Nonalcoholic fatty liver disease decrease in obese adolescents after multidisciplinary therapy

**Background** Despite the increasing prevalence of nonalcoholic fatty liver disease, its pathogenesis and clinical significance remain poorly defined and there is no ideal treatment.

**Objective** The aim of this study was to assess the short-term (12-week) multidisciplinary therapy on visceral adiposity and nonalcoholic fatty liver disease control.

**Methods** We evaluated and compared the distribution of visceral adiposity and nonalcoholic fatty liver disease, by ultrasonography, in 73 post-puberty obese participants (17.01 ± 1.6 years old; body mass index 36.54 ± 2.86 kg/m²), submitted to a multidisciplinary treatment without medications, at the beginning and after 12 weeks of intervention. Descriptive and one-way analysis of variance, and paired t-test were performed.

**Results** The results indicated that after intervention the adolescents had a significant reduction in visceral adiposity (4.05 ± 1.55 to 3.37 ± 1.44) and nonalcoholic fatty liver disease prevalence (from 52 to 29% on the right side and from 48 to 29% on the left side). It is a positive result because nonalcoholic fatty liver disease can progress to cirrhosis, even in children and adolescents.

**Conclusions** The short-term treatment suggests a profound impact on the control of obesity-related co-morbidities in young people. Eur J Gastroenterol Hepatol 18:1241–1245 © 2006 Lippincott Williams & Wilkins.

**Keywords:** adolescents, fatty liver, therapy, ultrasound, visceral adipose tissue

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**Introduction**

Obesity is now recognized as a major public health issue worldwide. Excess body weight increases mortality rates, and several epidemiological and clinical studies have confirmed the pathogenic contribution of obesity to several diseases, namely arterial hypertension and type 2 diabetes mellitus, and also to cardiovascular mortality. In developed countries, the total burden of obesity and related conditions (high blood pressure, high cholesterol, physical inactivity) has been estimated to be around 30% of disability-adjusted life years. The pathogenesis of obesity is complex and not well known. It is believed to be mostly a disorder of energy balance: increased caloric intake and decreased energy expenditure [1,2].

Nonalcoholic fatty liver disease (NAFLD) is a new, emerging clinical problem among patients. NAFLD includes a broad spectrum of liver tissue alterations, ranging from pure steatosis to cirrhosis [3,4] through nonalcoholic steatohepatitis (NASH). Fatty liver affects 2.6% of children, 10–25% of adolescents and 22.5–52.8% of obese children [5,6]. The prevalence of overweight and obesity has increased dramatically in Brazil. It has become clear that overweight children are likely to become overweight adults [7,8]. Although there is no accepted pharmacological treatment that can reverse fatty liver disease, all patients should be given a low-fat diet and triglyceride (TG)-lowering agents. They should also be encouraged to exercise [6].

Although the prevalence and manifestations of NAFLD in children and adolescents have not been fully appreciated, the disorder is being observed with increasing frequency as the prevalence of obesity has risen in this population [8,9].

The purpose of this study was to assess the short-term (12 weeks) changes in visceral and subcutaneous adipose
tissue and hepatic steatosis prevalence in obese adolescents submitted to an exercise and nutritional education program associated with multidisciplinary intervention.

Patients and methods
Population
A total of 73 post-puberty obese adolescents, including 24 boys and 49 girls aged 15–19 years (17.01 ± 1.6 years), with a body mass index (BMI) of 36.54 ± 2.86 kg/m² admitted in our unit were included. The inclusion criteria were severe primary obesity (BMI > 95th percentile of the Centers for Disease Control reference charts) [10] and Pubertal Stage of Tanner criteria higher than 3 [11]. The exclusion criteria were identified genetic, metabolic or endocrine disease, chronic alcohol consumption, previous drug use and other causes of liver steatosis.

Among all the patients, 31.7% presented metabolic syndrome and none presented hypertension in accordance with the World Health Organization criteria [12]. Characteristics of the population are shown in Table 1. Patients are adapted to overcome the deep psychological and social distress, as well as the heavy physical burden they are facing. Psychological support can take place either on a group or on an individual basis every 15 days.

Study protocol
Medical follow-up included initial examination and appropriate tests, followed by a regular clinical surveillance by the pediatrician every month. Pubertal stage was assessed by Tanner criteria (stage 3 or 4) [11]. Individuals were submitted to a multidisciplinary intervention for 12 weeks. The visceral/subcutaneous adiposity and hepatic steatosis were measured before intervention and after intervention. Effectiveness of weight loss was considered in those who lost a minimum of 4.5 kg [13]. The study was conducted in accordance with the guidelines in the Declaration of Helsinki and was formally approved by the Ethical Committee of the Federal University of São Paulo-Paulista Medicine School (no. 0135/04). All patients and their families provided a written consent form after they had been informed of the study protocol.

Anthropometric measurements
Participants were weighed wearing light clothing and no shoes on a Filizola scale to the nearest 0.1 kg. Height was measured to the nearest 0.5 cm by using a wall-mounted stadiometer. BMI was calculated as body weight (wt) divided by height (ht) squared (wt/ht²).

Serum analysis
Blood samples were collected in the outpatient clinic around 8:00 a.m. after an overnight fast, the fasting blood glucose (FBG) and immunoreactive insulin (I). Insulin resistance was assessed by the homeostasis model assessment insulin resistance index (HOMA-R) [14] and the quantitative insulin sensitivity check index (QUICKI) [15]. HOMA-R was calculated as [FBG (mg/dl)/ (mU/l)/405, and QUICKI as 1/(log I + log FBG). Total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol (LDL) and TG were analyzed using a commercial kit (CELM, Barueri, Brazil).

Hepatic steatosis, visceral and subcutaneous adiposity measurements
Abdominal ultrasonographic procedures before and after intervention were performed by the same examiner using a 3.5-MHz multifrequency transducer (broad band) located 1 cm from the umbilicus. The examiner was blind to the patient’s medical history. The ultrasonographic measurements of intra-abdominal (‘visceral’) and subcutaneous fat were taken. Ultrasonography-determined subcutaneous fat was defined as the distance between the skin and the external face of the recto abdominis muscle, and visceral fat was defined as the distance between the internal face of the same muscle and the anterior wall of the aorta [16]. The intraexamination coefficient of variation for ultrasonography was 0.8%.

Table 1  Anthropometrics, glucose, lipids, insulin, HOMA-R, QUICKI, subcutaneous and visceral adipose tissues in obese adolescents before and after intervention for weight loss

<table>
<thead>
<tr>
<th>Variables/time</th>
<th>Baseline</th>
<th>After intervention</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body mass (kg)</td>
<td>102.30 ± 17.41</td>
<td>97.70 ± 17.18</td>
<td>0.0001</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.67 ± 0.87</td>
<td>1.67 ± 0.88</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>36.54 ± 2.86</td>
<td>34.40 ± 2.86</td>
<td>0.05</td>
</tr>
<tr>
<td>Subcutaneous fat (cm)</td>
<td>3.33 ± 0.74</td>
<td>2.94 ± 0.72</td>
<td>NS</td>
</tr>
<tr>
<td>Visceral fat (cm)</td>
<td>4.05 ± 1.55*</td>
<td>3.37 ± 1.44</td>
<td>0.01</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>161.50 ± 28.05</td>
<td>162.74 ± 25.55</td>
<td>NS</td>
</tr>
<tr>
<td>HDL</td>
<td>46.65 ± 9.94</td>
<td>45.77 ± 7.39</td>
<td>NS</td>
</tr>
<tr>
<td>LDL</td>
<td>94.02 ± 23.68</td>
<td>94.67 ± 23.64</td>
<td>NS</td>
</tr>
<tr>
<td>TG</td>
<td>102.92 ± 41.38</td>
<td>111.87 ± 52.75</td>
<td>NS</td>
</tr>
<tr>
<td>Glucose</td>
<td>90.73 ± 6.63</td>
<td>89.00 ± 26.84</td>
<td>0.04</td>
</tr>
<tr>
<td>Insulin</td>
<td>17.23 ± 8.26</td>
<td>15.03 ± 25.87</td>
<td>NS</td>
</tr>
<tr>
<td>HOMA-R</td>
<td>4.06 ± 1.84</td>
<td>3.27 ± 1.27</td>
<td>0.006</td>
</tr>
<tr>
<td>QUICKI</td>
<td>0.31 ± 0.02</td>
<td>0.32 ± 0.01</td>
<td>0.03</td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TG, triglycerides; HOMA-R, homeostasis model assessment insulin resistance; QUICKI, quantitative insulin sensitivity check index; BMI, body mass index.

*Subcutaneous fat vs. visceral fat P < 0.01 at baseline condition.
physical activity of the same age and sex [18]. No fixed caloric intake was, however, prescribed; they were only encouraged to reduce their food intake. The baseline and postintervention food intake were measured by 3 days’ recordatory inquiry [19] (Table 2). The patients received nutritional training every 3 weeks (food pyramid; recordatory inquiry; weight-loss diets; diet vs. light; fat and cholesterol) to change the poor habits of energy intake during the weight reduction phase. In addition, the parents were encouraged to call a dietician if they needed further information. The nutritional education program concerns change in nutritional behavior, and information about qualitative and quantitative aspects of food requirement.

Leisure activity program

The adolescents had two sessions per week during the intervention. Each session lasted for 60 min and included, alternatively, recreational team sports (soccer, handball, basketball, etc.), gymnastics and walking performed in groups. Information about lifestyle changes related to activity was also provided and spontaneous activity (walking, stair climbing, etc.) was encouraged.

Statistical analysis

All data were analyzed by means of Stat soft package with significance set at \( P < 0.05 \) and expressed as means ± SD. Descriptive statistics, one-way analysis of variance and paired \( t \)-tests were performed to compare measures before and after the weight loss program.

Results

Anthropometrics and body fat

The results of body mass, BMI, subcutaneous fat and visceral fat before and after weight loss are shown in Table 1. Weight loss and weight management were observed in 48% each, and 4% of patients increased body weight. Both body mass and BMI showed a significant reduction after treatment. In the same way, visceral fat decreased significantly from 4.05 ± 1.55 to 3.37 ± 1.44 cm. Subcutaneous fat did not change with treatment. At baseline conditions, visceral adiposity was higher than subcutaneous fat. After intervention, however, neither presented significant differences.

Serum analysis

No significant differences were seen in cholesterol, high-density lipoprotein cholesterol, LDL and TG when preintervention and postintervention values were compared. Glucose and insulin concentrations presented a significant reduction, as well as HOMA-R, when compared with the values observed at baseline condition, and an increase in QUICKI (Table 1).

Food intake

No significant differences between values in carbohydrate consumption were observed after intervention when compared with baseline data. The nutritional education program was, however, successful in promoting decrease in total energy intake (\( P = 0.002 \)) and lipid consumption (\( P = 0.05 \)) and in increasing protein intake (\( P = 0.039 \)).

Hepatic steatosis

We observe that, at baseline, 52% of all the patients presented NAFLD on the right side and 48% on the left side. After intervention, there was a significant reduction in NAFLD prevalence to 29% on both the right and left sides (\( P < 0.05 \)).

Table 3 also shows that 41% of all the patients with NAFLD presented grade 1 on both sides of the liver at preintervention. At postintervention, grade 1 was reduced to 23 and 26% (right and left sides, respectively). Grade 2 was observed from 8 to 6% on the right side, and from 7 to 2% on the left, at preintervention and postintervention. Grade 3 was present in only 3% on the right side of the liver of all the patients at baseline and no incidences were observed after treatment.

Discussion

Obesity is the most significant single risk factor for the development of NAFLD, both in children and in adults. Obesity is also predictive of the presence of fibrosis, potentially progressing via NASH to advanced liver disease. Other predictive factors for liver disease progression have been identified, but at present the treatment of obesity remains the most effective preventive strategy. Therefore, modifications in lifestyle, and in particular weight reduction and regular exercise, represent the mainstay of the treatment and prevention [2,17].

In this sense, the most important piece of evidence in the present investigation is the observation that the
prevalence of NAFLD in obese adolescents is very high (52%) and similar to that observed by other authors. A recent review mentioned that the prevalence of hepatic steatosis rises to 52.8% in obese children when compared with nonobese children (2.6%) of the same age [2]. Despite the limitations of the accuracy of echotomography in assessing hepatic steatosis, our results suggested its importance in clinical investigations. On the other hand, after our intervention with lifestyle modifications, we observed a significant reduction to 29%.

Considering the grading for steatosis, they presented a variation from grade 1 to grade 3. It represents a poor metabolic conditioning that the liver is submitted to, because in grade 1 < 33% of the hepatocytes are affected, but in grade 3 > 66% of them are affected [17]. Our patients had a prevalence of 3% in grade 3, but it was reversed with treatment. These results are very important because the degree of steatosis in all predictive factors for the development of fibrosis/cirrhosis in patients with NAFLD has been a consistent issue.

A limitation of the present study was the lack of histological data that would better describe the actual effect of the intervention on the prevalence and grade of NAFLD. Increasing interest, however, is seen in ultrasound-diagnosed NAFLD in the ambulatory care setting [20].

The primary metabolic abnormalities leading to hepatic lipid accumulation consist of alterations in the uptake, synthesis, degradation or secretion of lipid molecules, resulting from insulin resistance [4]. Increased delivery of free fatty acids (FFAs), increased hepatic synthesis of FFAs, decreased FFAs β-oxidation in the liver and/or decreased synthesis or secretion of very low-density lipoproteins represent key aspects of the steatosis-associated fat homeostasis. Studies with both animals and humans have suggested that the visceral adipose tissue may be a major source of massive FFA flow to the liver [21].

In fact, in the present investigation we demonstrated that our patients had, at the beginning of the treatment, more visceral adiposity than that observed in subcutaneous fat. Our treatment was, however, effective in promoting a significant reduction in visceral adiposity, being similar to that observed in the subcutaneous fat after treatment. These adaptations to the lifestyle program in visceral adiposity were accompanied by a significant reduction in the total energy intake from 1908.17 ± 770.95 to 1576.15 ± 422.88 and lipid consumption from 32.11 to 29.83%. Nevertheless, a limitation to the interpretation of our findings is the lack of consistency and/or unrealistic reporting of the dietary intake by obese individuals.

Development of NAFLD is strictly related to reduced tissue sensitivity to insulin [22,23]. Elevated levels of insulin exert a different influence on adipocytes and hepatocytes [24]. In the present investigation, we observed that 44.90% had hyperinsulinemia and 10% presented insulin resistance. On the other hand, these metabolic and hormonal alterations with obesity were attenuated with lifestyle modifications. After intervention, the hyperinsulinemia decreased to 38.46% and HOMA-R to 5.12%. Adiponectin is a modulator of insulin sensitivity, and suggests a possible protective role against fatty liver [25]. Therefore, the level of adiponectin probably increases in these patients after intervention.

Elevated levels of leptin are found in the majority of patients with NASH [25]. According to the results obtained in animal studies, leptin may also exert an antisteatotic effect [26]. Systemic leptin concentration is reduced, in obese humans, after weight loss [27]. It is suggested that a decrease in hyperleptinemia and improvements in insulin sensitivity, after the weight loss program, may have contributed to the explanation of a decrease in prevalence of the hepatic steatosis observed in the present investigation.

According to Scheen and Luyckx [24], only progressive weight loss has benefits for liver damage. Rapid and massive weight reductions, as in morbidly obese participants undergoing bariatric surgery, may promote or worsen NAFLD and NASH, and even result in liver failure. Finally, Bouneva and Kirby [28] pointed out that exercise is still a key factor in any successful weight loss program. Thus, the development of an achievable exercise program for each patient is essential. It is, of course, to be expected that the program will help sedentary obese people move from inactivity to a fit condition. Exercise does not need to be intense to promote weight loss, and maximal physical exertion is not required. Consequently, a treatment based on lifestyle modifications with changes promoted by long-term therapy is important.

Conclusion
The short-time leisure activity associated to multidisciplinary intervention promotes a significant decrease in the prevalence of hepatic steatosis, accompanied by a significant decrease in visceral adipose tissue and lipid consumption. Even though it is suggested that after treatment prevention of hepatic cirrhosis and support central/visceral obesity control occur, other studies with long-term therapy including TG-lowering agents to NAFLD prevention and control are needed.

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References


