markers associated with endoplasmic reticulum stress and liver dysfunction. Indeed, it was verified a positive correlation between saturated fatty acids intake with insulin resistance, which represents a key role in the NAFLD genesis, suggesting that saturated fat intake must be limited as a nutritional strategy in NAFLD prevention and treatment [8].

Papandreou et al. [34], demonstrated that the saturated fatty acids intake were proportionally increased to the degree of hepatic steatosis. Indeed, they observed in multiple regression analysis of factors associated with fatty liver that only HOMA-IR and saturated fatty acids were the most significant after adjustment for age, sex and diet. Diets rich in fatty acids mainly saturated and trans-fatty acids, as well as carbohydrate-rich diets, favor an acute increase in insulin resistance independent of adiposity. High-saturated fatty acids intake may also promote steatohepatitis directly by modulating hepatic TG accumulation and oxidative activity as well as indirectly by affecting insulin sensitivity and postprandial triglyceride metabolism.

In this study, a positive correlation between the energy, saturated fatty acid intake and visceral fat in NAFLD patients (Fig. 1a and b) was shown in accordance to previous research [12]. In addition, Katsuki et al. [35] found a strict relation between visceral fat and AgRP concentrations, reinforcing that elevated saturated fatty acids consumption have implications in visceral fat, orexigenic systems and in some important parameters of NAFLD development.

One of the most important findings of our results is the positive correlation between saturated fatty acids intake and the orexigenic neuropeptides (NPY and AgRP) in NAFLD obese adolescents (Fig. 2a and b). High intake of saturated fat and cholesterol increase the risk of diabetes elevating insulin secretion, and this hampers mediate NPY release [36,37].

In addition to energy intake per se, macronutrient composition of the diet also influences NPY and AgRP in the hypothalamus. Each dietary preference pattern reflects the result of a balance between the actions of and those of other hormones and neuropeptides, such as ghrelin, which are sensitive to ingestion. This way, dietary preference for either carbohydrate or fat is associated with NPY status [38].

Solga et al. [39] demonstrated that high carbohydrates intake was associated with greater levels of inflammation in obese adolescents with NAFLD. High carbohydrates intake, mainly sucrose, glucose, fructose and foods with high glycemic index, cause an increase in de novo lipogenesis, which leads to an increased conversion of glucose to fatty acids. Zelber-Sagi et al. [40] verified the higher intake of soft drinks is associated with increased NAFLD development. Indeed, the high glycemic index carbohydrate leads to a quick increase in the glycemic index carbohydrates that stimulates the release of insulin from the pancreas and decreases the increase in insulin levels as a result of the increase in glucose during exercise, which are hormones [6]. Our data corroborated this finding, showing the positive correlation between carbohydrate intake and NPY (in mg), stimulating an orexigenic pathway in these NAFLD patients (Fig. 3).

This way, to choose low-glycemic index carbohydrates produces small fluctuations on blood glucose and levels and could be considered an important co-adjutor to long-term health, since would reduce the NAFLD risk [41].

The key observation in this clinical study is the presence of correlation between the saturated fatty acids intake and the orexigenic neuropeptides in NAFLD adolescents, reinforcing that the nutritional plan should be based on a balanced and individualized diet, prioritizing the complex carbohydrates, including fibers, decreasing lipid consumption, mainly the saturated fatty acid intake.

Conclusion

Our data suggested that the diet composition exerts an important role in the NAFLD genesis and treatment well as, in the orexigenic pathways of these patients, being essential to consider that the excessive saturated fatty acids intake was a determinant risk factor to increase the NAFLD development. Indeed, the term inter-disciplinary intervention was effective to improve important NAFLD parameters in pediatric population.
Orexigenic neuropeptides secretion in NAPFLD de Pinato et a.

Acknowledgements
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Conflicts of interest statement: none declared.

References
Anexo 6.

Capítulo de Livro Internacional:

Nutritional and Clinical Strategies on Prevention and Treatment of NAFLD and Metabolic Syndrome

Ana R. Dâmaso, Aline de Piano, Lian Tock, and Rajaventhin Srirajaskanthan

CONTENTS

8.1 Introduction .................................................................................................................. 11
8.2 Procedures and Treatment Regimens ......................................................................... 11
  8.2.1 Concepts of Multidisciplinary Intervention on NAFLD and MS Control .............. 11
  8.2.2 Clinical Therapy .................................................................................................... 11
    8.2.2.1 Medical Program ......................................................................................... 11
    8.2.2.2 NAFLD Image Diagnostic .......................................................................... 11
  8.2.3 Psychological Therapy .......................................................................................... 11
  8.2.4 Exercise Therapy .................................................................................................. 11
  8.2.5 Nutritional Therapy ............................................................................................. 12
    8.2.5.1 Establishing a Meal Plan ........................................................................... 12
  8.2.6 Practical Applications .......................................................................................... 12
8.3 Summary Points, Policy Makers, and Future Research .............................................. 12
References ......................................................................................................................... 12

8.1 INTRODUCTION

The term nonalcoholic fatty liver disease (NAFLD) has been used to describe larger spectrum of steatosis liver diseases commonly associated with the metabolic syndrome (MS), and represents a constellation of related health diseases. However, obesity-associated NAFLD was first described nearly 50 years ago, and was only partially confirmed recently due to the complexity of the biochemical machine th
plays an important role between the inflammatory process and cellular mechanisms of NAFLD-related diseases (Zivkovic et al., 2007).

Nowadays, NAFLD is regarded as the hepatic manifestation of the MS involving the multifactorial disease involving a complex interaction of genetics, diet, lifestyle, and is defined as the accumulation of lipids, primarily in the form of triglyceride in individuals who do not consume significant amounts of alcohol (2 ethanol/day) (de Piano et al., 2007).

In this manner, imbalances in major lipid signaling pathways that are highly interconnected contribute to disease progression in chronic inflammation, autoimmunity, allergy, cancer, atherosclerosis, hypertension, heart hypertrophy, as well as metabolic and degenerative diseases. The resulting commonality of various different signaling components means that different diseases share common points of intervention (Wymann and Schneider, 2008).

Given the close relationship among obesity, MS, and the development of NAFLD, it is not surprising that many NAFLD patients have multiple components of the MS. Thus, management strategies for such patients need to be predominantly support by diet therapy to promote weight loss as well as improve related comorbidities; however, experiences with multidisciplinary approaches, including clinical, exercise, and psychological counseling, are recommended for the long-term success of diet and lifestyle interventions.

This chapter reviews the clinical strategies on MS and NAFLD treatment based on actual multidisciplinary therapy conceptions with focus on nutritional recommendations contributing to the control of these diseases and comorbidities.

8.2 PROCEDURES AND TREATMENT REGIMENS

8.2.1 Concepts of Multidisciplinary Intervention on NAFLD and MS Control

Despite the increasing prevalence of NAFLD, its pathogenesis and clinical significance remain poorly defined and there is no ideal treatment. However, as mentioned above and considering the multifactor altered mechanisms associated with NAFLD etiology, it would be expected to a role in integrated health intervention.

In this sense, 5 years ago we started, as suggested by World Health Organizat (WHO) (2000) and inspired by the Adipositas Rehabilitiation Zentrum, INSULZ Therapy Model from Germany (Siegfried et al., 2006), a multidisciplinary approach with the objective of primarily treating obesity. In subsequent years, it was observed that about 50% of obese adolescents had a positive ultrasonography (US) diagnosis for NAFLD and 28% presented MS by WHO criteria. Although the prevalence of NAFLD was reduced (from 50% to 29%) after short-term therapy, as well as 1 (from 28 to 8%) after long-term therapy, some obese adolescents continued to show altered metabolic and hormonal analyzed parameters (Tock et al., 2006; Carant et al., 2007).

As described above, the next step is keeping in mind the importance of promoting the best way to control these comorbidities, as part of the clinical approach of normalizing...
Nutritional and Clinical Strategies on Prevention and Treatment of NAFLD

insulin resistance, creating good health expectations for patients as long as poss and improving their quality of life (data not published).

Another noteworthy question about therapeutic strategies is the relevance of integrated approach between nutritional therapy and psychological counseling, considering in particular several eating disorders (e.g., bulimia, anorexia) as well altered behaviors (e.g., anxiety, depression). When dealing with undesirable conditions such as metabolic and hormonal disorders, which result in imbalance between food intake and energy expenditure, one the most important target is to treat obese MS, and NAFLD. This clearly induces an amplification of the empowerment-based approach to control of comorbidities, which sometimes delays the expected beneficial effects on patients’ lives.

Finally, the interconnection between nutritional therapy and exercise therapy essential to energy balance control and induces both professionals to work together to support this type of intervention. Through this consensus, one the most promising means of treating these pathologies is integrated.

In fact, in a recent review published in Hepatology, Bellentani et al. (2008) concluded that although very few studies have tested the effectiveness of intensive behavior therapy in NAFLD, aimed at lifestyle modifications to produce stable weight by reduced calorie intake and increased physical activity, it is important that behavior therapy should simultaneously address all clinical and biochemical defects. Indeed, Bellentani et al. suggest that there is a need for multidisciplinary teams (nutrition psychologists, and physical activity supervisors) to treat patients with NAFLD.

8.2.2 Clinical Therapy

8.2.2.1 Medical Program

To accomplish their health and clinical goals, patients with NAFLD and MS need to undergo a long-term weight loss multidisciplinary program. The main focus of clinical treatment are as follows: identified genetic, metabolic, or endocrine causes; chronic alcohol consumption; previous drugs utilization; enteral and parenteral diets; fast weight loss; viral hepatic diseases; and other causes of liver steatosis.

Examination of NAFLD obese patient presents some distinct challenges for the clinician, including increased size and limited mobility, which create a barrier to proper assessment of physical examination: increased chest wall abdominal fat, which can impair effective auscultation and palpation of these anatomical areas; increased risk for a host of diseases, many of which will not be recognized before the clinical evaluation because they are clinically difficult to detect, and require appropriate screening for early detection (e.g., diabetes, hyperlipidemia). Finally, physicians must keep in mind those primary eating disorders (e.g., bulimia) as well as psychiatric and related conditions (e.g., depression, loss of self-esteem) that are increasingly present in obese NAFLD patients and may have an important impact on subsequent medical therapy. These conditions can affect successful weight management and produce adverse health consequences in their own right. In this manner, clinical examination includes the usual elements of patient history and physical condition as well as recognition of comorbid conditions and diseases that are more prevalent in NAFLD patients, which are necessary to accomplish this goal.
At the beginning, after undergoing short- and long-term multidisciplinary therapy, the patients must be evaluated in all parameters included in the medical screening organogram presented in Figure 8.1. During the routine, the patients visit the clinician once a month.

8.2.2.1.1 Anthropometric and Body Composition Measurements
At the beginning and throughout the course of treatment, the weight, height, and body mass index calculated as body weight (wt) divided by height (ht) squared (wt/ht²), plus anthropometric measurements of the subjects must be recorded. Body composition may be estimated by plethysmography in the BOD POD body composi
system. The advantage of this method over dual-energy X-ray absorptiometry is that it allows the operator to estimate the body composition of patients with larger body habitus (up to 140 kg); however, it does not incorporate the measurement of body fat distribution (Fields et al., 2004). Considering the limitations as well as variation between body compositions, it is suggested to use two or three methods in the same subjects as part of the multidisciplinary therapy. The choice of method, naturally, depends on the objectives that the health team wants to attain during disease control.

8.2.2.1.2 Laboratory Studies

Based on clinical history and physical examination, laboratory testing is often desired by clinical suspicion. A fasting blood sample should be part of the routine screening panel for insulin resistance, hypothyroidism, dyslipidemia, hepatic transaminases, altered profile [alanine aminotransferase (ALT), aspartate aminotransferase (AST) and γ-glutamyl transferase (GGT)] as well as other risks for inflammatory processes related to NAFLD, including proinflammatory [tumor necrosis factor α (TNF-α), leptin, protein C reactive, interleukin-6] and anti-inflammatory cytokine profile [adiponectin], which contribute to the knowledge about NAFLD development control (Schwimmer et al., 2003). Blood samples for all these analyzed parameters must be repeated after short- and long-term therapy.

8.2.2.2 NAFLD Image Diagnostic

8.2.2.2.1 Hepatic Steatosis, Visceral, and Subcutaneous Adiposity Measurements

NAFLD diagnosis and treatment can be accomplished by laboratory methods, including US, computerized tomography (CT), and magnetic resonance (MR). Although CT and MR offer somewhat smaller errors in hepatic and visceral fat estimation compared to US, this method is more useful in clinical routine because of its cost and easy application. Future studies using these methods in the same NAFLD patients are essential for the proper assessment of compositional change with weight loss in a clinical trial (Saadeh et al., 2002; D’Amaso et al., 2008).

8.2.3 Psychological Therapy

A diagnosis must be established via validated questionnaires considering specific psychological problems caused by obesity and MS described in the literature, such as depression, disturbances of body image, anxiety, and decrease in self-esteem. Considering the high prevalence of obese patients with NAFLD (about 60%), these questions were included as part of the therapy for all subjects in treatment (de Piñero et al., 2007). During the multidisciplinary intervention, the psychologist must discuss with patients about body image and eating disorders (e.g., bulimia, anorexia nervosa); binge eating, their signals, symptoms, and consequences for health; relation between feelings and food; familiar problems such as alcoholism; and other important topics to improve each behavior disturbance related to obesity, MS as well NAFLD.
An individual psychological therapy was recommended when behavior and nutritional problems were identified. After both short- and long-term multidisciplinary therapy and 12 months of intervention, patients must be reevaluated. Figure 8 shows the psychological algorithm suggested for this type of intervention.

**FIGURE 8.2** Organogram of psychological plan to be established at baseline and after short- and long-term multidisciplinary therapy.
8.2.4 Exercise Therapy

The main aim of the exercise therapy is to promote lifestyle changes to motivate NAFLD patients to incorporate physical activity in their regimen as well as maintain a negative energy balance and, consequently, stable weight loss.

An exercise program should be realistic and should focus on long-term weight loss after inquiring about the medical background, exercise history, and preferences of subjects. NAFLD patients may need a personalized aerobic training and/or composition session with aerobic exercise plus resistance training including 60-minute session, three times a week (180 min/week), under the supervision of a sports therapist. Each program needs to be based on the results of an initial oxygen uptake test for aerobic exercises (cycle ergometer and treadmill). The intensity may be set at a workload corresponding to ventilatory threshold 1 (50–70% of oxygen uptake) according to recommendations on the type and amount of physical activity that produce health benefits, focusing on the idea of accumulating moderate-intensity activity throughout the day (Matsudo and Matsudo, 2006).

At the end of short- and long-term multidisciplinary therapy, aerobic tests should be performed to assess physical capacities and adjust the physical training intensity for each individual. During aerobic and resistance sessions, the patients’ heart rates need to be monitored. The suggested exercise program was based on American College of Sports Medicine (2001) recommendations. Information about lifestyle changes related to activity must also ensure that routine physical activity (walking, stair climbing, etc.) is encouraged.

In NAFLD and MS management, it was suggested that patients could benefit from relationships between exercise effects and these diseases. Table 8.1 identifies the main topics to be encouraged in exercise classes.

Figure 8.3 shows the exercise therapy as a suggested organogram.

<table>
<thead>
<tr>
<th>TABLE 8.1</th>
<th>Main Exercise Topics Suggested for MS and NAFLD Long-Term Multidisciplinary Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise Class</td>
<td>Themes</td>
</tr>
<tr>
<td>1</td>
<td>General concepts for lifestyle changes</td>
</tr>
<tr>
<td>2</td>
<td>Hormonal regulation of energy balance</td>
</tr>
<tr>
<td>3</td>
<td>Different exercise and energy expenditure</td>
</tr>
<tr>
<td>4</td>
<td>Aerobic vs. strength training effects on obesity and comorbidities</td>
</tr>
<tr>
<td>5</td>
<td>Effects of exercise and nutrition on MS control</td>
</tr>
<tr>
<td>6</td>
<td>Effects of exercise and nutrition on NAFLD control</td>
</tr>
<tr>
<td>7</td>
<td>Effects of exercise and nutrition on immune system</td>
</tr>
<tr>
<td>8</td>
<td>Effects of exercise and nutrition on type II diabetes control</td>
</tr>
<tr>
<td>9</td>
<td>Effects of exercise and nutrition on weight loss management</td>
</tr>
<tr>
<td>10</td>
<td>Effects of exercise and nutrition eating disorders</td>
</tr>
<tr>
<td>11</td>
<td>Yo-yo effects of rapid weight loss</td>
</tr>
<tr>
<td>12</td>
<td>Short- and long-term effects of exercise and nutrition on obesity and comorbidities</td>
</tr>
</tbody>
</table>
FIGURE 8.3 Organogram of exercise program to be established at baseline and after short- and long-term multidisciplinary therapy.

8.2.5 Nutritional Therapy

As described at the beginning of this chapter, considering the strong association among obesity, MS, and development of NAFLD, management strategies for the prevention and treatment of these diseases need to be based on a long-term approach.
multidisciplinary therapy including all associated comorbidities. The nutritional plan must consider strategies to promote gradual weight loss, glycemic control, reduction in low-density lipoprotein cholesterol (LDL-C), triglycerides, and very low density lipoprotein cholesterol (VLDL-C) serum concentrations, mainly reduction in visceral adiposity. A recent study verified the correlation between visceral fat accumulation with increased degree and risk of developing NAFLD (Dámaso et al., 2008).

Dietary standards recommend specific nutrients, but not the foods that contain them. To apply these standards on food choices, a better plan with options in terms of food groups or exchange lists are needed to support the patients in relation to what nutrients they require. The most commonly used tool in planning the daily menu is the food guide pyramid. Nutritional intervention is essential in evaluating food intake, deficiencies, or excess nutrients. Most methods of evaluating dietary intake involve different tools, such as 24-hour recall, 3-day food diary, food frequency, and diet history (Table 8.2).

A nutritional plan must be based on the levels recommended by the Dietary Reference Intake (DRI) according to age and gender (National Research Council, 2002). Patients with NAFLD and MS need to be encouraged to reduce their food intake and follow a balanced diet.

At the beginning of multidisciplinary approach, diet history, 24-hour recall, 3-day dietary record, and food frequency questionnaires should be completed for each patient. It is important to observe that obese people can underreport their food consumption. The degree of underreporting may be substantial. However, this validated method to evaluate nutrition consumption (Hill and Davis, 2001). Portions need to be measured in terms of familiar volume and size and with reference to atlas of local food portions. These dietary data must be fed into a computer by the same dietician; thus, nutrient composition is analyzed by a computerized nutrition program to establish an adequate meal plan.

For NAFLD and MS control, it was suggested that patients undergo a week dietetics lessons (food pyramid, recordatory inquiry, weight loss diets, diet vs. fig

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**TABLE 8.2**

**Nutritional Tools to Identify Eating Patterns in NAFLD and MS Patients**

<table>
<thead>
<tr>
<th>Method</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-Hour recall</td>
<td>It is conducted by a trained interviewer who asks the individuals to recall exactly what they ate in the preceding 24-hour period.</td>
</tr>
<tr>
<td>Food diary</td>
<td>Individuals are instructed to record all food and drink they consume during a defined period ranging from 1 to 7 days. At least one weekend should be included since most people eat differently.</td>
</tr>
<tr>
<td>Food frequency</td>
<td>It presents a list of foods or food categories. Individuals respond to questions from a trained observer regarding how often each food is consumed per day, week, or month.</td>
</tr>
<tr>
<td>Diet history</td>
<td>A typical diet history could include some essential questions, as familiar disease history, age beginning to gain weight, habits foods, and all information to prove a more accurate picture of the individual's typical intake.</td>
</tr>
</tbody>
</table>
The organogram of diet plan is illustrated in Figure 8.4. Studies have shown that restrictive diets can aggravate NAFLD; they are associated with higher inflammation and degree of fibrosis in the liver because these diets promote a quick and intense weight loss through high influx of free fatty acids to the liver (Bellentani et al., 2008). Another point that must be evaluated in diet composition is that both excessive carbohydrate and excessive fat intake could play a role in increasing blood glucose, free fatty acids, or insulin concentrations, independently or simultaneously (Zivkovic et al., 2007).

### Establishing a Meal Plan

#### Calories

A proper nutritional plan must be individualized according to nutritional needs and energy expenditure. A target of 5–10% of baseline weight is often used as an initial weight loss goal. According to literature, every 0.250 kg of fat mass is equivalent to 3500 calories.
Nutritional and Clinical Strategies on Prevention and Treatment of NAFLD

FIGURE 8.4 Organogram of dietetic plan to be established at baseline and after short- or long-term multidisciplinary therapy.

to 3500 kcal. Thus, to achieve a weight loss of 0.500–1 kg/week, it is necessary to promote an energetic deficit of 1000 kcal/day (0.500 kg = 1000 kcal × 7 days/week (McIlby and Hickey, 2006). First of all, it is necessary to calculate the energy expenditure and the average energy consumption by 3 days’ recordatory. Next, the nutritionist needs to calculate the energy intake by subtracting 500–1000 kcal from the estimated total daily calories previously calculated (using specific formulas according to age and gender), always incorporating new adequate food habits and stimulating an increase in the energy expenditure by a change in physical activity.
For example, according to the DRI (2002) specific formula, using the individual anthropometric measurements (including height and ideal average weight) and a

### Macronutrient Distribution

**First step:** Considering that basal energy expenditure (BEE) = 1800 kcal

**Second step:** Multiply by the appropriate activity factor: BEE × 1.3 (light activity) = 1800 kcal × 1.3 = 2340 kcal

**Third step:** Subtract 500–1000 kcal to create a deficit predicting 0.5–1 kg of weight loss per week = 2340 – 1000 = 1340 kcal/day.

#### 8.2.5.1.2 Carbohydrate

Solga et al. (2004) showed that high carbohydrate intake was associated with greater levels of inflammation in obese patients with NAFLD. High carbohydrate intake mainly sucrose, glucose, fructose, and foods with high glycemic index, cause increase in *de novo* lipogenesis, which leads to an increased conversion of glucose fatty acids. Indeed, the high glycemic index carbohydrate leads to a quick increase with a subsequent decrease in insulin levels and an increase in glucagon and ghrelin which are orexigenic hormones (Zivkovic et al., 2007).

The glycemic index describes the difference in the impact of ranking carbohydrates on the body according to their effect on blood glucose levels. A low glycemic index carbohydrate, which produces small fluctuations on blood glucose and insulin levels, is an important and coadjuvant tool in promoting long-term health, reducing the risk of NAFLD, and improving some parameters of MS (Anderson et al., 2006).

The glycemic effect of foods depends on a number of factors: type of starch (arlose vs. amylopectin), fat, protein, and organic acids content of the food, as well as the meal. Although a food rich in lipids can present a low glycemic index, the ingestion of this type of food must be limited. To control NAFLD and MS, it is important to evaluate the glycemic index and the glycemic load, which represents the effect on blood glucose considering the quantity and quality of carbohydrate amount per serving (Table 8.4).

Patients' diet must include foods rich in fiber, particularly soluble fiber dissolved in water. This type of fiber is very viscous when dissolved in the stomach and slc

| TABLE 8.4 Reference Values to Glycemic Index and Glycemic Load Classification |
|-------------------------------------------------|-----------------|-----------------|
| Glycemic Index               | Glycemic Load   |
| High                           | ≥70             | ≥20             |
| Medium                         | 56–69           | 11–19           |
| Low                            | ≤55             | ≤10             |

*Source: www.glycemicindex.com.*