Research Article

The Effect of Moderate Weight Loss on a Non-Invasive Biomarker of Liver Fibrosis: A Randomised Controlled Trial

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Abstract
Background: Referral to weight loss programmes is the only effective treatment for non-alcoholic fatty liver disease (NAFLD). Clinicians should advise weight loss and screen for liver fibrosis using the Enhanced Liver Fibrosis (ELF) score. ***Aim:*** To examine if the ELF score changes with weight loss. ***Design and Setting:*** Randomised controlled trial (ISRCTN85485463) in UK primary care during 2007–2008. ***Method:*** Adults with a BMI of 27–35 kg/m^2 and ≥1 risk factor for obesity-related disease were randomised to attend a community weight loss programme (n = 45) or receive usual weight loss advice from a practice nurse (n = 28). Weight and the ELF score were measured at baseline and 1 year. Analysis of covariance examined mean changes in the ELF score between groups and its relationship with weight loss. ***Results:*** Mean (SD) BMI was 31.10 kg/m^2 (2.55) with evidence of moderate levels of liver fibrosis at baseline (mean ELF score: 8.93 [0.99]). There was no evidence that the community weight loss programme reduced the ELF score compared with usual care (difference +0.13 points, 95% CI: −0.25 to 0.52) despite greater weight loss (difference: −2.66 kg, 95% CI: −5.02 to −0.30). Mean weight loss in the whole cohort was 7.8% (5.9). There was no evidence of an association between weight change and change in ELF; the coefficient for a 5% weight loss was −0.15 (95% CI: −0.30 to 0.0002). ***Conclusion:*** We found no evidence that the ELF score changed meaningfully following moderate weight loss. Clinicians should not use the ELF score to measure improvements in NAFLD fibrosis following weight loss programmes.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) covers a range of conditions from excess fat in the liver through inflammation and fibrosis (non-alcoholic steatohepatitis, NASH), to advanced fibrosis, and cirrhosis. It is estimated that about 25% of adults worldwide have NAFLD [1]. Among people with obesity, about 50–75% are also affected by NAFLD [2]. Obesity is associated with more severe forms of the disease and with a worse prognosis for people with NAFLD [3]. Obesity and insulin resistance are associated with the development and progression of NAFLD with NAFLD being widely regarded as the hepatic manifestation of the metabolic syndrome [4]. The incidence of cardiovascular disease in people with severe NAFLD is 2.5-fold higher compared with matched controls [5]. Hepatocellular carcinoma associated with NAFLD has increased 10-fold, and liver transplantation due to NASH cirrhosis has increased 2-fold in the last decades [6, 7].

The high prevalence of NAFLD and its association with an increased risk of morbidity and mortality render it a serious and costly condition. For people with NAFLD, the presence of fibrosis is the strongest predictor of long-term outcomes. Advanced fibrosis is associated with a 14 times higher risk of liver events and three times higher risk of premature mortality [8, 9]. There is a need to identify methods to measure fibrosis to inform the prognosis and aid clinical decision making about the choice of emerging therapies.

Currently, fibrosis can only be reliably assessed with a liver biopsy. However, even with biopsies there are methodological limitations including sampling error and inter- and intra-observer variability. In addition, the cost, risk of complications, and low patient acceptability means that biopsies cannot be repeated often or in large samples [10]. The Enhanced Liver Fibrosis (ELF) score is emerging as a promising blood biomarker for fibrosis, as it has excellent accuracy for diagnosing histologically confirmed advanced fibrosis with an area under the curve of 0.90 in people with NAFLD and its specificity and sensitivity increasing with increases in the cut-off value [11, 12]. It has been found to have the highest diagnostic accuracy for advanced fibrosis compared with other non-invasive biomarkers, and, therefore, it is recommended for diagnosing advanced fibrosis in people with NAFLD by the National Institute for Health and Care Excellence (NICE) [13]. Furthermore, its use as a NAFLD screening tool by clinicians has led to appropriate stratification of NAFLD patients and reduced unnecessary referrals to secondary care [14].

There is, however, less certainty that ELF can be used to monitor the progress or improvement in NAFLD. An observational study of a weight loss programme in children with obesity was associated with reductions in ELF at the end of the programme, but 23% of children with reductions in their BMI-SDS score showed increases in ELF [15]. In a randomised controlled trial of liraglutide, a GLP-1 agonist, among people with NASH, there was a weight loss of 4.7 kg at 1 year compared with placebo, which was associated with a –0.4-point decrease in the ELF score [16]. However, it is unclear whether this is attributable to the weight loss or a specific effect of the enhanced insulin secretion. Accordingly, there is no evidence that ELF is responsive to change following weight loss through lifestyle modification, the recommended and most commonly advised treatment for NAFLD [13, 17], and it is unclear whether this would be a suitable outcome measure in trials of lifestyle interventions.

Community weight loss groups lead to similar weight loss to liraglutide at a fraction of the cost and are among the most commonly used weight loss programmes. The aim of the current study was to examine whether a community weight loss programme reduces ELF score over 12 months compared with a weight-loss intervention which is less effective. In observational analyses, we examined whether greater weight loss was associated with greater change in ELF score and whether the association was stronger for those with higher ELF scores and therefore more fibrosis at baseline.

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Methods

Participants and Setting

This was a secondary analysis of a published randomised controlled trial (ISRCTN85485463) [18]. Adults with a BMI of 27–35 kg/m^2 and at least one other risk factor for metabolic syndrome or obesity-related disease were recruited from Germany, Australia, and the UK. This analysis included only the UK participants with blood samples at baseline and 1 year (n = 73).

Interventions

Participants were equally randomised to a community weight loss programme (Weight-Watchers) or usual care. The WeightWatchers weight loss programme comprised of weekly group meetings over a 12-month period during which participants were weighted and received support and motivation. Participants were advised to follow a hypo-energetic diet based on healthy eating principles using a "points" system equating to about 1,100–1,500 kcal/day. Participants were encouraged to aim for at least 150 min of moderate intensity physical activity weekly. Participants in the usual care group received regular weight loss advice and support from a primary care practitioner.

Assessments

Weight was measured with calibrated scales, and glucose and insulin were assessed from fasted blood samples. The ELF score was measured in serum and automatically computed by the analyser (ADVIA Centaur XP, Siemens Healthcare Diagnostics) based on the following algorithm combining hyaluronic acid, propeptide of type III procollagen, and tissue inhibitor of metallo-proteinases-1: ELF = 2.278 + 0.851 ln(HA) + 0.751 ln(PIIINP) + 0.394 ln(TIMP1). The ELF score was interpreted as none/mild fibrosis for values below 7.7, moderate fibrosis for values between 7.7 and 9.7, and severe fibrosis for values of at least 9.8 [19].

Analysis

To analyse the difference in ELF between trial arms, we used analysis of covariance with a term for trial arm and baseline ELF score. We examined whether the effect of treatment on ELF score depended upon baseline ELF by adding a multiplicative interaction term between baseline ELF and trial arm.

We also conducted an observational analysis of the relationship between changes in weight and the ELF score at 1 year using general linear regression adjusting for baseline values. We examined whether the association between weight loss and change in ELF was larger for those with higher baseline ELF scores by adding a multiplicative interaction term between baseline ELF and weight change.

For both analyses, missing ELF scores at baseline (n = 5) and weight at follow-up (n = 4) were imputed using multiple imputation by chained equations with predictive mean matching (5 imputations and 100 iterations). The sensitivity analysis included only complete cases. We also conducted an independent-sample t test on the changes of ELF among those who lost less than or at least 10% of their weight, as a 10% weight loss has been associated with histological fibrosis regression [20]. An outlier that was >3 SDs from the mean was excluded from the t test, but exclusion of the outlier from the regression models did not materially affect the estimates. Analysis was conducted in R, v3.5.0.

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Table 1. Baseline characteristics of the cohort

|	Standard care	Community weight loss groups	Total
N	28	45	73
Female sex	28 (100)	42 (93.3)	70 (95.9)
Ethnicity			
White	27 (96.4)	42 (93.3)	69 (94.5)
Black/mixed	1 (3.6)	3 (6.7)	4 (5.5)
Type 2 diabetes	1 (3.6)	2 (4.4)	3 (4.1)
Age, years	55.19 (10.23)	52.9 (13.46)	53.78 (12.29)
Weight, kg	82.02 (2.44)	83.21 (2.64)	82.75 (2.55)
BMI, kg/m^2	31.25 (2.44)	31 (2.64)	31.1 (2.55)
Glucose, mmol/L*	4.95 (0.83)	4.8 (0.7)	4.9 (0.8)
Insulin, pmol/L	50.03 (27.37)	53.62 (32.25)	52.24 (30.32)
HbA1c, %	5.66 (0.3)	5.74 (0.44)	5.71 (0.39)
HOMA2-IR	5.88 (2.92)	6.26 (3.4)	6.12 (3.21)
Total cholesterol, mmol/L	5.59 (1.06)	5.56 (1.22)	5.57 (1.15)
LDL cholesterol, mmol/L*	3.65 (1.25)	3.2 (1.5)	3.3 (1.4)
HDL cholesterol, mmol/L	1.4 (0.39)	1.54 (0.44)	1.48 (0.42)
Triglycerides, mmol/L*	1.44 (0.85)	1.2 (0.6)	1.3 (0.8)
ELF score	9.03 (0.78)	8.88 (1.11)	8.93 (0.99)
HA	52.17 (44.36)	51.97 (66.8)	52.05 (58.86)
PIIINP	8.8 (3.03)	9.41 (4.51)	9.17 (4)
TIMP1	210.32 (58.41)	198.61 (53.55)	203.1 (55.36)

Data are presented as *n* (%) or mean (SD), unless otherwise indicated. * Data are presented as median (interquartile range). ELF, enhanced liver fibrosis; HA, hyaluronic acid; PIIINP, amino-terminal propeptide of type III procollagen; TIMP-1, tissue inhibitor of metalloproteinase 1.

Results

Demographic, anthropometric, and biochemical markers were similar between the intervention and comparator groups (Table 1). The mean (SD) BMI of participants was 31.10 (2.55) and the mean (SD) ELF score at baseline was 8.93 (0.99) indicating moderate fibrosis, with 3 participants (4%) having an ELF score above the cut-off of 10.51 for advanced fibrosis. At baseline, BMI did not correlate with the ELF score (r = 0.20, p = 0.09). Percentage weight change at 12 months in the intervention group was –9.0% (5.9) and in the usual care group was –5.8% (5.4) (between-group difference: –2.66 kg, 95% CI: –5.02 to –0.30). Compared with baseline, the ELF score decreased by –0.05 (0.99) points in the intervention group and –0.25 (0.75) points in the usual care group. There was no evidence of a significant effect of the intervention on the ELF score (between-group difference: +0.13 (95% CI: –0.25 to 0.52, p = 0.50). The interaction between treatment and baseline ELF score was not significant (–0.02 (95% CI: –0.56 to 0.52, p = 0.93).

Percentage weight change in whole cohort was –7.8% (5.9) and the change in ELF was –0.12 (0.90) points. There was no evidence of an association between weight change and change in ELF; the coefficient for a 5% reduction in weight was –0.15 (95% CI: –0.30 to 0.0002, p = 0.056). There was a significant interaction between weight change and the ELF score at baseline such that people with higher baseline ELF scores reduced while those with lower scores increased at 12-month follow-up (p = 0.002 for interaction) (Fig. 1). There was no significant difference in changes in ELF in those who lost at least 10% of their weight compared with those who lost less than 10% (p = 0.14). Changes in insulin resistance

Fig. 1. Median (interquartile range) changes in the Enhanced Liver Fibrosis score in the whole cohort by percentage of achieved weight loss at 1 year. Values above the yellow and red lines indicate cut-off values for possible moderate and severe liver fibrosis, respectively.
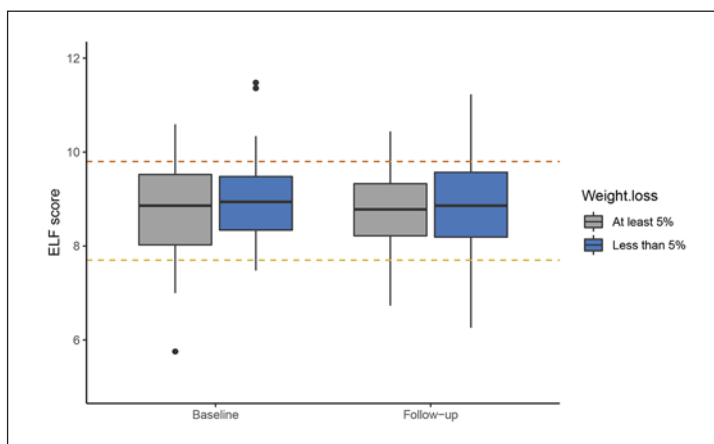
(HOMA2-IR) were not associated with the ELF score at 12 months (–0.001, 95% CI: –0.01 to 0.002).

These findings were essentially unchanged in a complete cases sensitivity analysis. There was no evidence of an effect of the intervention on the ELF score (between-group difference: 0.06 points, 95% CI: –0.33 to 0.45, *n* = 68). Weight change in the whole cohort was not associated with changes in the ELF score (–0.1, 95% CI: –0.25 to 0.002, *n* = 64).

Discussion

Summary

In this secondary analysis of a randomised controlled trial, we found no evidence of an effect of a community weight loss programme on changes in the ELF score and no association between weight loss and the ELF score in people who had, on average, an ELF score compatible with moderate fibrosis.

Strengths and Limitations

To our knowledge, this is the first study to quantify expected changes in the ELF score following weight loss through lifestyle modification. The confidence intervals were precise enough to probably exclude significant differences in ELF following weight loss through lifestyle modification in this population. Strengths of the study include the randomised controlled design and long-term follow-up. However, the results of this study should be interpreted with caution given the small sample size and lack of assessment of changes in other liver biomarkers, such as alanine transaminase or blood markers of liver fibrosis such as the NAFLD fibrosis score and the fibrosis-4 (FIB-4) score. As progression of liver fibrosis is slow, 1 year is the minimum recommended follow-up to detect fibrosis changes [21]. Fibrosis improved at 1 year in a large single-arm weight loss trial in NASH [20], although there was no evidence of changes in fibrosis in randomised trials with smaller samples [22]. Most participants in our study consumed some alcohol, but none had a diagnosis indicative of alcohol abuse. We did not screen specifically for NAFLD or other liver disease, such as hepatitis. However, the prevalence of hepatitis B and C infection is <1%, so it is not likely to be quantitatively important in these results. Furthermore, the population studied here was affected by overweight, and the liver biomarker showed some evidence of liver dysfunction, such that NAFLD is the most likely diagnosis.

Comparison with Existing Literature

Secondary analysis of a previous trial of a novel agent to treat NASH showed that people who lost 5% of their BMI had an improvement in another non-invasive biomarker of liver fibrosis: liver stiffness measured with magnetic resonance elastography [23]. However, it is not clear whether this is an effect of weight loss per se or confounded by specific effects of the pharmacotherapy on fibrosis. In a systematic review and meta-analysis, weight loss interventions in people with NAFLD and NASH led to similar weight loss as in the current study and in improvement in biopsy-proven steatosis and the NAFLD activity score [22]. Furthermore, the direction of the association between weight loss interventions and biopsy-proven liver fibrosis went in the expected direction, albeit not significant (change in fibrosis score: –0.13, 95% CI: –0.54 to 0.27), and we would have expected to see a reduction in fibrosis if the estimate were more precise.

Implications for Research and/or Practice

Using the ELF test to assess weight loss treatment efficacy in improving liver fibrosis may be of limited value and, until validated non-invasive biomarkers are available, biopsy remains the gold-standard assessment for liver fibrosis. However, given the invasive nature of liver biopsies, research on the validation of the ELF and other low-risk, low-cost tests is critical as this can facilitate follow-up of patients with liver fibrosis and population-based studies on disease progression. Although assessment of the ELF score is currently limited in primary care [17], its use should be expected to rise, given the current NICE guidance and its utility in primary- to secondary-care NAFLD referrals [13, 14]. Future weight loss trials should examine the effect of lifestyle interventions specifically in people with a biopsy-proven fibrosis. Follow-up data after bariatric surgery could also be used to test if larger weight loss might reduce ELF score. Genetic and epigenetic factors, inflammation, comorbidities, and the gut microbiota are also implicated in fibrosis progression in NAFLD [24, 25]. These were balanced in our randomised comparison but should be carefully accounted for in future observational studies.

In conclusion, we found no evidence that the ELF score meaningfully changed in an unselected population with overweight with moderate fibrosis following a lifestyle intervention with modest weight loss.

Acknowledgment

Statement of Ethics

This study received ethics approval from Nottingham Research Ethics Committee, UK (Ref. 07/Q2404/40), the ethical committee of the Faculty of Medicine of the Technische Universität München, Germany (Ref. 1812/07), and the ethics review committee (Royal Prince Alfred Hospital zone) of the Sydney South West Area Health Service, Australia (Ref. X07–0089). All patients provided written informed consent.

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Disclosure Statement

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Author Contributions

All authors contributed to the conception, design, analysis, and interpretation of the data. D.A.K. drafted the manuscript, and all authors critically revised and approved the final version of the manuscript.

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