Patanwala, I, Molnar, L, Akerboom, K and Lane, KE

Direct access lifestyle training improves liver biochemistry and causes weight loss but uptake is suboptimal in patients with non-alcoholic fatty liver disease.

Title page:

Title of article: Direct access lifestyle training improves liver biochemistry and causes weight loss but uptake is suboptimal in patients with non-alcoholic fatty liver disease.

Authors:

Dr Imran Patanwala[1],

Lili Molnar[2],

Katherine Akerboom[1]

Dr Katie E. Lane[2]

Affiliations

[1]University of Liverpool, Liverpool, United Kingdom; Royal Liverpool and Broadgreen University Hospitals NHS Trust, Gastroenterology and Hepatology, Liverpool, United Kingdom E-mail: Imran.Patanwala@liverpoolft.nhs.uk. [2]Faculty of Science, School of Sport and Exercise Sciences, Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, United Kingdom L17 6BD. E-mail: K.E.Lane@ljmu.ac.uk

Corresponding author:

Dr Katie E. Lane, Faculty of Science, School of Sport and Exercise Sciences, Research Institute for Sport and Exercise Sciences, Liverpool John Moores University, Liverpool, United Kingdom L17 6BD. E-mail: K.E.Lane@ljmu.ac.uk Tel: 01512315204 fax: 01512315204

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None declared

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ETHICAL APPROVAL

Open access referral to lifestyle trainers was a service improvement offered to all patients attending the NAFLD clinic and therefore this was a service evaluation study, which did not need ethical approval. Data extracted for analysis was anonymised at source.

Authorship contributor statement:

IP (Guarantor of the article) contributed to study design, article scrutiny, draft writing and agreed the final version. LM conducted the data collection and statistical analyses and agreed the final version of the article. KA coordinated the lifestyle trainers and organised the intervention. KEL (Guarantor of the article) composed article drafts including the final version.

ORCID ID'S

Imran Patanwala 0000-0003-4541-5886

Katie E. Lane 0000-0002-9092-2927

Abstract:

Objective: To evaluate the uptake and effectiveness of an existing open access lifestyle intervention forged in collaboration between a third sector organisation, funded by local government and a secondary care non-alcoholic fatty liver disease (NAFLD) service in the North West of England.

Method: A service outcome evaluation using pre-post comparison design was conducted to analyse changes between baseline clinical health records and 12 week follow up for NAFLD patients who completed the lifestyle intervention. Lifestyle factors, weight loss, changes in alanine aminotransferase (ALT) enzymes and lipid profiles were compared between patients who completed the programme versus 1:1 matched patients who did not.

Results: Only 16 of 167 NAFLD patients offered the intervention completed the programme. Intervention patients achieved significant weight loss (-2.3% $p \leq 0.05$) over 12 weeks, where the non-intervention group had non-significant weight gain (+0.95%). ALT improved by 20IU/L in the interventional group and 15 IU/L in the non-intervention group; however, this was not statistically different.

Conclusion: This study presents first of its kind evaluation of a service collaboration in the UK. Only 1 in 10 patients offered the opportunity completed the programme, a limitation that could affect future strategies. Patient and public involvement research is needed to identify barriers to participation, address adherence issues and identify support mechanisms for lifestyle interventions with NAFLD patients.

Short summary:

1. What is already known about this subject?

- Non-alcoholic fatty liver disease (NAFLD) represents a looming public health crisis with estimated prevalence of 20-30% of the population and younger generations increasingly becoming affected.
- Lifestyle intervention is the first line treatment; however, participation rates are low in NAFLD patients and there is a lack of available localised support schemes.

2. What are the new findings?

- This study presents a first of its kind service evaluation of a collaboration in the UK successfully providing a privately delivered, open access lifestyle training programme funded by local government and embedded in a secondary care NAFLD care pathway.
- Less than 10% of patients offered the intervention completed the 12 week program. NAFLD patients in the lifestyle intervention group achieved significant weight loss (-2.3% $p \leq 0.05$) coupled with significant improvements to body mass index (BMI) (-0.76 kg/m^2 $p \leq 0.05$).
- Alanine aminotransferase (ALT) enzyme levels improved by 20IU / L, however this was not significant, possibly due to the short study duration.

3. How might it impact on clinical practice in the foreseeable future?

- Second tier weight management service providers may offer value in specific patient cohorts, such as those with NAFLD. However, prior to commissioning services such as lifestyle training more research is needed into the reasons for its low uptake in NAFLD

patients and to consider holistic behavioural modification to increase the effectiveness of intervention programmes.

Keywords: Non-alcoholic fatty liver disease, lifestyle intervention, weight loss, alanine aminotransferase enzyme, lipid profiles

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) represents a looming public health crisis and during the next decade is expected to become the primary cause of end stage liver disease and transplantation[1]. Lifestyle intervention is the first line treatment for NAFLD patients, however there is a lack of available localised support schemes and intervention participation rates are low in NAFLD patients[2 3].

Estimated prevalence of NAFLD in the general British population is 20-30% with younger generations increasingly becoming affected[2]. NAFLD occurs due to accumulation of liver fat (steatosis) usually as a consequence of the metabolic syndrome (MetS), a combination of insulin resistance, dyslipidaemia, obesity and hypertension leading to generation of lipotoxic intermediates, and a cycle of liver cell stress, inflammation and fibrosis[4]. Approximately one in five people (5% of the population) who have NAFLD will go on to develop the more serious non-alcohol related steatohepatitis (NASH), where the liver becomes inflamed[2 5]. Progression to cirrhosis, the most serious stage of NAFLD has increased dramatically over the last 10 years. NAFLD is evolving to become the commonest cause for hepatocellular cancer (HCC) and liver transplant in the western world[6].

Obesity is closely associated with NAFLD and NHS spending on conditions linked to obesity reached more than £6.05bn per annum in 2017[7]. NAFLD and NASH are typically asymptomatic and medical attention is frequently devoted to the other associated features of MetS including obesity, insulin resistance, type 2 diabetes, hyperlipidaemia and hypertension, which also affect prognosis, increasing the risk of cardiovascular mortality in this group of patients[4]. In fact, mortality in patients with NAFLD is predominantly due to non-hepatic comorbidity. Coupled with obesity related comorbidities there are clear associations of NASH with increased risk of cardiovascular disease (CVD), cerebrovascular disease[8], malignancy[9], and abnormal lipoprotein subclasses[8 10]. In addition, emerging evidence suggests links to poor coronavirus disease 19 (COVID-19) outcomes in NAFLD patients possibly linked to immune dysregulation both intrahepatic and extrahepatic with a higher risk of progression to severe COVID-19 and longer viral shedding time in a cohort of 202 COVID-19 patients studied in China[11].

Lifestyle modification to lose 7-10% of total body weight by diet and exercise is the first line treatment for NAFLD[2 6 12], however evidence suggests that 50% of patients do not adhere to lifestyle interventions[13-15]. Coupled with this a lack service provision for the management of MetS and the need for improved access to lifestyle interventions were identified as key issues in a cross-sectional survey of 175 UK gastroenterologists and hepatologists regarding NAFLD diagnosis and management[4]. The long term NHS plan of universalised personalised care[16] using social prescribing to improve access to better lifestyle has not yet found its roots and the delivery of such a system may take some time to set up. Some local authorities in England commission second tier weight management services and whilst their value in reducing the prevalence of obesity in the general population is unclear[17], they may offer value in specific patient cohorts, such as those with NAFLD.

Moreover, they present an opportunity for the NHS to collaborate with non-healthcare organisations and private sector companies to optimise outcomes for this patient cohort.

The aim of this study was to evaluate the uptake and effectiveness of an existing open access lifestyle intervention forged out of a collaboration between a privately run lifestyle intervention service, funded by local government and a secondary care NAFLD service based in the North West of England.

METHODS

Participants and Design

A service outcome evaluation using pre-post comparison design was conducted to analyse changes between first visit clinical health records and after 12 weeks follow up for NAFLD patients who were offered and completed the lifestyle intervention to determine if improvements occurred. The study evaluated an existing programme of lifestyle intervention in a secondary care clinic as part of a care pathway for NAFLD management. All patients attending a dedicated multidisciplinary NAFLD clinic at the Royal Liverpool and Broadgreen University Hospitals NHS Trust from April 2018 to March 2019 were offered a referral to a lifestyle trainer programme funded by Liverpool Council. The diagnosis of NAFLD was made in a pragmatic real world setting using a combination of non-invasive blood test and biomarkers, negative imaging, values of controlled attenuation parameter (CAP) obtained at liver stiffness measurements and/or histology and in the absence of excessive and/or harmful alcohol consumption (equating to less than 14 units of alcohol per week for men and women[18]) and secondary causes for fatty liver disease.

The lifestyle intervention programme involved the patient seeing a health trainer in community hubs or GP practices weekly or fortnightly for 12 weeks. Personalised advice and support was offered to complete objectives in a Personalised Health Plan (PHP) based on Public Health England (PHE) guidelines[19]. The PHP had a holistic approach towards wellbeing, and examined patients eating; drinking and smoking habits; physical fitness, self-confidence; starting weight and height were also measured. Guidance and recommendations followed PHE Guidelines (e.g. Physical activity guidelines[19] for adults and The Eatwell Guide[20]), and aimed to bring patients lifestyles closer to the guideline recommendations. Patients were asked to record everything they consumed in a 7-day estimated intakes food diary during the weeks prior to baseline and study endpoint[21]. Patients were asked to rank their emotional wellbeing on a scale of 0 to 100 and key health indicators such as BMI; consumption of fruit, vegetables, dairy products and fried foods were recorded at baseline and endpoint. Weight loss, changes in alanine aminotransferase (ALT) enzymes and lipid profiles were compared between patients who completed the programme and matched patients who did not.

An equal sized control group of age and sex matched patients (Table 1) who were offered but did not opt in to the programme were selected with a 1:1 ratio to measure naturally occurring changes not caused by the intervention. The group that did not take part in the intervention were not aware their biochemistry would be compared to the group that completed the intervention although they did visit the clinic at the same time points and duration. Clinical health record data was collected for both groups at baseline visit and at the 12 week follow up.

Data analysis

Anonymised data was analysed using Statistical Package for the Social Sciences (SPSS), version 26 (IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp) statistical software.

RESULTS

Lifestyle intervention was offered to 167 NAFLD patients. A total of 16 (9.6%, 95% CI 6% - 15%) patients completed the 12 week programme. Median age of the intervention cohort was 58 years, half the cohort were female. There were no significant differences between the intervention and non-intervention (control) groups with regards to age, sex, weight, total cholesterol, triglycerides and ALT (Table 1)

Table 1 - Demographic data, anthropometric variables, metabolic syndrome parameters, and ALT levels for intervention and non-intervention patients at baseline.

	Intervention (*n*=16)	**Non-intervention (*n*=16)**	***P***
Age (y)†	53.50 ± 14.17	52.81 ± 13.18	0.836
Male/female‡	8/8	8/8	1.00
Initial weight (kg)	105.09 ± 24.61	97.96 ± 24.46	0.213
TC (mmol/L)	4.68 ± 1.83	4.45 ± 0.93	0.594
TGL (mg/dL)	3.7 ± 5.28	2.35 ± 2.28	0.462
ALT (IU/L)	76.27 ± 69.41	79.63 ± 117.86	0.187

TC, total cholesterol; TGL, triglyceride; ALT alanine aminotransferase. Values are expressed as mean ± SD. † Mann-Whitney test. ‡Chi-square test; $P < 0.05$*.

NAFLD patients in the intervention group achieved significant weight loss (-2.3% $p \leq 0.05$) coupled with significant improvements to BMI (-0.76 kg/m^2 $p \leq 0.05$) over the study duration in comparison to baseline measurements whilst the non-intervention group were noted to have non-significant weight gain (+0.95%). A reduction in ALT was noted in both groups (- 20.6

IU/L vs -15.75 IU/L p = 0.579) but this was non-significant compared to baseline and between groups. Similarly, there was no impact of the intervention or weight loss on the total cholesterol or triglyceride levels pre and post intervention (Tables 1, 2 and 3).

Table 2 - Comparison of weight loss, changes in lipid profile and ALT levels for intervention and non-intervention patients

TC, total cholesterol; TGL, triglyceride; ALT, alanine aminotransferase. Values are expressed as mean ± SD. *$P \leq 0.05$ (Wilcoxon signed rank test).

	Intervention (*n*=16)	**Non-intervention (*n*=16)**	***P***
Weight (kg)	2.78 ± 3.98	-0.95 ± 2.47	0.021*
TC (mmol/L)	0.22 ± 1.04	0.07 ± 0.36	0.665
TGL (mg/dL)	0.18 ± 1.03	-0.8 ± 0.49	0.456
ALT (IU/L)	20.60 ± 46.58	15.75 ± 47.67	0.451

Table 3 - Comparison of weight, lipid profiles and ALT levels for intervention and non-intervention patients at baseline and endpoint

	Intervention (*n*=16)			**Non-intervention (*n*=16)**		
	Baseline	**Final**	***P***	**Baseline**	**Final**	***P***
Weight (kg)	105.09 ± 24.61	102.68 ± 25.50	0.008**	97.96 ± 24.46	98.91 ± 25.87	0.421
TC (mmol/L)	4.68 ± 1.83	4.46 ± 1.6	0.396	4.45 ± 0.93	4.37 ± 1.01	0.359
TGL (mg/dL)	3.7 ± 5.28	3.51 ± 4.7	0.675	2.35 ± 2.28	2.43 ± 1.97	0.279
ALT (IU/L)	76.27 ± 69.41	55.67 ± 35.4	0.187	79.63 ± 117.86	63.88 ± 74.76	0.451

TC, total cholesterol; TGL, triglyceride; ALT, alanine aminotransferase. Values are expressed as mean ± SD. $P < 0.05$* $P \leq 01$**, $P \leq 0.001$*** (Wilcoxon signed rank test).

In terms of patient lifestyles and behaviours, significant improvements were noted for general emotional health score and fruit intake, alongside significant reductions in fried food intake ($p \leq 0.05$) at the end of the 12 week intervention. Improvements in importance of healthy eating scores were approaching significance, patients improved minutes of light exercise by 69 (± 51.87) minutes per week (not significant) but did not increase their vegetable intake (Table 4).

Table 4 - Comparison of intervention patients baseline and final lifestyle data

	Baseline (n=16)	**Final (n=16)**	***P***
General emotional health (score)	56.25 ± 15.43	75.38 ± 7.76	0.003**
BMI (kg/m^2)	34.15 ± 7.09	33.39 ± 7.89	0.018*
Importance of healthy eating (score)	74.66 ± 16.41	80 ± 18.70	0.053
Fruit intake (portions/day)	0.55 ± 0.39	1.05 ± 0.49	0.006**
Vegetable intake (portions/day)	1.15 ± 1.08	1.1 ± 0.9	0.888
Fried food intake (portions/day)	0.35 ± 0.5	0.15 ± 0.16	0.017*
Light Exercise (mins/week)	143 ± 132.66	212 ± 159.56	0.102

Values are expressed as mean ± SD. P < 0.05* P ≤ 0.01** (Wilcoxon signed rank test).

DISCUSSION

This study presents a first of its kind service evaluation of a collaboration in the UK successfully integrating a privately delivered, open access lifestyle training programme funded by local government and embedded in a secondary care NAFLD care pathway. The study involved 167 patients offered lifestyle intervention of whom only 16 (9.58%, 95% CI 6% - 15%) completed the 12 week intervention representing a 1 in 10 participation rate. Weight loss in the intervention group was significantly different to the control group (- 2.79 Kg vs + 0.95 Kg, equating to 2.3% of baseline weight, $p = 0.008$) and led to improvements in BMI. A drop in ALT was noted in both groups though this was not statistically significant (- 20.6 IU/L vs - 15.75 IU/L $p = 0.579$). Similar published studies to this one have successfully reported positive impacts of interventions using small numbers of NAFLD patients[22 23].

Lack of uptake and non-adherence with interventions appears to be a consistent problem amongst NAFLD patients. Although all require lifestyle and dietary intervention, less than 50% will readily accept the need for this and fewer numbers will agree to take part and complete a designed intervention programme[13 23]. This may in part be due to the asymptomatic nature of both NAFLD and NASH[2]. Although participant uptake and recruitment is not well evidenced, some recent literature mirrors the intervention uptake issues encountered in this study. Kenneally, et al. [24] noted small sample sizes for the majority of studies identified in a systematic review of nutrition interventions in NAFLD patients. The authors found weight loss by energy restriction leads to an improvement in NAFLD but further clarification is needed as trials were heterogeneous with large variations in participant numbers and duration. NAFLD patients are 18–20 % more likely to report poor physical health or are unable to perform daily activities compared to healthy controls. Besides fatigue, NAFLD patients may also experience other symptoms such as anxiety, depression, cognitive impairment, and loss of self-esteem[13 25].

These symptoms significantly impact patients well-being and health-related quality of life[26] which in turn, may affect the implementation of dietary recommendations or other self-management advice.

Significant weight loss was achieved by patients completing this 12 week intervention, however long term energy and weight control is challenging for many NAFLD patients[13]. The success of shorter term lifestyle interventions may not be sustained over longer periods after the interventions end without targeted support and follow up[27]. Ultimately, patients with NAFLD are required to self-manage their diet and behaviour. The long term, larger scale evidence on lifestyle intervention and dietary management for those with this condition is conflicting[28]. Prior to any further larger scale long term trials, a patient and public involvement research approach may be useful to establish potential barriers to lifestyle and dietary interventions in NAFLD patients. This would then inform the design of powered, longer-term large-scale lifestyle interventions in greater numbers of NAFLD patients with the provision of regular medical support from clinicians, dietitians, nutritionists and health trainers, which may lead to further improvements in the parameters measured in this study.

Reductions in ALT were noted in both groups, ALT improved by 20IU / L in the intervention group and 15 IU / L in the control group, over the 12 week period but these did not reach statistical significance. This may be due to the small sample size and a possible Type II error. The lifestyle intervention patients did increase their exercise levels by 69 minutes (± 51.87) per week over the study duration. The exact mechanisms of how exercise and weight loss may improve NAFLD are not well understood, but regular exercise may change body composition leading to decreased fat mass without overall weight loss[24]. Alcohol intake is regularly assessed for all patients in the fatty liver clinic and patients with alcohol consumption higher than 14

units per week were excluded from this study sample. However, it is possible that even further reductions in alcohol consumption within these limits were made by some patients during the study period which may have contributed to improved ALT levels in both groups. Dietary intakes and exercise levels were not recorded for the control group, therefore it is possible independent lifestyle changes such as taking regular exercise may have been made, which in turn could also lead to the small reductions in ALT for this group in the absence of weight loss. Finally, regular follow up for all patients in a dedicated fatty liver clinic where soft outcomes such as improvements in liver biochemistry which are visible and tangible benefits are commonly discussed might have impacted the results and introduced a bias. Whilst this suggests that the fatty liver clinic is promoting a healthier lifestyle in patients, it presents a potential to confound the results. However, the group that did not take up the intervention were not aware that their biochemistry would be compared to the group that completed the intervention.

A small but significant increase in fruit by 61.7%, but not vegetable intake was noted in the current study, however overall fruit and vegetable consumption (baseline 0.55 ± 0.39 and endpoint 1.05 ± 0.49 ($p = 0.006$) for fruit and baseline 1.15 ± 1.08 and endpoint 1.1 ± 0.9 (NS) for vegetables respectively) fell far short of both national population averages (4.2 portions)[29] and the recommended 5 portions a day[20]. There was a reduction in the use of fried food and snacking by 13% and 21% respectively. Unfortunately these improvements did not translate to patients lipid profiles and there were no significant changes to total cholesterol and blood triglycerides at the end of the study, which may be due to the short study duration. Full nutritional evaluation of the 7-day estimated food intakes was not completed; this is a limitation that should be addressed in future studies.

Completing the programme was associated with an improvement in self-rated emotional wellbeing (56.25% to 75%). A mean increase to general emotional health scores (19% ± 4.31) was noted for the patients completing the intervention showing a significant positive effect on general well-being ($p = 0.003$). This may be linked to the use of lifestyle trainers to support patients during the intervention and coupled with previous evidence[30 31] suggests lifestyle interventions with a well-being support element may offer an effective strategy in the treatment of NAFLD.

This pragmatically conducted, real world service evaluation exercise provides important preliminary data to evaluate the efficacy of an existing open access lifestyle intervention in NAFLD patients. However, there are limitations, which must be considered. The 16 patients that took part represented only 1 in 10 patients offered the intervention. Poor uptake of the lifestyle intervention and subsequent small sample size limits the efficacy of comparison between the intervention and the control groups. Coupled with low participation and recruitment rates in NAFLD patients discussed earlier intervention recruitment may have been limited by selection bias. Vilar-Gomez, et al. [32] conducted a 52-week long intensive intervention with 293 NASH patients who agreed to have paired biopsies and had reasonable control of metabolic parameters such as HBA1C. With this elaborate lifestyle intervention program, 30% of patients lost more than 5% of their body weight and 25% achieved resolution of steatohepatitis. The uptake of the intervention was reported at 96% though it is important to note that the study was designed to assess the histological impact of intervention. Even with comprehensive intervention in this selected motivated cohort of patients only 30% achieved weight loss of > 5% which reflects the real world challenges faced by patients and their healthcare providers in achieving weight loss. Whilst histological improvement was not seen in all patients, the reported impact of lifestyle intervention in terms of NASH resolution was

comparable to the efficacy reported from pharmacotherapy for NASH currently being recommended[33] or approved for use in NASH[34]. The limited number of patients that took part in our lifestyle intervention are likely to have been motivated to make changes, where the matched control group were not. Whilst both groups received regular follow up in the NAFLD clinic with ongoing advice and encouragement to address lifestyle in clinic, the intervention group benefited from additional focussed support provided by trained lifestyle health trainers for 12 weeks. Coupled with this the 12 week study duration represents a short term intervention and may not have been long enough to see significant improvements in NAFLD biomarkers. It is important to note that this study did not evaluate the reasons for non-participation, which is a significant limitation and will be evaluated in a future planned study.

In conclusion, offering lifestyle intervention in an integrated NAFLD care management pathway resulted in significant weight loss of 2.3% of baseline body weight in 16 NAFLD patients after 12 weeks with significant improvements to BMI; however, uptake was suboptimal with a participation completions rate of less than 10%. This study highlights the challenge of engaging patients to accept such a programme when offered to them in a real world setting. There was no impact of this degree of weight loss on biochemical liver indices over 12 weeks. Further well-planned research using powered randomised controlled trials of longer duration in larger cohorts of NAFLD patients is urgently needed to ratify the present findings and prior to local government commissioning lifestyle intervention services. Focused patient and public involvement research is needed to identify potential barriers to participation, address adherence issues and identify appropriate support mechanisms for lifestyle interventions with NAFLD patients.

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