

RESEARCH

Piloting a multidisciplinary clinic for the management of non-alcoholic fatty liver disease: initial 5-year experience

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ABSTRACT

Objective A multidisciplinary approach is advocated for the management of Non-Alcoholic Fatty Liver Disease (NAFLD), but few clinical data exist to support this. The objective of this study was to investigate the effectiveness of a multidisciplinary NAFLD clinic using surrogate markers of liver injury and cardiovascular risk.

Design Retrospective survey of clinical practice.

Setting The multidisciplinary NAFLD clinic in a secondary/tertiary care setting with hepatology, diabetology, dietetic and exercise therapy input: initial 5-years' experience (2007–2012).

Patients 180 patients with NAFLD but without hepatic comorbidities were followed up for a median of 19.5 (range 3–57) months. 52% had type 2 diabetes mellitus, 48% were Europoid Caucasian, 17% were South Asian.

Interventions Multiple clinical interventions were employed including lifestyle (diet and exercise) advice, pharmacological intervention for cardiovascular risk factors, weight loss and exercise therapy.

Main outcome measures Change in alanine aminotransferase (ALT), weight, HbA1c, lipid profile and blood pressure.

Results Median ALT fell from 61 (12–270) U/l to 50 (11–221) U/l, –18%, $p < 0.001$, and weight fell from 90.5 (42.7–175.0) kg to 87.3 (45.9–175.3) kg, –3.5%, $p < 0.001$. There were significant improvements in total cholesterol overall, triglycerides (among dyslipidaemic patients), HbA1c (among diabetic patients) and systolic blood pressure (among hypertensive patients). 24% of patients achieved $\geq 7\%$ weight loss during follow-up and 17% maintained this weight loss throughout.

Conclusions Improvement in liver biochemistry and cardiovascular risk factors was seen in

patients attending the multidisciplinary NAFLD clinic. Refinement of this approach is warranted in light of these data, novel therapies and a growing evidence base.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a burgeoning public health problem, associated with the global epidemic of obesity and type 2 diabetes mellitus (DM). Estimates of prevalence depend on case definition and the populations studied, but exceed 20% in many adult populations.^{1–2} A proportion have non-alcoholic steatohepatitis (NASH) with or without advanced fibrosis which is associated with increased liver-related,^{3–5} and cardiovascular morbidity and mortality,^{6–7} related to the development of the chronic liver disease and association with the metabolic syndrome of abdominal obesity, insulin resistance or type 2 DM, dyslipidaemia and hypertension.⁸ An increasing proportion of liver transplantation in the USA and Europe is carried out as a result of NAFLD/NASH,⁹ and while the rate of disease progression is relatively slow, global trends in DM and obesity mean that the impact of NAFLD/NASH is set to increase.

Current therapy aims to optimise both cardiovascular and liver-related risk factors as there is no recognised direct pharmacological therapy to address all aspects of the disease. Lifestyle changes driven by dietary intervention and exercise are the first line of therapy to induce and maintain weight loss, with the aim of

reducing fat mass, hyperinsulinaemia and insulin resistance, thus decreasing lipotoxic liver damage and multi-system metabolic consequences.^{10 11} Pharmacological therapy is predominantly aimed at reducing cardiovascular risk, but there is evidence that both vitamin E and pioglitazone improve biochemical and histological endpoints.¹² Numerous longitudinal studies have demonstrated the benefit of lifestyle interventions on surrogate endpoints, such as liver biochemistry,^{11 13 14} hepatic lipid assessed by magnetic resonance techniques,^{15 16} and confirmed in a randomised controlled trial using histological endpoints.¹⁷ A multidisciplinary, personalised approach is advocated to achieve these goals, although evidence to support this is limited.^{10 18–21} Real clinical data are required to establish a benchmark of current clinical practice to which other interventions may be compared.

The multidisciplinary, personalised approach to managing NAFLD/NASH has been adopted since 2007 in a secondary/tertiary care setting (Imperial College Healthcare NHS Trust). This clinic aims to provide a holistic and patient-centred approach, involving diagnosis, staging, lifestyle intervention (diet and exercise), treatment of metabolic, cardiovascular risk factors and resultant liver disease.

Thus, the aim of this study was to investigate the effectiveness of the multidisciplinary NAFLD clinic through the assessment of surrogate markers of liver injury and cardiovascular risk.

METHODS

This study was a retrospective survey of clinical practice, and all patients who had attended the NAFLD clinic on more than one occasion were eligible for inclusion in the analysis. The diagnosis of NAFLD was made histologically or on the basis of increased hepatic echogenicity on abdominal ultrasound with or without raised aminotransferase values, or on the basis of raised aminotransferase values with metabolic risk factors, in the absence of evidence of hepatic comorbidity, including current or recent alcohol excess (14 units/week for women, 21 units alcohol/week for men) or positive viral or autoimmune serology.

Clinical data were entered prospectively into the departmental database and extracted retrospectively. Results of any liver biopsies, abdominal ultrasound scans and transient elastography were also recorded. Clinical histology was reported descriptively with steatohepatitis defined as the presence of ballooned hepatocytes with an inflammatory cellular infiltrate in the context of hepatic steatosis.

Patients were defined as having hypertension if the blood pressure was $\geq 140/90$ mm Hg, or if the patient was taking antihypertensive medication; type 2 diabetes was defined according to WHO definitions,²² or if taking oral hypoglycaemic medication; dyslipidaemia was defined as triglycerides >1.7 mmol/l, or fibrate treated, high density lipoprotein (HDL) cholesterol

<1.0 mmol/l (M), or <1.3 mmol/l (F); obesity if BMI ≥ 30 . Interventions were targeted to those patients who were deemed to benefit from them and according to contemporary guidelines.^{23–26} Accordingly, the cohort was divided into patients with and without DM and into subgroups of (1) abnormal baseline alanine aminotransferase (ALT), (2) baseline type 2 DM, (3) baseline hypertension, (4) baseline dyslipidaemia and (5) baseline obesity.

Statistical analysis

Statistical analysis was performed using SPSS v19 (SPSS, Chicago, IL, USA). Data were non-parametrically distributed. Continuous variables were quoted as median (range), and categorical variables as numbers and percentages. Wilcoxon signed rank test, Mann–Whitney U and Spearman rank tests were used where appropriate with significance at the 5% level. Endpoints were analysed from baseline to latest response and to maximal improvement. The difference between median values was quoted as percentage change, and pairs of data were excluded in the event of missing values. Logistic regression was performed to identify predictors of patient response with backward selection at the 25% level.

Clinical interventions

The clinic is staffed by a hepatologist and a diabetologist with dietetic support. All patients underwent clinical dietary and lifestyle assessment and were given personalised lifestyle advice tailored to their requirements, including advice on smoking cessation. All patients were offered a 12-week course of weekly supervised exercise therapy at the hospital gym, instigated at their request. Patients were prescribed medication for the management of cardiovascular risk, diabetes and weight loss on an individual basis, or continued on current medications. orlistat was offered to obese patients not responding to lifestyle intervention, and continued according to UK guidelines.²⁶ The management of hypertension, dyslipidaemia and blood glucose control was individualised and in accordance with UK guidelines.^{23–25}

Dietetic interventions were based on a consultation with a dietician, employing a food-frequency questionnaire, or a seven-day food diary. Advice was given on food groups and portion size restriction. Specifically, patients were advised to increase consumption of fruit and vegetables, fish and whole-grains, and to decrease consumption of processed sugars, refined carbohydrates and saturated fat. Where applicable, patients were advised on calorie restriction by up to 500 kCal/day. Exercise intervention included advice on taking 150 min of moderate exercise per week, with more intensive exercise as tolerated. Weekly supervised exercise therapy was offered with a combination of cardiovascular and resistance training over a 12-week period.

An approach to the multidisciplinary NAFLD clinic may be summarised as the MEATLOAF (acronym expanded/explained (**bold**, underlined) in box 1) consultation framework, which is modifiable in accordance with local policy and resources, and can be updated according to new evidence.

RESULTS

Baseline characteristics

One hundred and eighty subjects, aged 49 (25–72) years were included, with a follow-up of 19.5 (3–57) months (table 1). Clinic visits spanned June 2007 to end March 2012. Most subjects were men (73.9%), approximately half (48.4%) were Europoid Caucasian and approximately half (52.1%) were diabetic. Nine patients (0.5%) had enrolled in interventional clinical trials, none of whom had received a trial intervention for more than 6 weeks at the time of analysis; 93 patients (52% of the total) had undergone liver biopsy, with simple steatosis found in 27% of those biopsied, NASH +/- mild to moderate fibrosis in 47%, bridging fibrosis in 22% and cirrhosis in 4%. Indications for liver biopsy included patients with uncertain diagnosis, persistently raised ALT despite lifestyle changes, indeterminate or high-risk NAFLD fibrosis score or raised liver stiffness on transient elastography (greater than 7 kPa); 107 patients (59%) underwent transient elastography, with a median stiffness (range) of 6.1 (2.9–38.6) kPa.

At the latest clinic appointment, approximately half the patients and 71% of diabetic patients were taking antihypertensive medications, of which angiotensin converting enzyme inhibitors (ACE-I), or angiotensin receptor blocker (ARB) medications, were the most frequently prescribed (see online supplementary table 1); 89% of the diabetic patients were receiving oral hypoglycaemic (metformin and/or sulphonylurea) medications, and 24% were taking insulin or insulin analogues. The majority of patients, overall (61%), and 83% of diabetic patients were taking HMG-CoA reductase inhibitors ('statins'); 29% of the cohort had undergone a trial of the lipase inhibitor, orlistat, as an aid to weight loss. Four patients (2%) underwent bariatric surgery.

Change from baseline to latest visit

For the total cohort, there were significant decreases in ALT, weight and total cholesterol from baseline to the latest clinic visit, but HbA1c, HDL, triglycerides and blood pressure did not differ (table 2). Normalisation of ALT (to ≤ 40 U/l) occurred in 36.7% of the total cohort; 48 (26.7%) subjects achieved a $\geq 5\%$ weight reduction and 30 patients (16.8%) achieved a $\geq 7\%$ reduction in weight (see online supplementary figure 1).

Box 1 The MEATLOAF Consultation for the Management of NAFLD

Make the diagnosis

- ▶ Raised ALT and/or steatosis on ultrasound examination
- ▶ Low to moderate alcohol consumption
- ▶ No hepatotoxic drugs
- ▶ Negative chronic liver disease screen

Establish metabolic syndrome components

- ▶ Hypertension
- ▶ Dyslipidaemia
- ▶ Obesity
- ▶ Diabetes/impaired glucose tolerance

Assess lifestyle

- ▶ Detailed dietary history (consider food frequency questionnaire, 7-day food diary)
- ▶ Daily activity/occupation
- ▶ Formal exercise (type, frequency, duration, intensity)

Therapeutic approaches

- ▶ Dietary advice/dietetic consultation
- ▶ Exercise counselling/gym referral
- ▶ Pharmacological modification to each component of the metabolic syndrome as per guidelines (eg, NICE)
- ▶ Adjust medications according to potential secondary benefit (eg, angiotensin receptor blockers may have antifibrotic effects, GLP-1 agonists may promote weight loss)
- ▶ Liver specific therapies (consider pioglitazone or vitamin E)

Liver biopsy? (Staging)

- ▶ Calculate non-invasive algorithms (eg, NAFLD fibrosis score (NFS))
- ▶ Consider transient elastography
- ▶ Consider biopsy if:
 - Diagnosis uncertain/poor response
 - Indeterminant or high-risk non-invasive markers
 - Obese or DM or age >50
 - Patient request
 - Potential clinical trial candidate

Offer clinical trials

- ▶ Investigator-led studies
- ▶ Commercial trials of novel agents or 'repurposing' of existing therapies

Advice and targets

- ▶ Provide target weight, BP, cholesterol triglyceride, HbA1c (if appropriate) to patient and primary care physician
- ▶ Provide information leaflets

Follow-up (suggested)

- ▶ 3–6 months if major therapeutic changes
- ▶ 6 months if NASH/significant fibrosis/compensated cirrhosis
- ▶ 6–12 months if stable on therapy
- ▶ 12 months or discharge if simple steatosis or very low risk on non-invasive tests.

Table 1 Baseline characteristics of total cohort

Characteristics	Total	Diabetic cohort	Non-diabetic cohort
Number (%)	180 (100)	92 (100)	88 (100)
Age, years	49 (23–74)	53 (25–74)	44 (40–58)*
Gender, m/f	133 (73.9), 47 (26.1)	58 (63.0), 34 (37.0)	75 (85.2), 13 (14.8)
Caucasian, northern European	64 (35.6)	33 (35.9)	31 (35.2)
Caucasian, southern European	23 (12.8)	12 (13.0)	11 (12.5)
Indian subcontinent	31 (17.2)	17 (18.5)	14 (15.9)
SE Asian/Oriental	13 (7.2)	6 (6.5)	7 (8.0)
Middle East	27 (15.0)	13 (14.1)	14 (15.9)
African/Afro-Caribbean	4 (2.2)	4 (4.3)	0 (0.0)
Ethnicity, other/unspecified	18 (10.0)	7 (7.7)	11 (12.5)
ALT, U/l	61 (12–270)	54 (12–157)	65 (29–270)*
AST, U/l	38 (18–210)	36 (18–210)	38 (22–137)
BMI, kg/m ²	30.8 (19.8–52.4)	32.7 (19.8–52.4)	29.8 (21.4–49.0)*
Waist, cm	107 (83–158)	110 (83–148)	104 (83–158)*
HbA1c, mmol/mol	45 (27–120)	53 (36–120)	39 (27–49)*
Systolic BP, mm Hg	134 (98–191)	135 (105–191)	134 (98–173)
Total chol, mmol/l	4.44 (2.08–7.95)	4.08 (2.08–7.95)	4.85 (2.70–7.58)*
HDL, mmol/l	1.11 (0.59–1.75)	1.05 (0.59–1.75)	1.14 (0.71–1.68)*
Triglyceride, mmol/l	1.83 (0.26–7.85)	1.93 (0.58–7.85)	1.68 (0.26–7.00)
Obese	100 (55.5)	61 (66.3)	39 (44.3)
Diabetes	92 (52.1)	92 (100.0)	0 (0.0)
Hypertension	109 (60.6)	68 (73.9)	41 (46.6)*
Abnormal ALT	142 (78.9)	71 (77.1)	71 (80.7)
Dyslipidaemia	122 (67.8)	65 (70.6)	57 (64.8)
1 MS feature	39 (21.7)	4 (43.4)	35 (39.7)
2 MS features	42 (23.3)	14 (15.2)	28 (31.8)
3 MS features	52 (28.9)	37 (40.2)	15 (17.0)
4 MS features	35 (19.4)	35 (38.0)	0 (0.0)*
Alcohol intake, units/week	0 (0–21)	0 (0–21)	1 (0–21)

Data expressed as median (range) or number (%).

Metabolic syndrome features from the WHO proposal (1999), consisting of (1) diabetes or altered glucose regulation, (2) arterial blood pressure $\geq 140/90$ or drug treated, (3) obesity defined by BMI and (4) dyslipidaemia. Microalbuminuria excluded. Variables marked with * differ significantly ($p < 0.05$) between patients with and without diabetes.

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; Chol, cholesterol; F, female; HDL, high density lipoprotein; M, male.

Baseline to greatest change

For the total cohort, the maximal reduction in serum ALT was from 61 (12–270) U/l to 39 (10–192) U/l, -36% , $p < 0.001$ in 10 (1–57) months, and in weight from 90.5 (42.7–175) kg, to 86.9 (45.9–175.3) kg, -4% , $p < 0.001$, in 12 (1–57) months; 73% of subjects had a decrease in ALT of $\geq 10\%$, and 44% of subjects had a decrease in ALT of $\geq 30\%$ during follow-up (see online supplementary figure 2). Normalisation of ALT (to ≤ 40 U/l) occurred in 53.5% of the total cohort; 56 (33.1%) subjects achieved a $\geq 5\%$ weight reduction, 40 patients (23.6%) achieved a $\geq 7\%$ reduction, and 25 patients (14.8%) achieved a $\geq 10\%$ weight reduction at some point in their follow-up.

Subgroup analysis

Changes in ALT and metabolic syndrome components in those affected (abnormal or high baseline values)

are shown in table 3. A smaller proportion of diabetic patients (12%) achieved a weight loss of $\geq 7\%$ than non-diabetic patients (22%), and the change in median weight was -1.3 kg in those with diabetes and 4.0 kg for those without diabetes, but this was not statistically significant. Changes in weight or ALT did not differ between patients who had received orlistat and those who had not (data not shown).

Baseline predictors of patient response

High baseline ALT, baseline total cholesterol and the use of lipid-lowering medication predicted a $\geq 10\%$ improvement in ALT on univariate analysis. On multivariate analysis, only baseline ALT remained a significant predictor. Higher baseline waist circumference predicted a $\geq 7\%$ weight reduction on univariate and multivariate analysis. There was a significant

Table 2 Change in variables from baseline to latest clinic visit for the total cohort

Measure	N=	Baseline	Recent	Δ (%)	p Value
ALT, U/l	180	61 (12–270)	50 (11–221)	–18	<0.001
Weight, kg	180	90.5 (42.7–175.0)	87.3 (45.9–175.3)	–3.5	<0.001
HbA1c, mmol/mol	121	46.5 (27–120)	45.4 (22–105)	–2.4	0.73
tchol, mmol/l	140	4.47 (2.30–7.95)	4.36 (2.01–7.12)	–2.5	0.001
HDL, mmol/l	140	1.09 (0.59–1.75)	1.08 (0.53–2.70)	–0.9	0.80
TG, mmol/l	140	1.83 (0.26–7.85)	1.67 (0.32–7.94)	–8.7	0.41
SBP, mm Hg	154	135 (98–191)	134 (100–176)	–0.4	0.36
DBP, mm Hg	154	82 (57–114)	82 (59–111)	0	0.64

Data expressed as median (range).

N=the number of patients with paired data available for this variable.

Bold values represent significant values.

ALT, alanine aminotransferase; DBP, diastolic blood pressure; HbA1c, glycosylated haemoglobin; HDL, high density lipoprotein; SBP, systolic blood pressure; tchol, total cholesterol; TG, triglyceride.

correlation between change in weight and change in ALT ($r=0.43$, $p<0.001$) between baseline and latest visit.

DISCUSSION

In the setting of a multidisciplinary NAFLD clinic, there was overall improvement in ALT, weight and total cholesterol, while HbA1c, triglyceride and systolic blood pressure improved in those with the respective abnormalities at baseline. Fewer patients with diabetes achieved 7% weight loss compared with those without diabetes, and trends towards smaller improvements in ALT, systolic blood pressure and total cholesterol were observed; 17% of patients had sustained a weight loss of greater than 7% over the median 19-months follow-up, while 24% of patients achieved 7% or greater weight loss during the assessment period.

This analysis presents real-life clinical data in an ethnically and socioeconomically diverse population. The majority of referrals were from primary care via either hepatology services or diabetes services. Although the cohort is broadly representative for an inner city secondary/tertiary care setting, this cohort does not represent the total number of patients with NAFLD in

our region as many patients remain under the care of their primary care physician or gastroenterologist, while treatment-resistant cases may be more readily referred to the NAFLD clinic and less likely to be discharged back to primary care, representing a potential selection bias.

We report that over half the cohort maintained a >10% improvement in ALT from their first to their latest visit, with over one-third achieving normalisation of ALT. This was accompanied by a reduction in aspartate aminotransferase. Aminotransferase values are frequently used as surrogate markers of the degree of liver injury. Changes in ALT and AST (aspartate aminotransferase) correlate with change in histological inflammation in NAFLD after adjusting for baseline disease severity and other histological features and in a series of 102 patients in a clinical trial setting,²⁷ so aminotransferases may serve as a surrogate marker of inflammatory change in NAFLD. ALT is also a meaningful outcome measure, as its use is ubiquitous in the management of liver diseases, so these data are readily compared with those from other clinics. However, it should be noted that significant liver injury can be present when ALT values lie within normal limits.²⁸

Table 3 Change in variables from baseline to latest clinic visit for subgroups with abnormalities at baseline

Subgroup	Measure	Number	Baseline	Recent	Δ (%)	p Value
Raised ALT	ALT, U/l	145	66 (41–270)	55 (14–221)	–16.7	<0.001
Obese	Weight, kg	101	101.0 (64.8–175.0)	96.9 (62.0–175.3)	–4.9	<0.001
Diabetes	HbA1c, mmol/mol	77	53 (36–120)	52 (32–105)	–1.9	0.018
Dyslipidaemia	tChol, mmol/l	99	4.95 (2.80–7.95)	4.43 (2.39–7.12)	–10.5	<0.001
Dyslipidaemia	HDL, mmol/l	99	1.02 (0.59–1.75)	1.01 (0.53–1.92)	–1.0	0.24
Dyslipidaemia	TG, mmol/l	99	2.17 (0.58–7.85)	1.87 (0.34–7.94)	–13.8	<0.001
Hypertension	SBP, mm Hg	95	143 (105–191)	136 (104–176)	–4.9	0.012
Hypertension	DBP, mm Hg	95	82 (68–114)	82 (66–108)	0	0.018

Data expressed as median (range).

Definitions: raised ALT greater than 40 U/l; Obese, body mass index ≥ 30 kg/m²; dyslipidaemia and diabetes as per WHO proposal (1999). Number refers to the number of patients with paired data available for this variable.

Bold values represent significant values.

ALT, alanine aminotransferase; DBP, diastolic blood pressure; HbA1c, glycosylated haemoglobin; HDL, high density lipoprotein; SBP, systolic blood pressure; tChol, total cholesterol; TG, triglyceride.

A 7% reduction in weight has been associated with significant improvements in histological steatosis, parenchymal inflammation and ballooning injury, compared with those with a lesser degree of weight loss over a 1-year period.¹⁷ Some 17% of the present cohort maintained this target at a median follow-up of 19.5 months and 26% maintained a weight loss of 5%. However, in our cohort, 24% of patients achieved at least 7% weight loss at some point during follow-up (median 10.8 months), demonstrating that the long-term maintenance of improvements represents an ongoing clinical challenge. Direct comparisons between these data and those from interventional clinical studies should be interpreted with caution on account of differing patient characteristics, interventions and end points.

The patients with diabetes had more features of the metabolic syndrome and, specifically, were older and had a higher BMI. Patients with diabetes may represent a harder-to-treat group on account of a greater number of metabolic risk factors; there are common factors which predispose to DM and to resistance to intervention (which may be behavioural); medications to treat diabetes commonly promote weight gain and they are more likely to have accessed lifestyle advice and medical therapy in primary or secondary care, and consequently, have already undergone intervention to cardiovascular risk factors prior to attending the NAFLD clinic. This latter point is supported by the significantly lower total cholesterol values seen in those with diabetes in association with a much higher prevalence of statin use. In the present study, patients who had taken orlistat did not exhibit a greater degree of weight loss or improvement in ALT compared with those who did not, in line with a previous randomised controlled trial,²⁹ although this subgroup comprised those patients who did not respond to initial lifestyle intervention and, thus, may represent a more challenging group to treat.

The main strength of this study is the presentation of prospectively collected clinical data from routine clinical practice in the setting of the multidisciplinary NAFLD clinic, which may serve as a reference by which newer interventions may be judged. This contrasts with epidemiological studies of the natural history of disease, where there is little evidence of interventions. Studies of lifestyle interventions in NAFLD have demonstrated improvements in weight, aminotransferase values and hepatic lipid and have been reviewed elsewhere.^{13 16 30–32} These prospective interventional studies have been of shorter duration (3–12 months) than the follow-up period of this study, and have included more intensive intervention, with resource implications if applied in the NHS.

This article makes a case for a multidisciplinary approach to the management of NAFLD. Although based in a secondary/tertiary care setting, we acknowledge that aspects of the MEATLOAF framework could

be adopted in primary care by an appropriately skilled multidisciplinary team. Indeed, the multidisciplinary NAFLD clinic exists in partnership with primary care, particularly with respect to initial assessment, including the use of serum markers such as the NAFLD fibrosis score, monitoring and maintenance of changes. However, specific benefits of the present model include higher case numbers, use of transient elastography and/or liver biopsy, access to clinical trials and novel therapies, and specialist intervention and surveillance for complications of advanced liver disease.

As with all retrospective analyses, there are limitations. In this 5-year pilot, surrogate end points are used and, with the available data, it has not been possible to assess adherence to dietary and lifestyle interventions. The lifestyle interventions were not standardised and there was no control arm, so the contribution of specific interventions or potential confounding factors cannot be evaluated. Thus, this represents the overall outcome in the multidisciplinary clinic on an intention-to-treat basis. Future analyses should also assess standardised interventions, adherence to dietary and exercise regimes using a combination of patient-reported data and objective assessments, such as physical activity measured by accelerometers, duration of response and cost-benefit.

These data demonstrate that management in a multidisciplinary NAFLD clinic is associated with improvements in surrogate markers of liver injury and cardiovascular risk. It is now important to refine clinical practice according to the expanding evidence base, by prospectively collecting data that will enable the contributions of each intervention within this multidisciplinary framework to be evaluated.¹¹ NAFLD is a growing health challenge, and there is a need to build on these initial experiences to optimise therapy, to maintain positive changes and to improve outcome overall.

Key points

- ▶ NAFLD/NASH is increasingly prevalent and is associated with increased liver-related and cardiovascular mortality.
- ▶ A multidisciplinary approach to management has been proposed but with little supporting data to date.
- ▶ The MEATLOAF consultation framework is suggested to structure multidisciplinary intervention in NAFLD/NASH.
- ▶ Patients attending the multidisciplinary NAFLD clinic demonstrated improvements in aminotransferase values, weight and cardiovascular risk factors.

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Contributors JFLC and MRT initiated the service evaluation. JFLC, QMA, MSY and MRT ran the multidisciplinary NAFLD clinic. QMA designed and produced the NAFLD clinic

database. JFLC, SR and CMP acquired and analysed the data. All authors participated in data interpretation. JFLC, SR and CMP drafted the manuscript. JFLC, QMA, MSY and MRT critically revised the manuscript. All authors read and approved the final version.

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REFERENCES

- Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. *Aliment Pharmacol Ther* 2011;34:274–85.
- Armstrong MJ, Houlihan DD, Bentham L, *et al.* Presence and severity of non-alcoholic fatty liver disease in a large prospective primary care cohort. *J Hepatol* 2012;56:234–40.
- Younossi ZM, Stepanova M, Rafiq N, *et al.* Pathologic criteria for nonalcoholic steatohepatitis: interprotocol agreement and ability to predict liver-related mortality. *Hepatology* 2011;53:1874–82.
- Ekstedt M, Franzen LE, Mathiesen UL, *et al.* Long-term follow-up of patients with NAFLD and elevated liver enzymes. *Hepatology* 2006;44:865–73.
- Ong JP, Pitts A, Younossi ZM. Increased overall mortality and liver-related mortality in non-alcoholic fatty liver disease. *J Hepatol* 2008;49:608–12.
- Anstee QM, Targher G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. *Nat Rev Gastroenterol Hepatol* 2013. [Epub ahead of print]. doi:10.1038/nrgastro.2013.41.
- Bhala N, Angulo P, van der Poorten D, *et al.* The natural history of nonalcoholic fatty liver disease with advanced fibrosis or cirrhosis: an international collaborative study. *Hepatology* 2011;54:1208–16.
- Alberti KG, Zimmet P, Shaw J. The metabolic syndrome—a new worldwide definition. *Lancet* 2005;366:1059–62.
- Afzali A, Berry K, Ioannou GN. Excellent posttransplant survival for patients with nonalcoholic steatohepatitis in the United States. *Liver Transpl* 2012;18:29–37.
- Ratziu V, Bellentani S, Cortez-Pinto H, *et al.* A position statement on NAFLD/NASH based on the EASL 2009 special conference. *J Hepatol* 2010;53:372–84.
- Thoma C, Day CP, Trenell MI. Lifestyle interventions for the treatment of non-alcoholic fatty liver disease in adults: a systematic review. *J Hepatol* 2012;56:255–66.
- Sanyal AJ, Chalasani N, Kowdley KV, *et al.* Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis. *N Engl J Med* 2010;362:1675–85.
- Musso G, Cassader M, Rosina F, *et al.* Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. *Diabetologia* 2012;55:885–904.
- St George A, Bauman A, Johnston A, *et al.* Effect of a lifestyle intervention in patients with abnormal liver enzymes and metabolic risk factors. *J Gastroenterol Hepatol* 2009;24:399–407.
- Kantartzis K, Thamer C, Peter A, *et al.* High cardiorespiratory fitness is an independent predictor of the reduction in liver fat during a lifestyle intervention in non-alcoholic fatty liver disease. *Gut* 2009;58:1281–8.
- Chalasani N, Younossi Z, Lavine JE, *et al.* The Diagnosis and Management of Non-alcoholic Fatty Liver Disease: Practice Guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. *Gastroenterology* 2012;142:1592–609.
- Promrat K, Kleiner DE, Niemeier HM, *et al.* Randomized controlled trial testing the effects of weight loss on nonalcoholic steatohepatitis. *Hepatology* 2010;51:121–9.
- Bellentani S, Dalle GR, Suppini A, *et al.* Behavior therapy for nonalcoholic fatty liver disease: The need for a multidisciplinary approach. *Hepatology* 2008;47:746–54.
- Cobbold JF, Anstee QM, Thomas HC. Investigating mildly abnormal serum aminotransferase values. *BMJ* 2010;341:c4039.
- Anstee QM, McPherson S, Day CP. How big a problem is non-alcoholic fatty liver disease? *BMJ* 2011;343:d3897.
- Dowman JK, Armstrong MJ, Tomlinson JW, *et al.* Current therapeutic strategies in non-alcoholic fatty liver disease. *Diabetes Obes Metab* 2011;13:692–702.
- World Health Organisation. *Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia*. Geneva, Switzerland: WHO Press, World Health Organisation, 2006.
- National Institute for Health and Clinical Excellence. Type 2 diabetes: the management of type 2 diabetes. NICE clinical guideline 87, 2009.
- National Institute for Health and Clinical Excellence. Hypertension: clinical management of primary hypertension in adults. NICE clinical guideline 127, 2011.
- National Institute for Health and Clinical Excellence. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE clinical guideline 67, 2010.
- National Institute for Health and Clinical Excellence. Obesity: guidance on the prevention, identification, assessment and management of overweight and obesity in adults and children. NICE clinical guideline 43, 2006.
- Suzuki A, Lymp J, Sauver JS, *et al.* Values and limitations of serum aminotransferases in clinical trials of nonalcoholic steatohepatitis. *Liver Int* 2006;26:1209–16.
- Mofrad P, Contos MJ, Haque M, *et al.* Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. *Hepatology* 2003;37:1286–92.
- Harrison SA, Fecht W, Brunt EM, *et al.* Orlistat for overweight subjects with nonalcoholic steatohepatitis: a randomized, prospective trial. *Hepatology* 2009;49:80–6.
- Lazo M, Solga SF, Horská A, *et al.* Effect of a 12-month intensive lifestyle intervention on hepatic steatosis in adults with type 2 diabetes. *Diabetes Care* 2010;33:2156–63.
- Oza N, Eguchi Y, Mizuta T, *et al.* A pilot trial of body weight reduction for nonalcoholic fatty liver disease with a home-based lifestyle modification intervention delivered in collaboration with interdisciplinary medical staff. *J Gastroenterol* 2009;44:1203–8.
- Vilar GE, Rodriguez De MA, Gra OB, *et al.* Clinical trial: a nutritional supplement Viucid, in combination with diet and exercise, in patients with nonalcoholic fatty liver disease. *Aliment Pharmacol Ther* 2009;30:999–1009.