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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.[1 2] The clinical spectrum of NAFLD consists of simple steatosis, steatohepatitis and cirrhosis. Important fibrosis and occasionally cirrhosis can occur at paediatric age.[3 4] 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.[5 6]

What is already known on this topic

- Non-alcoholic fatty liver disease (NAFLD) has a high prevalence among obese children.
- Lifestyle intervention is the primary therapy for NAFLD, but its efficacy has not been well determined.
- Factors related to improvement in NAFLD during treatment have not been determined.

What this study adds

- Markers of NAFLD normalise in about 60% of children who complete an intensive 6-month lifestyle intervention programme.
- Improvement in insulin sensitivity is the parameter most strongly related to improvement in NAFLD, but it explains only a small part of the observed treatment effect.
- Other factors related to successful treatment of NAFLD need to be identified so that these can be a focus for new lifestyle and drug interventions.

At present, lifestyle intervention remains the only accepted therapy for NAFLD.[7] 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.[8,–,13] 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 >30 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).[14] 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. Steatohepatitis was defined as ALT and/or AST serum level >35 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.[15] Diabetes mellitus was defined as fasting blood glucose >7.0 mmol or a 2 h blood glucose >11.1 mmol/l during the OGTT.[16] 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.[17 18] 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.[19]

[TABLE 1]

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 $\chi 2$ 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.

[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.

[FIGUUR 1]

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 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).

[TABLE 3]

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.

[TABLE 4]

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 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[8 11 13 20,–,22] or children selected based on insulin resistance.[13 23] 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,[9 10 12 24] mean ALT decrease of 10 U/l (95% CI –14 to –6) and mean AST decreased to 5 U/l (95% CI –7 to –3).[24] Taken together, these studies show that the current standard of care is at best moderately effective for NAFLD in children. Therefore, studies into more effective lifestyle and/or drug interventions are of paramount importance. At present, there is a lack of randomised controlled trials comparing lifestyle and/or drug interventions.[7]

The correlation between NAFLD and insulin resistance has been well established in children in cross-sectional studies.[2 3 25 26] Insulin resistance is considered one of the main pathophysiological mechanisms in NAFLD that results in an increase in lipolysis in visceral adipose tissue and a consequent increase in the influx of free fatty acids into the liver. However, few studies have examined the correlation between change in NAFLD during treatment and change in insulin resistance and other clinical parameters. Moreover, these few studies usually only determined univariate correlations.[9 11] In this study, multivariate regression analysis was performed to determine the association between change in NAFLD and baseline or changes in several basic clinical and biochemical parameters. In all three models of NAFLD (ultrasonography determined steatosis, ALT and AST), improvement in insulin resistance is identified as the parameter independently related to improvement in NAFLD. Change in BMI z-score was not significant in

multivariate regression analysis in all three models. Nobili et al[20] 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[24] 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.[27]

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.[28,–,30] Drugs that improve insulin sensitivity have only been studied in open-label, uncontrolled studies in children.[7] 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 tarnsaminases 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 intraobserver 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] We assume, however, that given the relatively large sample size and longitudinal follow-up, the changes in these parameters represent changes in NAFLD. In the multivariate regression analysis, we used change in serum ALT and AST as a continuous variable, thus also including those with transaminases within the normal range at baseline. The upper limits of transaminases are arbitrary and debated, and it has been shown that transaminases within the normal range decrease in those with NAFLD in response to treatment.[36] Therefore, the change in ALT and AST within the normal range in this large cohort can be considered a treatment effect on NAFLD. Notably, improvement in the HOMA-IR index was also independently correlated with improvement in γ-GT (data not shown). The use of more accurate modalities to detect steatosis and inflammation/fibrosis, such as MRI, MR proton-spectroscopy and/or histology, in future studies would possibly allow the identification of other significant biochemical or anthropometric parameters that relate to change in NAFLD.

Although patients were partially treated in an inpatient and outpatient setting, comparison of these treatments was not possible in this cohort because patients were not randomly assigned to either programme. Patients treated in an inpatient setting had a longer duration of obesity, significantly higher BMI z-score and higher waist circumference (data not shown). In multivariate regression analysis, patient setting was found to be not significantly associated with response to therapy. Including patient setting in multivariate regression analysis until the end did not alter the results.

In this study, the prevalence of steatosis and elevated ALT at baseline was higher in the 28 children who did not have endpoint measurements compared with those who had endpoint measurements. There is no theoretical basis to assume that children with steatosis and elevated ALT are more likely not to complete a lifestyle intervention programme. In two other studies describing drop out, such a difference was not observed.[20 24] We therefore assume that this difference is based on coincidence.

This study shows a moderate efficacy of lifestyle intervention on NAFLD in a well-defined cohort of severely obese children. Improvement in insulin resistance is identified as the clinical parameter most strongly associated with improvement in 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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