Lifestyle intervention for non-alcoholic fatty liver disease: prospective cohort study of its efficacy and factors related to improvement


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Lifestyle intervention for non-alcoholic fatty liver disease: prospective cohort study of its efficacy and factors related to improvement

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ABSTRACT

Background Non-alcoholic fatty liver disease (NAFLD) has a high prevalence in obese children. Lifestyle intervention is the primary treatment for NAFLD. However, limited data are available regarding the efficacy of lifestyle interventions.

Objectives To prospectively determine the efficacy of a lifestyle intervention programme on NAFLD in severely obese children and identify the clinical parameters related to improvement in NAFLD.

Methods Children admitted to a lifestyle intervention programme were screened for NAFLD. Steatosis was defined as increased echogenicity of the liver on ultrasonography. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were used as surrogate markers for steatohepatitis. The lifestyle intervention programme consisted of physical exercise, dietary counselling and behavioural counselling for a period of 6 months.

Results 144 children were included with a mean age of 14.1 (±2.3) years, BMI z-score of 3.35 (±0.40) kg/m². Lifestyle intervention significantly reduced the prevalence of steatosis (31.2–11.9%, p<0.001) and the prevalence of elevated serum ALT (25.7–11.1%, p<0.001) and serum AST (13.3–4.3%, p<0.002). In multivariate regression analysis, improvement in the degree of steatosis and decrease in ALT and AST were all significantly related to improvement in insulin resistance. Improvement in insulin resistance only explained a small part of the observed changes in transaminases.

Conclusions A lifestyle intervention of 6 months is moderately effective in improving NAFLD in severely obese children. Improvement in insulin resistance is the clinical parameter most strongly associated with improvement in NAFLD. Other factors related to the successful treatment of NAFLD need to be identified so that these can be a focus for new lifestyle and drug interventions.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is well established as one of the complications of obesity. In severely obese children, NAFLD has a reported incidence ranging from 22% in a school-based population to 52% in those referred to obesity centres. The clinical spectrum of NAFLD consists of simple steatosis, steatohepatitis and cirrhosis. Important fibrosis and occasionally cirrhosis can occur at paediatric age. In adults, NAFLD is increasingly recognised as an independent risk factor for cardiovascular disease and also in children it has been found to be associated with cardiovascular risk factors.

At present, lifestyle intervention remains the only accepted therapy for NAFLD. Remarkably little is known about the efficacy of lifestyle interventions. Most studies are small or were performed in selected populations, often in patients treated in tertiary liver centres. Although it is considered of paramount importance to identify which lifestyle interventions are most effective, the factors associated with response to lifestyle interventions have not been studied.

The aim of this study is to determine the effect of lifestyle intervention on NAFLD in children identified by screening among those referred to a tertiary obesity centre. Moreover, we aim to identify the clinical parameters associated with response to the lifestyle intervention.

MATERIALS AND METHODS

Population All children who participated in a Dutch tertiary centre-based lifestyle intervention programme...
between November 2004 and May 2008 were eligible. Inclusion criteria for this programme were severe primary obesity (body mass index adjusted for age (‘BMI-for-age’) >35 kg/m²) and primary obesity (‘BMI-for-age’ >80 kg/m²) together with obesity-related comorbidity. For participation in this study, additional exclusion criteria were (a history of) the use of steatogenic and/or antidiabetic drugs, diabetes mellitus, alcohol abuse, hepatitis B, hepatitis C or autoimmune hepatitis. The majority of children were referred by hospital-based paediatricians. The study protocol was approved by the Medical Ethics Committee of the Academic Medical Centre of the University of Amsterdam.

**Intervention**

The lifestyle intervention programme consisted of scheduled exercise (three times per week for 1 h) and the promotion of self-initiated physical activities. Nutrition modification therapy was given using a non-diet approach and focused on the quality of the dietary intake and eating behaviour. Behaviour modification therapy was given and consisted of coping skills training focusing on self-regulation, self-awareness, goal setting and stimulus control. The programme was facilitated by physical education teachers, a dietician and a child psychologist. Care givers were separately educated on nutrition and behaviour modification during this programme. Children attended the sessions in an outpatient setting consisting of 12 days of treatment over a 6-month period with homework assignments or an inpatient setting consisting of 5 days of admission per week for a period of 6 months. Children were allocated to either setting based on the order of inclusion unless the treating physician judged that the patient was unfit for outpatient treatment in which case he/she was allocated to inpatient treatment.

**Measurements**

Ultrasonography of the liver, blood sampling, an oral glucose tolerance test (OGTT) and physical examination were performed at the start and at the end of 6 months of treatment. Steatosis was diagnosed based on ultrasonography findings and scored using a scale adapted from Saverymuttu et al (table 1). Ultrasonography was performed by a single experienced radiologist blinded to clinical data. The Philips ATL HDI 5000 ultrasound imaging platform with a 3.5 MHz transducer was used (Philips Healthcare, Eindhoven, The Netherlands). Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were used as surrogate markers for steatohepatitis.

<table>
<thead>
<tr>
<th>Score 0 (normal):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal echogenicity of liver parenchyma</td>
</tr>
<tr>
<td>Normal visualisation of diaphragm and intrahepatic blood vessels</td>
</tr>
<tr>
<td>Score 1 (mild steatosis):</td>
</tr>
<tr>
<td>Slightly increased echogenicity of liver parenchyma</td>
</tr>
<tr>
<td>Normal visualisation of diaphragm and intrahepatic blood vessels</td>
</tr>
<tr>
<td>Score 2 (moderate steatosis):</td>
</tr>
<tr>
<td>Markedly increased echogenicity of liver parenchyma.</td>
</tr>
<tr>
<td>Slightly decreased visualisation of diaphragm and intrahepatic blood vessels.</td>
</tr>
<tr>
<td>Score 3 (severe steatosis):</td>
</tr>
<tr>
<td>Severely increased echogenicity of liver parenchyma</td>
</tr>
<tr>
<td>No or severely decreased visualisation of diaphragm and intrahepatic blood vessels and posterior part of right liver lobe</td>
</tr>
</tbody>
</table>

Steatohepatitis was defined as ALT and/or AST serum level >55 U/l. In multivariate regression analysis, improvement in NAFLD was expressed as the change in serum ALT and AST. Insulin sensitivity was measured using the ‘Homeostasis Model Assessment of insulin resistance’ formula (HOMA-IR): fasting insulin (mU/l) fasting glucose (mmol/l)/22.5. Diabetes mellitus was defined as fasting blood glucose >7.0 mmol or a 2 h blood glucose >11.1 mmol/l during the OGTT. Hepatitis C and hepatitis B infections and autoimmune hepatitis were excluded by serology. BMI was expressed as age-corrected BMI (BMI z-score) calculated from the data for a Dutch reference population as described previously. Waist circumference was defined as the mean of three measurements of the smallest torso circumference between the inferior margin of the last rib and the crista iliaca at the end of normal expiration.

**Statistical analysis**

Children missing end of treatment measurements were excluded from the analysis. The effect of the intervention on NAFLD was analysed using McNemar’s test for paired categorical data and χ² test for independent categorical data. Changes in continuous variables were analysed using paired Student t test. Regression analyses were performed to identify factors predictive of improvement in steatosis and decrease in ALT and AST. All parameters with p<0.10 in univariate analysis were included in multivariate regression analysis (backward selection). The intraobserver variability of ultrasonography steatosis scoring was determined by repeated ultrasound in 100 patients.

**RESULTS**

During the inclusion period, 180 children were treated in the lifestyle intervention programme. Eight were excluded (7 metformin use; 1 alcohol abuse). Twenty-eight children missed end of treatment measurements: 21 children dropped out during the treatment phase and 7 children did not show up at the end of treatment examinations. Those who dropped out were not significantly different for any baseline feature except for a higher prevalence of steatosis (60.7% vs 31.2%, p=0.002) and a higher prevalence of elevated serum ALT (46.4% vs 25.5%, p=0.04). Baseline features of the 144 children who completed treatment are shown in table 2.

**Steatosis and serum transaminases**

All biochemical and anthropometrical parameters showed significant improvement after treatment (table 2). The mean weight reduction achieved was 12.2%. After treatment, there was a significant decrease in the prevalence of steatosis from n=45 (31.2%) to n=17 (11.9%) and the prevalence of elevated serum ALT from n=37 (25.7%) to n=16 (11.1%) and elevated serum AST from n=19 (13.3%) to n=6 (4.3%) (figure 1). Worsening in the grade of steatosis after treatment was observed in three cases (3x1 grade). Serum liver transaminases were in the normal range in pre-treatment serum and elevated in post-treatment serum in six children. Intraobserver agreement for the ultrasonography steatosis score was observed in 57% of cases, whereas 38% showed a difference of one stage and 5% showed a difference of two stages between observations.

**Factors associated with improvement in NAFLD**

Improvement in the ultrasonography determined stage of steatosis was related to a younger age, non-Caucasian ethnicity, inpatient treatment, decrease in BMI z-score, decrease in...
ALT 28.2 (±12.6) 22.6 (±6.6) <0.001
AST 31.2 (±21.2) 22.8 (±12.7) <0.001
LDL cholesterol (mmol/l) 2.46 (±0.78) 2.17 (±0.70) <0.001
HDL cholesterol (mmol/l) 1.22 (±0.29) 1.26 (±0.31) 0.01
HOMA-IR 3.4 (±1.7) 2.4 (±1.6) <0.001
γ-glutamyl transpeptidase (γ-GT) 22.4 (±9.5) 18.9 (±12.8) 0.001
Waist (cm) 105.0 (±12.6) 96.4 (±13.0) <0.001
 γ-glutamyl transpeptidase.

Those with no steatosis pre-treatment (score 0) were excluded because they could not improve their steatosis score (n=45 analysed).
*Three stages based on Tanner stages: ‘prepubertal’ equals G/M1&P1; ‘postpubertal’ equals G/M5&P5; ‘pubertal’ equals all other Tanner stages.
† Only one patient in ‘prepubertal’ stage; no regression analysis possible.
‡ Only one patient in ‘prepubertal’ stage; no regression analysis possible.
§ Three stages based on Tanner stages: ‘prepubertal’ equals G/M1&P1; ‘postpubertal’ equals G/M5&P5; ‘pubertal’ equals all other Tanner stages.

Figure 1 Prevalence of steatosis, elevated alanine aminotransferase (ALT) and elevated aspartate aminotransferase (AST) before (white bar) and after (black bar) 6 months of treatment.

γ-glutamyl transpeptidase (γ-GT). HOMA-IR index and an increase in high-density lipoprotein cholesterol in univariate logistic regression analysis (table 3). In multivariate logistic regression analysis, only a decrease in the HOMA-IR index remained significantly associated with improvement in steatosis stage (OR 1.61, 95% CI 1.2 to 3.4).

In univariate linear regression analysis, a decrease in serum ALT was associated with male gender, inpatient treatment, decrease in BMI z-score, decrease in HOMA-IR index, decrease in waist circumference and decrease in low-density lipoprotein (LDL) cholesterol (table 4). In multivariate linear regression analysis, only a decrease in the HOMA-IR index remained significantly associated with a decrease in serum ALT; a decrease of 1 point in the HOMA-IR index resulted in a 2.6 U/l (95% CI 0.8 to 4.4) decrease in ALT.

In univariate linear regression analysis, a decrease in serum AST was associated with Arab African ethnicity, inpatient treatment, decrease in HOMA-IR index and decrease in LDL cholesterol (table 4). After combining these associated factors in a multivariate logistic regression analysis only a decrease in the HOMA-IR index remained significantly associated with a decrease in serum AST; a decrease of 1 point in the HOMA-IR index resulted in a 1.4 U/l (95% CI 0.36 to 2.46) decrease in AST.

The linear regression model for change in transaminases and HOMA-IR index had an R² value of 0.06 and 0.05 for ALT and AST, respectively. This means that a change in the HOMA-IR index only explained 5–6% of the observed changes in serum transaminases.

DISCUSSION
This study shows the efficacy of a 6-month lifestyle programme on NAFLD in a large unselected cohort of severely
Table 4 Prediction of a decrease in serum ALT and AST after 6 months of treatment by univariate linear regression analysis (n=144)

<table>
<thead>
<tr>
<th>Variable</th>
<th>ALT</th>
<th>AST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B† (95% CI)</td>
<td>p Value</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>7.9 (1.2 to 14.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>−0.6 (−2.0 to 0.9)</td>
<td>0.44</td>
</tr>
<tr>
<td>Duration of overweight (years)</td>
<td>−0.1 (−1.3 to 1.2)</td>
<td>0.93</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arab African</td>
<td>7.8 (4.7 to 20.3)</td>
<td>0.22</td>
</tr>
<tr>
<td>African</td>
<td>−3.4 (−17.0 to 10.3)</td>
<td>0.63</td>
</tr>
<tr>
<td>Middle East</td>
<td>2.0 (−6.1 to 10.1)</td>
<td>0.63</td>
</tr>
<tr>
<td>Tanner stage†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prepubertal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pubertal</td>
<td>−0.3 (−14.8 to 14.2)</td>
<td>0.97</td>
</tr>
<tr>
<td>Postpubertal</td>
<td>−1.2 (−16.3 to 13.9)</td>
<td>0.87</td>
</tr>
<tr>
<td>Outpatient treatment</td>
<td>−7.5 (−14.0 to 1.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Decrease in BMI z-score (per 0.1 SD)</td>
<td>0.8 (−0.7 to 1.6)</td>
<td>0.07</td>
</tr>
<tr>
<td>Decrease in waist circumference (per cm)</td>
<td>0.4 (0.1 to 0.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Decrease in HOMA-IR (per 1.0 point)</td>
<td>2.6 (0.8 to 4.4)</td>
<td>0.005</td>
</tr>
<tr>
<td>Increase in HDL cholesterol (per mmol/l)</td>
<td>−7.6 (−25.7 to 10.5)</td>
<td>0.41</td>
</tr>
<tr>
<td>Decrease in LDL cholesterol (per mmol/l)</td>
<td>5.8 (0.1 to 11.5)</td>
<td>0.05</td>
</tr>
<tr>
<td>Decrease in diastolic BP (per mm Hg)</td>
<td>−0.1 (−0.3 to 0.2)</td>
<td>0.50</td>
</tr>
<tr>
<td>Decrease in systolic BP (per mm Hg)</td>
<td>0.1 (−0.2 to 0.3)</td>
<td>0.70</td>
</tr>
</tbody>
</table>
| ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein.

*In case of a significant p value, a positive B value indicates a higher decrease in ALT/AST during treatment.

†Three stages based on Tanner stages: ‘prepubertal’ equals G/M1&P1; ‘postpubertal’ equals G/M5&P5; ‘pubertal’ equals all other Tanner stages.

obese children. Steatosis, serum ALT and serum AST normalised in 62%, 57% and 68% of the participants, respectively, who completed the lifestyle programme. Furthermore, this study establishes that improvement in insulin sensitivity is the parameter most strongly associated with improvement in NAFLD achieved by lifestyle intervention.

The study population was identified by screening children referred to a tertiary obesity centre for the presence of NAFLD. This study population is therefore not comparable with other paediatric studies that recruited children referred to tertiary liver centres mostly for evaluation of elevated transaminases or children selected based on insulin resistance. Comparing paediatric studies with a similar selection of patients, we have found a similar efficacy of lifestyle intervention: normalisation of ultrasonography determined steatosis occurred in 50–89% of patients, and in multivariate regression analysis in all three models. Nobili et al using multivariate regression analysis also found that change in fasting insulin was an independent predictor of change in ALT in their control group of children only treated with lifestyle intervention. By contrast, Reinehr et al did not find a significant correlation between change in transaminases and HOMA-IR in children treated with lifestyle intervention. The latter study only used univariate analysis. In adults, a correlation between improvement in NAFLD and fasting glucose has also been established.

This study establishes a clear link between improvement in insulin resistance and improvement in NAFLD during lifestyle intervention. Although it has not been established whether insulin resistance is a cause or consequence of NAFLD, this finding supports studies into lifestyle and drug interventions targeted at insulin resistance in children with NAFLD. Recently, it was shown that increasing physical activity alone can improve NAFLD independent of weight changes in adults and children. A possible mechanism could be the positive effect of exercise on peripheral and hepatic insulin sensitivity.

Drugs that improve insulin sensitivity have only been studied in open-label, uncontrolled studies in children. A paediatric, randomised controlled trial with metformin as a monotherapy in NAFLD is now underway (ClinicalTrials.gov identifier: NCT00063635). Thiazolidinediones, such as pioglitazone...
and rosiglitazone, have not been studied in children, data in adults are limited and a beneficial effect has not been well established. 7 31

It should be noted, however, that the HOMA-IR index only explains 5~6% of the change in tansminases in this study. Thus, other factors not included in this study are related to the observed treatment effect. In order to identify the other factors related to the improvement in NAFLD, larger studies including more associated factors (eg, genetic) are needed.

The limitation of almost all studies on NAFLD in children, including this study, is the inaccuracy of the tools used to detect NAFLD. Ultrasonography cannot detect subtle (changes in) liver steatosis. 32 34 Moreover, it is operator dependent, which is underscored by the moderate intra-observer agreement observed in this study. Serum transaminases and γ-GT have been found to be the clinical variables correlating best with histological non-alcoholic steatohepatitis in children; however, they cannot replace histology. 25 35

Thus, other factors not included in this study are related to successful treatment of NAFLD. Future studies should focus on identifying other factors related to successful treatment of NAFLD and exploring lifestyle and drug interventions based on these factors.

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Contributors  All authors contributed equally to this study.

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