlled trial.	Twelve-weeks of moderate-intensity	Significant decrease in insulin resistance (HOMA-	Interval training improved SI. High intensity interval exercise

	adolescent females.		interval training (MIIT) or high-intensity (HIIT) interval training exercise.	IR) occurred in both HIIT and MIIT groups (-29.2 ± 5.3 and -18.4 ± 8.6 %, respectively.	produced greater benefits than moderate intensity interval exercise.
Kurose, *et al*., 2014 [59]	Forty three, obese patients.	Exercise intervention.	Thirty minutes on a cycle ergometer or treadmill, 3 times per week for 6 months, with training intensity adjusted to anaerobic threshold.	HOMA-IR improved.	Aerobic exercise improved SI. Additionally, insulin resistance was the only independent factor influencing improvement in endothelial function.
Reichkendler *et al*., 2014 [60]	Sixty-one, healthy, sedentary, moderately overweight, young men.	Randomised controlled trial.	Eleven weeks of physical activity at moderate dose (300 kcal/day); high dose (600 kcal/day); or sedentary living.	In both exercise groups, peripheral SI improved. Homeostasis model assessment of insulin resistance decreased.	Physical activity improved SI and small additional health benefits were found when exercising at ~3,800 vs ~2,000 kcal/week in young moderately overweight men.
Di Raimondo *et al*., 2014 [61]	One hundred and seventy-six subjects with metabolic syndrome.	Exercise intervention.	Walking for 1 h, 5 days a week for 24 weeks at an intensity higher than the one classified as 'comfortable' by the patient.	Mean fasting glucose improved.	Regular walking at a moderate to hard intensity improved glycaemic control.
Lee *et al*., 2013 [62]	Forty-four, obese, adolescent girls.	Randomised controlled trial.	Three months of 180 min/wk aerobic exercise vs resistance exercise vs a non-exercising control group. SI was evaluated by a 3-h hyperinsulinemic (80 $mU \cdot m^2 \cdot min^{-1}$) euglycemic clamp.	Compared with control, aerobic exercise improved SI but resistance exercise did not.	In obese, adolescent, girls, aerobic exercise but not resistance exercise was effective in improving SI and did so independently of weight loss or calorie restriction.
Bacchi *et al*.,	Thirty-one,	Randomized	Effects of 4-months of	Post-training, SI was	Resistance training and aerobic

2013 [63]	sedentary, adults, with type 2 diabetes, and non-alcoholic fatty liver disease.	controlled trial.	aerobic or resistance training on SI.	increased and hepatic fat content reduced in both groups.	training were both effective in improving SI and reducing hepatic fat content in patients with non-alcoholic fatty liver disease.
Motahari-Tabari *et al*., 2015. [64]	Fifty-three, type 2 diabetic women.	Exercise intervention vs non-exercise control condition.	Eight weeks of walking for 30 minutes three times a week.	Exercise improved HOMA-IR, fasting plasma insulin and glucose.	The exercise intervention was effective in lowering plasma glucose, insulin levels and insulin resistance.
Herzig *et al*., 2014 [65]	One hundred and thirteen pre-diabetic males and females.	Exercise intervention vs non-exercise control condition.	Three sessions of 60 minutes walking per week, for 3 months vs non-exercise control.	The exercise intervention improved HOMA-IR, fasting insulin and glucose.	Compared to controls, the exercise group improved HOMA-IR and fasting insulin, but did not improve $VO_{2\ max}$ or fasting glucose.
Damirchi, *et al*., 2014 [66]	Twenty-one, middle-aged, men with Metabolic Syndrome (MetS).	Exercise, intervention vs control condition.	Six-weeks of aerobic exercise: 3 sessions per week, for 25 – 40 minutes of walking or running at 50 – 60%$VO_{2\ peak}$. Followed by 6 weeks of detraining.	HOMA-IR improved after 6 weeks of training, but had returned to baseline after 6 weeks of detraining.	Regular exercise improved insulin sensitivity, but needs to be maintained as insulin sensitivity is lost if regular exercise ceases.
Solomon *et al*., 2013 [67]	One hundred and five participants, with impaired glucose tolerance or type 2 diabetes.	Observational clinical study.	Twelve to 16 weeks of aerobic exercise training.	Glycosylated haemoglobin, fasting glucose, and 2-hour oral glucose tolerance test were improved post-intervention in 69%, 62%, and 68% of subjects, respectively, while SI improved in 90% of the participants.	Training-induced changes in glycaemic control were related to changes in glucose-stimulated insulin secretion, but not SI. Training-induced changes in β-cell function may be a key determinant of training-induced improvements in glyacemic

					control.
Grieco *et al*., 2013 [68]	Forty-five, healthy, recreationally active, young adults.	Randomised controlled trial.	Six-week exercise intervention. Four groups: moderate-intensity (50% heart rate reserve [HRR]); vigorous-intensity (75% HRR); maximal-intensity intervals (95/50% HRR); and non-exercising control group.	There were no significant changes in insulin effectiveness (homeostasis model assessment (HOMA) and quantitative SI check index (QUICKI) in any exercise group.	The exercise intervention did not significantly affect insulin effectiveness in a young adult population as assessed by HOMA or QUICKI.
Chen *et al*., 2015 [69]	Twenty three, men and women with metabolic syndrome (MetS) and 87 men and women without metabolic syndrome. Mean age 48 and 49 years respectively.	Pre vs post exercise intervention comparison.	Three months home based exercise program of three x 30 minute sessions per week at a moderate intensity of either 'stepper' or 'cardio-dance'.	HOMA-IR was maintained in the non-MetS group (1.8 vs 1.9), but deteriorated in the MetS group (3.6 vs 4.3).	The authors reported that 72% of the non-MetS group but only 39% of the MetS group achieved the minimum exercise compliance, and suggested that this may have affected the poor outcome in the MetS group.
Duvivier *et al*., 2013 [74]	Eighteen, healthy subjects.	Cross-over design to compare daily regimens of activity and exercise.	Four days of each of the following regimens: (i) 14 hr/d sitting; (ii) 13 hr/d sitting + 1 hr/d vigorous exercise; (iii) 8 hr/d sitting + 4 hr/d walking + 2 hr/d standing.	Oral Glucose Tolerance Tests (OGTT) were undertaken the morning after 4 days on each regimen. Area Under the Curve (AUC) for insulin was lower following the walking and standing regimen compared to the others.	Reducing sitting time by walking and standing was more effective than one hour of vigorous exercise in maintaining SI.
Earnest *et*	Men at risk for	Randomised,	Three months of	Twenty-four hour and 72 h	Eucaloric AER and INT appear

al., 2013 [75]	insulin resistance.	controlled, exercise intervention trial.	eucaloric (12 kcal/kg/wk) steady state aerobic training (AER) compared with interval training (INT).	post-exercise fasting OGTT improved. HOMA-IR was improved with INT and AER. Stratification of participants based on pre-training values for HOMA-IR revealed that both low and high HOMA-IR participants demonstrated significant reductions with INT, whereas only high HOMA-IR showed significant improvements with AER.	to affect fasting glucose OGTT similarly. Both INT and AER benefitted those with high HOMA-IR, while INT also benefitted those with low HOMA-IR, thereby suggesting that INT may have a greater impact by benefitting across a wider spectrum of HOMA-IR.
Gillen *et al.,* 2016 [76]	Twenty-five sedentary men (27 ± 8 years)	Randomised control trial.	For 12-weeks, three sessions per week of either: (i) Sprint Interval Training (3 x 20s maximal sprint, interspersed with 2 min cycling recovery at 50W), or (ii) 45 mins of moderate intensity cycling at ~75% HR_{max} (~110W), or (iii) non-exercise control. Insulin sensitivity was assessed via intravenous glucose tolerance tests.	Both exercise regimens produced significant and similar improvements in SI as measure via intravenous glucose tolerance tests performed before and 72 hrs post-exercise. Likewise $VO_{2\ peak}$ improved (~19%) in both exercise groups, as did skeletal muscle mitochondrial content. There were no statistically significant changes in the control group.	Sprint Interval Training produced similar fitness and SI improvements to prolonged moderate intensity exercise, despite requiring a five-fold lower exercise volume and time commitment.
Shepherd *et al.,* 2015 [77]	Ninety, previously inactive volunteers.	Randomised control trial.	Ten weeks, 3 sessions per week of either: (i) HIIT (15 – 60s with target HR >90% HR_{max},	HOMA improved in both groups, but was achieved with less time commitment and greater adherence in	HIIT may provide a time-efficient alternative to continuous moderate intensity exercise.

			with 45 – 120 s active recovery for a total of 18 – 25 minutes, including warm up) or (ii) 30 - 45 min continuous exercise at an intensity ~70% HR_{max}.	the HIIT group.	
Arad *et al.,* 2015 [80]	Twenty-eight overweight/obese African American women.	Randomised control trial, with diet determined to maintain body weight. Exercise intervention n = 14; control n = 14.	For 14-weeks, three sessions per week of HIIT (4 x 30-60s at 75-90% Heart Rate Reserve (HRR) with 180-210s at 50% HRR between high intensity bouts) or non-exercise control. Insulin sensitivity was assessed using 3 hr euglycaemic-hyperinsulinemic clamp.	Whilst some parameters of exercise metabolism improved, there were no improvements in SI compared to control group.	HIIT did not improve SI when weight was maintained.
Lanzi *et al.,* 2015 [81]	Nineteen obese men.	Randomised control trial.	Two week exercise intervention, 4 sessions per week of either: (i) HIIT (10 x 60s at 90% HR_{max}, with 60s recovery), or (ii) 40 -50 min continuous exercise at an intensity identified as that eliciting maximal fat utilisation (Fat_{max}).	Aerobic fitness improved in both groups, but HOMA2-IR only improved in the Fat_{max} group.	In the short-term (2 weeks) exercise training of a continuous moderate intensity (Fat_{max}) was more effective than HIIT at improving glycemic control.
Fisher *et al.,*	Twenty-eight	Randomised	Six weeks, 5 sessions	Post-intervention, both	Both exercise regimens

2015 [82]	sedentary overweight/obese men (20 ± 1.5 y).	control trial.	per week of either: (i) HIIT (twenty minutes comprising of repeated bouts of 30s at 85% of peak Wingate power with 4 min recovery at 15% of peak Wingate power), or (ii) 45 - 60 min continuous exercise at an intensity of 55-65% $VO_{2\ max}$.	exercise groups displayed improvements in SI but neither exercise group displayed statistically significant improvements in HOMA-IR.	improved SI, as determined by OGGT, but not HOMA-IR (fasting insulin (µU/ml) x fasting glucose (mmol/L))
Matsuo *et al.,* 2015 [83]	Twenty-six men with metabolic risk factors.	Randomised control trial.	Eight-week exercise intervention, three sessions per week of either: (i) HIIT, (3 x 3min at~ 80-85% $VO_{2\ peak}$ with 2 min recovery at 50% $VO_{2\ peak}$, or (ii) 40min at 60 – 65% $VO_{2\ peak}$. Followed by four weeks of a low-calorie diet.	Both exercise interventions showed trends for improving HOMA-IR, and this was statistically significant in the HIIT group after the subsequent 4-week low calorie diet.	SI trended towards improvement with both HIIT and moderate intensity exercise, and was further improved with the low calorie diet in the HIIT group.
Inoue *et al*., 2015 [87]	Forty-five, post-pubertal, obese, adolescents.	Pre vs post intervention comparing an aerobic exercise regimen (AT), with two exercise regimens that included both aerobic exercise and resistance exercise (LP and DUP).	Twenty-six weeks of exercise intervention, 3 x 60 minute sessions a week.	Insulin sensitivity (HOMA-IR) improved in both the groups undertaking combined aerobic and resistance training, but statistically significant improvements were not found in the group undertaking aerobic exercise without resistance training (AT).	The combination of aerobic plus resistance exercise improved insulin sensitivity more effectively than aerobic exercise alone.

Dâmaso *et al*., 2014 [88]	One hundred and sixteen, obese, adolescents.	Pre vs post intervention comparing: (i) aerobic exercise regimen, with (ii) aerobic exercise plus resistance exercise regimen.	One year of: (i) an aerobic exercise regimen, or (ii) aerobic exercise plus resistance exercise.	Insulin sensitivity measured as HOMA-IR.	Whilst both exercise regimens improved important clinical parameters, the 'aerobic plus resistance exercise' regimen produced better metabolic outcomes than aerobic exercise alone.
Nikseresht *et al*., 2014 [89]	Thirty-four, sedentary, obese, middle-aged, men.	Exercise, interventions vs control condition.	Twelve weeks, of 3 sessions per week of: (i) 40 – 65 minutes of resistance training; (ii) aerobic interval training (4 x 4 minutes at 80 - 90% HR_{max}, with 3 minutes recovery between intervals); (iii) non-exercise control.	Fasting HOMA-IR.	Compared to control condition, both aerobic interval training and resistance training were equally effective in reducing insulin resistance.
Conceição *et al*., 2013 [90]	Twenty, post-menopausal women.	Exercise intervention, randomised controlled trial.	Resistance training: ten exercises, with 3 × 8-10 maximal repetitions three times per week.	Compared to control group, the resistance training group displayed decreases in fasting blood glucose.	Resistance training performed three times a week may reduce the metabolic syndrome Z-score with concomitant decreases in fasting blood glucose.
Molsted *et al*., 2013 [91]	Twenty-three patients treated by dialysis, with (n = 14) and without (n = 9) impaired glucose tolerance.	Control period, followed by the exercise intervention.	Sixteen weeks of strength training three times a week.	After the strength training, fasting insulin, 2-hr insulin and 'area under the curve' insulin (AUC) were significantly lower in patients with impaired glucose tolerance or type 2 diabetes.	Strength training was associated with a significant improvements in glucose tolerance in patients with impaired glucose tolerance or type 2 diabetes undergoing dialysis. The effect was not associated with muscle hypertrophy.
Mavros *et*	One-hundred and	Participants were	Twelve-months of	Within the resistance	Improvements in metabolic

al., 2013 [92]	three older adults with type 2 diabetes.	randomized to the resistance training intervention or non-exercise control group.	resistance training, 3 days per week, or sham exercise.	training group, changes in HOMA2-IR were associated with changes in skeletal muscle mass and fat mass. Changes in visceral adipose tissue tended to be related to changes in HOMA2-IR.	health in older adults with type 2 diabetes were mediated through improvements in body composition, only if they were achieved through high-intensity progressive resistance training.
Garnett *et al*., 2014 [93]	One-hundred and eleven obese, pre-diabetic, or insulin resistant, adolescents.	Repeated measures, exercise intervention with groups differing in dietary regimen.	Twelve weeks of 45 – 60 minutes, moderate to vigorous circuit training, twice a week.	OGTT following an overnight fast.	SI improved within 12 weeks of commencing the exercise intervention and was still improved compared to baseline at 12 months.
Trussardi Fayh *et al*., 2013 [97]	Forty-eight, obese Individuals, age 31.8 ± 6.0 years.	Randomised clinical trial.	Participants were allocated to a diet-only group or a diet and exercise group. The intervention was maintained until 5% of the initial body weight was lost.	Both regimens produced significant and similar decreases of visceral adipose tissue and HOMA-IR.	Five percent weight loss reduced abdominal fat and insulin resistance in obese individuals, but exercise did not add to the effect of weight loss on the outcome variables.

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A commonly advocated exercise prescription of 3 sessions per week of 30 minutes walking was used by Motahari-Tabari *et al*.,[64] who reported improvements in the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), fasting plasma insulin and fasting glucose in Type 2 diabetic women, following 8 weeks of this aerobic exercise regimen. Likewise, Herzig *et al*.,[65] found that 60 minutes of walking, three times a week for 3 months in pre-diabetics improved HOMA-IR, fasting and 2-h insulin, despite no improvements in fasting 2-h glucose or $VO_{2\ max}$. The finding of an improvement in SI without an improvement in $VO_{2\ max}$ concurs with some previously mentioned studies.[37]

Damirchi *et al*.,[66] also demonstrated an improvement in insulin sensitivity in middle-aged men with Metabolic Syndrome (MetS) following a 6-week aerobic exercise program of 3 sessions per week of 25 – 40 minutes walking or running at 50 – 60% $VO_{2\ peak}$, and also reported the interesting finding that this benefit was lost within 6 weeks of detraining. Solomon *et al*., reported improvements in glucose-stimulated insulin secretion, but not SI in participants with type 2 diabetes or impaired glucose tolerance, [67] and suggested that training-induced changes in β-cell function may be a key determinant of training-induced improvements in glycaemic control. Additionally, Skleryk *et al*., did not find any beneficial changes from 5 days a week of aerobic exercise at 65% $VO_{2\ peak}$ in overweight/obese sedentary males,[55] but their exercise intervention was only for 2 weeks and may not have been of sufficient duration to induce detectable changes. Likewise, Grieco *et al*.'s study on recreationally active young adults did not change insulin effectiveness,[68] although, given that the participants were already recreationally active it may be that their pre-study values were not sufficiently poor to be changed by the relatively short 6-week intervention.

Chen *et al*.'s study also produced results that were not in accordance with similar studies and they suggested that this may have been due to participants' lack of compliance and exercise intensity,[69] with their non-metabolic syndrome group attaining greater compliance and thereby maintaining their SI, whilst their metabolic syndrome group displayed poorer

compliance, which may have contributed to their decline in SI.

One exercise variable that is subject to manipulation in exercise interventions is that of exercise volume, and in general, studies that have examined a possible dose response report additional benefits from higher exercise doses (>1,900 kcal/wk), with increases in SI and improved β-cell function in adults with prediabetes.[34] Whilst such levels of activity may be desirable, compliance is often low even for much lower exercise volumes [70 - 73] and for those who are unable to meet these levels it is evident that much of the health benefit is attained from an exercise dose of only ~1,900 kcal/wk or even less, with only minor additional benefits to fitness, body fat and insulin sensitivity when exercising for 600 kcal/day compared with 300 kcal/day.[60] Indeed the commonly prescribed dose of 5 x 30 min of moderate intensity exercise/wk, which is reported on numerous occasions to be effective, would be around 475 – 950 kcal/wk.

Another exercise variable that is receiving attention in the research is that of exercise intensity, as many of the adaptations that play a role in the exercise-induced increases in SI display a response that is related to the intensity of the activity. For example, while low intensity training such as walking for 30 minutes, 3 – 4 days per week, for 6 months improves markers of glycaemic control (such as 'area under the curve' [AUC] for insulin), a further 6 months of higher intensity exercise (jogging 3- 4 days per week for 6 months) elicits substantially greater improvements.[6] Some reviews suggest that higher intensity exercise (>75% of $VO_{2\ peak}$) is more efficacious than lower intensity (<60% of $VO_{2\ peak}$).[6] However, these findings are equivocal as others have reported that lower intensity activity, such as prolonged bouts of standing and walking are more effective than vigorous exercise of the equivalent energy expenditure in improving insulin sensitivity as indicated by oral glucose tolerance tests.[74] Hence in the context of sustained bouts of continuous exercise the issue of the relative importance of exercise volume in terms of duration or total calorific cost of the

exercise, versus the intensity of the exercise remains to be resolved.

Interval training (HIIT and SIT) that utilise repeated brief bouts of exercise at intensities that are greater than those used in exercise sessions involving a more prolonged single continuous exercise bout has been demonstrated to induce significant increases in GLUT4 protein (up to 260%) and SI (25 – 35%).[17, 54, 58, 75] With the overall outcomes indicating comparable and in some cases superior improvements in SI compared to moderate intensity continuous exercise training [76], despite it involving substantially less time commitment and reduced total exercise volume. Additionally, Earnest et al., [75] found interval training to benefit low $HOMA_{IR}$ patients as well as High $HOMA_{IR}$ patients, whereas moderate intensity aerobic exercise only benefitted the High $HOMA_{IR}$ patients. Hence interval training could be beneficial to both, and for those with relatively mild insulin resistance it may be more effective in preventing further decline and/or restoring SI. As an extension of this, it may be speculated that HIIT could be a more effective preventative exercise regimen for asymptomatic healthy individuals. Furthermore, Madsen *et al.*,[36] reported that HIIT improved both HOMA-IR and β cell function in type 2 diabetic patients, hence it could be beneficial across the insulin resistance spectrum.

Shepherd *et al.*, [77] investigated the efficacy of HIIT in a ‘gym-setting’ with ninety previously inactive volunteers. In this study they reported that both HIIT and moderate intensity exercise improved SI, but HIIT achieved this with less than half the time commitment and greater adherence. Such findings are important given that a ‘lack of time’ remains the most commonly cited barrier to regular exercise participation.[78, 79] This, combined with reports of greater enjoyment when compared with sessions undertaken at a constant high intensity, is likely to improve compliance, although the higher intensity of the exercise may make it unsuitable for some ‘at risk’ individuals with cardiovascular issues. However, not all studies have reported HIIT to improve insulin sensitivity, including those of Arad *et al.*[80] in which

overweight/obese African American women undertook 14-weeks of HIIT (3 sessions a week), whilst maintaining a stable weight and that of Lanzi *et al.*[81] in which moderate intensity exercise was more effective that HIIT in improving HOMA2-IR in obese men, although the exercise intervention for this later study was only 2-weeks. The complexity of the issue is exemplified in the findings of studies such as that of Fisher *et al.,* [82] in which both HIIT and moderate intensity exercise improved SI, as determined by an OGGT, but did not improve insulin resistance as determined by HOMA-IR (fasting insulin (µU/ml) x fasting glucose (mmol/L)). In other work, whilst Matsuo *et al*. [83] reported beneficial trends in HOMA-IR following HIIT as well as moderate intensity exercise, the results only reached statistical significance when the participants went on to follow a 4-week low-calories diet.

Effects of resistance training upon SI

Whilst much of the early research into exercise and SI has focused on aerobic exercise, recent exercise interventions using resistance training (REX) have demonstrated that this mode of exercise can also improve indicators of glycaemic control in a variety of populations, including older overweight individuals with prediabetes [84] and postmenopausal women [85]. However, the training adaptations may not always change all indicators of glycaemic control as Eikenberg *et al*., [84], found that twice weekly resistance training for 12 weeks improved 2 hr OGTT results in their participants who commenced the study with impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), but not in those who commenced with impaired fasting glucose (IFG) without IGT. Likewise, REX did not alter fasting glucose concentrations, AUC or ISI.

At a molecular level, REX consisting of 2 – 3 sessions per week for 8 – 26 weeks, can increase GLUT 4 concentrations and translocation by 30 – 70%, and enhance SI by 10 – 48%.[6, 17, 86] Some studies suggest that these improvements could be partially dependent upon the training stimulus increasing muscle mass, as well as qualitative changes within the

muscle.[86] With the metabolic adaptations potentially involving changes in the type 2A fibres that are likely to be recruited during REX, as well as Type 1 fibres. As indicated elsewhere these adaptations may not be homogeneic between fibre types or exercise modalities. Furthermore, since both endurance exercise and REX increase SI, it is possible that a combination of these two training modalities could have additive benefits,[16] particularly if the molecular targets of these activities differ. Indeed the study by Inoue *et al.*, found that the combination of aerobic plus resistance exercise was better than aerobic exercise alone at improving insulin sensitivity in post-pubertal obese adolescents.[87] These results concur with the findings of Dâmaso *et al*., [88] whose findings also suggested that the combination of aerobic and resistance training had better metabolic outcomes than aerobic training alone for obese adolescents. Furthermore, Nikseresht *et al*.,[89] compared the efficacy of aerobic interval training and resistance training and found them to be equally effective in reducing insulin resistance and fasting insulin levels, but suggested that the aerobic program had better anti-inflammatory effects. Consequently the findings of various studies have contributed towards 'evidence-based' exercise recommendations now including both aerobic and REX guidelines for healthy individuals.[17]

A recent study by Conceição *et al*.,[90] adds further support to the incorporation of REX to improve glycaemic control in postmenopausal women.[90] However, the influence of changes in muscle mass through resistance exercise requires further elucidation since Molstead *et al*., reported improvements in fasting insulin, 2-hr insulin and the AUC for insulin in patients with impaired glucose tolerance or type 2 diabetes who had no increase in muscle mass, [91] whilst Mavros *et al*., reported that in their study the improvements in SI (HOMA2-IR) in older patients with T2DM were associated with changes in skeletal muscle mass.[92] Hence further work is required to elucidate the impact of quantitative (mass) and qualitative changes to the skeletal musculature on SI. Bacchi *et al*., in their study on patients with T2DM and non-alcoholic fatty liver disease found that both REX and aerobic exercise improved SI and reduced hepatic fat content.[63] Likewise, as previously mentioned,

Nikseresht *et al*.,[89] found resistance training to be as effective as aerobic interval training in reducing insulin resistance in obese middle-aged men. Whereas Lee *et al*., did not find REX to improve SI in obese adolescent girls, whilst aerobic exercise did.[62]

Circuit training is another variation of exercise mode, including elements of resistance training and HIIT, as the exercise sessions typically involve brief bouts of high intensity muscular resistance exercise interspersed with rest periods. In studies involving obese 10 – 17 year olds with pre-diabetes and/or insulin resistance, it has been demonstrated to improve insulin sensitivity, when undertaken with a dietary intervention.[93]

The effect of exercising in a fed or fasted state and other exercise-food manipulations

In 2010, Van Proeyen *et al.* [94] published a study in which they fed their participants a fat rich (50% of kcal) hyper-caloric (~+30% kcal/day) diet for 6 weeks. During this time the participants exercised (cycling and running) four times a week (2 x 60min and 2 x 90min). Some of these participants exercised in a fasted state, whilst others ate a carbohydrate rich breakfast ~90 min before the exercise, as well as receiving a carbohydrate drink during the exercise session (CHO-Fed). There was also a non-exercise control group. The overall outcome of this was that the group who trained in a fasted state did not increase their body mass, unlike those in the control and CHO-fed groups. The fasted group also displayed superior improvements in SI compared to the control group, whereas the CHO-fed group did not. Furthermore the fasted group showed greater increases in GLUT4, and elevated AMP-activated protein kinase α phosphorylation. The conclusions being that exercising in a fasted state may enhance the exercise induced benefits to SI, compared to exercising when carbohydrate had been recently ingested. The enhancements of these training effects appear to concur with the improved acute responses when exercising in a fasted state.[44] In related work, as mentioned previously Matsuo *et al*.[83] reported that beneficial changes

551 in HOMA-IR were enhanced when the participants underwent a low-calories diet for 4-weeks
552 following the exercise intervention, even though the exercise intervention had ceased, thus
553 further highlighting the interaction between exercise and diet in influencing SI.

554 Other exercise-feeding manipulations that have received recent attention include
555 undertaking exercise before meals – 'exercise snacks' [95]. From which, findings indicate
556 that brief bouts of exercise (6 x 1min incline walking at 90% HR_{max}) 30 minutes before main
557 meals improved glycemic control in individuals with insulin resistance.

558

559 *Exercise, SI and changes to body mass*

560 Numerous studies have reported that exercise induced improvements in SI are independent
561 of changes to body composition or diet induced weight loss, and that the benefits of exercise
562 and weight loss are additive.[5, 6], as reported by de Sousa *et al.,*[96] who found football
563 training couple with weight loss improved insulin sensitivity and blood lipid profile, whereas
564 weight loss alone did not. However these findings are not unequivocal as some studies
565 report weight loss to be the key component to improving SI, for example, Stuart *et al*., found
566 that aerobic training without weight loss did not improve SI in individuals with metabolic
567 syndrome, whereas exercise with weight loss did, thereby implying that the main influence
568 on improving SI was weight loss rather than exercise.[15] Similarly, Trussardi Fayhn *et al*.,
569 found that exercise training did not add to the effect that weight loss had on improving SI in
570 obese individuals.[97]

571 By way of comparison, several recent studies suggest that the combination of exercise
572 training and diet is more effective than diet alone in improving SI, and even when the
573 additional benefits of exercise plus diet vs diet alone were modest,[62, 94] the inclusion of
574 exercise improved other markers of metabolic health.[53] Likewise, Mavros *et al*., reported
575 that improvements in metabolic health in older patients with T2DM were mediated through

improvements in body composition only if they were achieved through high-intensity progressive REX.[93]

Non-responders and adverse responders to exercise interventions

Whilst there is unequivocal evidence for physical activity improving population and participant group mean values, indicating positive changes in the majority of participants, within the data it is evident that there is considerable variation in the magnitude of response to exercise interventions within the population: with some individuals displaying considerably greater changes in a variety of health-related outcome measures than others, despite adhering to the same exercise regimen.[98] Additionally, the magnitude of change in one factor, such as $VO_{2\ peak}$, is not necessarily associated with the magnitude of change in another factor. For example, in the HART-D study, a 9-month exercise training intervention for patients with T2DM,[99] 57% of participants displayed an increase in their peak oxygen uptake ($VO_{2\ peak}$), whilst the remaining 43% exhibited no change. Of those who did show an improvement, only around two-thirds increased their $VO_{2\ peak}$ by > 5% (high-responders to exercise), and one-third displayed < 5% increase (low-responders to exercise). Yet despite this disparity in the magnitude of change in aerobic capacity, the exercise intervention induced similar improvements in HbA_{1c} and body composition (reduction % body fat) in both responders and non-responders for $VO_{2\ peak}$. Hence the improvements in glycaemic control were associated with participating in the exercise training, but were not associated with changes to aerobic fitness, expressed as percentage improvement in $VO_{2\ peak}$, which was also a finding of the study by Herzig [65].

Furthermore, there is also evidence that a minority of the population may respond adversely to exercise intervention, as reported in the HERITAGE study on 1,687 men and women, in which 126 (8.4%) displayed an adverse change (increase >3.5 mU/L) in fasting insulin.[100]

The underlying reasons for these adverse changes are unknown, but their elucidation may further the cause of individualised exercise prescription.[100]

Conclusion

Recently (published 2013 - 2016) studies involving physical activity confirm previous research findings of its efficacy in improving SI. A lifestyle incorporating aerobic exercise and/or physical activity that complies with the guidelines of being of moderate intensity for at least 30 minutes on 3 – 5 days per week, is associated with improved SI and glycaemic control. Acute improvements in SI (2 – 72 h post exercise) occur after a single bout of exercise and chronic adaptations are evident from training studies involving interventions undertaken for at least 8-weeks. The benefits of physical activity/exercise are evident across all ages from children to older adults, including those categorised as asymptomatic/healthy, pre-diabetic/metabolic syndrome, and patients with T2DM. However, the findings are not unequivocal and even within studies not all indicators of insulin sensitivity and glycaemic control display improvements. Indeed, even with increases in the expression of IRS-1 and GLUT4, decreases in insulin resistance are not guaranteed [69]. A dose response is sometimes evident, and exercise sessions utilising higher intensities, including HIIT and SIT can produce greater benefits to SI, but not always. Indeed there remains the question of whether larger volumes of moderate intensity exercise or lower volumes of higher intensity may not only produce a different magnitude of adaptation, but could do so via stimulating different adaptations. Researchers are also assessing whether lower volume sessions may have the practical advantages of greater compliance, through increased enjoyment and a lesser time commitment, since lack of time is a commonly given reason for non-compliance with exercise recommendations.

Whilst aerobic exercise interventions usually benefit SI, improvements in SI are not always associated with changes to aerobic fitness ($VO_{2\ max}$), for reasons that may be explained by the different adaptations induced by the exercise in the cardiovascular system and peripheral musculature.

REX can improve SI through qualitative changes within the muscle as well as increases in muscle mass but the benefits are not evident in all REX studies. However there is a growing body of evidence for including both aerobic exercise and REX in exercise regimens, as this appears to more effectively improve SI than either mode of exercise alone.

The debate continues over the relative importance of exercise versus weight loss for improving SI and whether the combination of the two is more efficacious for achieving good glycaemic regulation.

The molecular bases for exercise-training-induced improvements in SI are linked to increases in GLUT4 concentration and acute exercise-induced increases in Akt that deactivate TCB1D4 increasing GLUT4 translocation to the membrane, an effect that persists for several hours post-exercise. Additionally, the increased capillarisation of the skeletal muscle is another factor linked to improved SI. The concentration of ceramides within muscle may provide the casual link between a high concentration of intramuscular saturated fatty acids and impaired SI.

Studies in which improvements to SI were not reported may have been a consequence of their interventions involving exercise intensities that were too low, durations that were too short or a population group whose glycaemic control was relatively good at baseline and/or were already ‘recreationally active’, and hence the capacity to change was limited.

What are the new findings?

In addition to adding further support to the established position that a lifestyle that includes regular physical activity is associated with a good SI and exercise interventions can improve SI, evidence is growing for the following key findings:

- Aerobic exercise may increase SI without a measurable increase in $VO_{2\ max}$ or $VO_{2\ peak}$.
- A dose effect may be evident, with greater exercise volumes and higher exercise intensities, including HIIT or SIT, producing greater benefits to SI.
- The combination of aerobic exercise training and REX may be more effective than either exercise mode alone.
- Exercise induced benefits may be augmented by appropriate dietary and feeding manipulations.
- Molecular research has identified key signalling molecules and proteins that are influenced by exercise and provide the link to resultant changes in SI.
- Evidence is accumulating for ceramides to be the causal link between obesity and a reduced SI.

Practical recommendations

- Despite the aforementioned general consensus, not all findings are consistent, and the specific details of the most efficacious forms of exercise/physical activity for improving or maintaining SI require further elucidation in order for exercise prescription to be optimised.
- Research needs to assess the interaction of dietary/feeding manipulations and exercise on SI and glycaemic control, as these may augment the beneficial outcomes of the interventions.

- Future research needs to consider the potential influence of exercise induced improvements to beta cell function and increased muscle capillarisation, alongside the contribution of intramuscular changes that result in improved SI, GLUT4 availability and glycaemic control.
- Studies will also need to consider potential differences in the adaptations induced by different: exercise modalities, Aerobic vs REX; exercise intensities and volumes, including interval training (HIIT and SIT); and differences in the adaptations of different fibre types.
- Likewise, the potential to adapt and improve SI is likely to be influenced by the basal state of the participants: with healthy participants, overweight/obese, pre diabetic metabolic syndrome, and diabetic patients all likely to differ in the magnitude of adaptation and improvement.
- Given the evident benefits of physical activity/exercise interventions for preventing diabetes, even amongst those with metabolic risk factors, studies aimed at identifying effective preventive strategies are paramount in order to prevent further increases in the prevalence of T2D, particularly since only 10% of current clinical trials focus on prevention and only ~12% use behavioural interventions such as physical activity rather than drugs, which are the focus of ~63.1% of studies.[101]

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