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Purpose of review

Nonalcoholic fatty liver disease is a common and serious form of chronic liver disease. It is characterized by lipid accumulation in the liver and is associated with all aspects – and may even be an initiating factor – of the metabolic syndrome. The purpose of this review is to summarize recent findings from human studies on dietary effects on hepatic lipid accumulation.

Recent findings

Epidemiological studies did not give consistent results. From intervention studies there is evidence to support a role for weight loss. Some studies have also suggested that decreasing total fat intake and increasing the intake of fish oils may be beneficial in the treatment of nonalcoholic steatohepatitis.

Summary

Only a few studies have focused on dietary effects on hepatic lipid accumulation. So far, there is only evidence to support a role for weight loss. Decreasing total fat intake and increasing the intake of fish oils may also be beneficial, but these conclusions are based on a limited number of studies, which sometimes lacked a proper control group. Also, other nutrients have not been studied in detail. Therefore, there is an urgent need for evidence-based dietary guidelines to prevent or even to treat nonalcoholic fatty liver disease.

Keywords

dietary fat, dietary fatty acids, energy intake, nonalcoholic fatty liver disease

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is a chronic liver disease that covers a wide variety of clinical conditions, ranging from simple steatosis (a fatty liver) without any signs of inflammation to severe inflammatory activity with significant fibrosis or even cirrhosis. This latter condition is called nonalcoholic steatohepatitis (NASH). Although no generally accepted definition exists, NAFLD can be defined as fat accumulation in the liver exceeding 5–10% by wet weight [1]. The prevalence of NAFLD is high and will increase in the very near future, which will put many people at risk of advanced liver diseases such as cirrhosis and hepatic cancer. In addition, patients with NAFLD have a higher prevalence of insulin resistance and cardiovascular disease [2,3••,4••]. Also other characteristics of the metabolic syndrome – for example hyperlipidemia and hypertension – are more common in these patients [5,6••]. In fact, it has been suggested that a fatty liver is a predisposing factor for the development of the metabolic syndrome [6••]. This indicates that not only the total amount and distribution of body fat but also tissue storage is important in determining the health consequences of obesity [4••].

What is especially worrying is that NAFLD is prevalent not only in adults but also in children. For the United States, for example, it has been estimated that the prevalence of NAFLD is 33% in adults, and 10% in children and adolescents [7]. The exact causes of NAFLD are still unknown, but it is clearly associated with an increased body mass index (BMI) [8]. Inherent to the definition, however, the cause of NAFLD is not alcohol related. It is important to note, however, that hepatic lipid accumulation can also be increased in subjects with a BMI under 25 kg/m^2 [8].

Owing to the health consequences of NAFLD, interest in this disease has increased over the last years. For a long time, many of the studies on NAFLD were performed in cellular and animal models, due to the inaccessibility of liver biopsies in humans. The introduction of noninvasive imaging technologies, such as magnetic resonance imaging and spectroscopy, and ultrasonography, has made it possible to determine liver fat content in human subjects in a noninvasive way and several reviews have recently been published [5,6••,9,10]. In these reviews, however, the focus was in particular on diagnostics, prevalence and prognosis, metabolic

aberrations, and drug therapy. Less attention has been paid to nutritional aspects. The aim of this review is now to summarize recent findings from human studies on the dietary effects on lipid liver accumulation and the severity of NAFLD. The focus will be on total energy intake and dietary macronutrient composition, which are well known determinants of the various components of the metabolic syndrome [11•]. Only those studies were selected that measured NAFLD using liver biopsies or noninvasive methods. Although serum concentrations of alanine aminotransferase (ALT) and other liver enzymes correlate with hepatic lipid accumulation, their sensitivity and specificity to diagnose NAFLD is low [6••].

Epidemiological studies

The practical difficulties to assess liver fat content in a large number of subjects have resulted in a limited number of epidemiological studies on diet as related to NAFLD. Only a few, relatively small, studies have been published (Table 1).

Musso *et al.* [12] compared daily food intake data of 25 patients with NASH with those of 25 controls. Total energy intake between the two groups was similar. Protein intake was, however, higher in the NASH group. Carbohydrate intake and total fat intake were similar, but patients with NASH consumed more

Table 1 Effects of dietary energy and macronutrient intakes on the presence or severity of nonalcoholic fatty liver disease: results from cross-sectional epidemiological studies

Study	Population	Diagnosis	Assessment of food intake	Statistically significant differences in dietary energy and macronutrient intakes		Remarks
Musso [12]	25 patients with NASH versus 25 controls matched for age, sex and BMI	Ultrasonography	7-day food diet record	Energy Carbohydrate Protein Total fat SAFA MUFA PUFA	 20.2 versus 16.7 En% 13.7 versus 10.0 En% 3.5 versus 4.7 En%	
Solga [14]	70 morbidly obese patients	Liver biopsy	24-h food recall	Energy Carbohydrate Total fat SAFA MUFA PUFA		Carbohydrate intake was positively – and fat negatively – related to degree of inflammation
Pietiläinen [13]	19 monozygotic twin pairs	Proton spectroscopy	3-day food diaries	Protein Carbohydrate Total fat SAFA MUFA PUFA Alcohol		Fat and SAFA intakes were positively correlated with percentage liver fat
Zelber-Sagi [15•]	108 patients with NAFLD versus 241 controls	Ultrasound	Semiquantitative food frequency questionnaire	Energy Protein Carbohydrate Total fat SAFA MUFA PUFA		Macronutrient intakes were comparable between the two groups Patients with NAFLD had higher intakes of carbohydrates from soft drinks and protein from meat
Cortez-Pinto [16]	45 patients with NASH versus 856 controls matched for age, sex and alcohol consumption	Liver biopsy	Semiquantitative food frequency questionnaire over 1 year	Energy Protein Carbohydrates Total fat SAFA MUFA n-6 PUFA n-3 PUFA	 99.8 versus 104.9 g 243.6 versus 261.5 g 79.7 versus 73.0 g 37.9 versus 31.8 g 9.3 versus 8.3 g	
Toshimitsu [17]	28 patients with NASH versus 18 patients with simple steatosis	Liver biopsy	3-day food diet record	Energy Protein Carbohydrate Total fat SAFA MUFA PUFA		No significant relationships were found using logistic regression analysis
Capristo [18]	20 male patients with NASH versus 20 age-matched controls	Not reported	7-day food diary	Energy	2210 versus 1880 kcal	

En%, percent of energy; MUFA, monounsaturated fatty acid; NASH, nonalcoholic steatohepatitis; PUFA, polyunsaturated fatty acid; SAFA, saturated fatty acid.

saturated and less polyunsaturated fatty acids than controls.

In 19 monozygotic twins Pietiläinen *et al.* [13] reported a positive association between the amount of liver fat and the intake of total and saturated fat. Solga *et al.* [14], however, found no relationship between the habitual intakes of saturated, monounsaturated and polyunsaturated fatty acids with the degree of steatosis, inflammation and fibrosis in 70 morbidly obese patients. In addition, no association was found between these three parameters and total energy intake. Total carbohydrate intake was, however, positively related to the degree of inflammation, but not with steatosis or fibrosis. The opposite relationship was found for total fat intake.

These findings are supported to some extent by one of the largest epidemiological surveys carried out so far. In that study, Zelber-Sagi *et al.* [15•] examined the dietary habits of 108 patients diagnosed with NAFLD versus those of 241 subjects without NAFLD. Subjects were randomly selected from the national population registry. After adjusting for potential confounding variables such as age, sex, BMI and total energy intake, patients with NAFLD had higher intakes of carbohydrates from soft drinks and of protein from meats. The intake of protein from fish rich in n-3 long-chain polyunsaturated fatty acids tended to reduce the risk for NAFLD. It was not mentioned whether the n-3 long-chain polyunsaturated fatty acids were also related with NAFLD.

Cortez-Pinto *et al.* [16], however, reported that patients with NASH had lower intakes of protein, but higher intakes of total fat, and of monounsaturated and n-6 polyunsaturated fatty acids. Consumption of n-3 polyunsaturated fatty acids was comparable between the two groups. Results were adjusted for energy intake and BMI.

Lower intakes of protein by patients with NASH were also reported by Toshimitsu *et al.* [17]. In that study, the dietary habits of 28 patients with NASH were compared with those of 18 patients with simple steatosis. Consumption of carbohydrates was higher in those with NASH. Results, however, did depend on the age of the subjects and were for the NASH group not always different from those of randomly selected healthy Japanese subjects, which makes it difficult to explain the results. In addition, logistic regression analysis did not reveal any statistically significant association between nutrient intakes and NASH.

Finally, one study [18] with 20 male patients with NASH and 20 healthy male control subjects reported a significantly higher energy intake in the patients with NASH.

A few cross-sectional studies have addressed the relationships between energy and macronutrient intakes with NAFLD or its severity. As shown in Table 1, results are conflicting and no uniform conclusions can be drawn. This can be due to a wide variety of factors such as the relatively small sample sizes of the study populations, differences in population and control groups, and inaccuracies in estimating dietary intakes. In addition, due to the cross-sectional nature, patients may have changed their dietary habits because of their disease. In general, cross-sectional studies do not allow conclusions to be drawn on cause–effect relationships. For this, properly controlled randomized intervention studies are needed.

Intervention studies

Several recent intervention studies have been carried out to examine the effects of dietary composition on NAFLD. In most of these studies, the focus was on weight loss through energy restriction or on the effects of total fat intake or fatty acid composition. Some studies, however, have also looked at the effects of vitamin E or energy restriction combined with physical activity.

Weight loss

As NAFLD is positively associated with BMI and other features of the metabolic syndrome, it is obvious that a weight loss programme may be a first approach for overweight and obese subjects to treat NAFLD. The number of trials on the relationship between diet-induced weight loss and NAFLD, however, is surprisingly limited. In fact, Clark [19] reviewed in 2006 the existing literature and identified only three trials that had included a control group. If anything, these studies did suggest some improvement in liver histology and a decrease in liver enzymes related to NAFLD. In only one of the studies, however, histological endpoints were used. Owing to these methodological constraints, it was concluded that there is as yet only little evidence to support a role for diet-induced weight loss in the treatment of NAFLD.

In a more recent study, Thomas *et al.* [20] showed in 10 patients that a reduction in total calorie intake of 500 kcal and advice to increase physical activity for 6 months decreased intrahepatocellular lipids (IHCLs) by 40% as measured by magnetic resonance imaging. Owing to a large between-subject variation this change did not reach statistical significance. Weight loss amounted to 3.4 kg or 4% of body weight. Interestingly, changes in IHCLs correlated positively with those in body weight, and in intra-abdominal and abdominal subcutaneous adipose tissue. Comparable results were found in an earlier study of Tiikkainen *et al.* [21].

Total dietary fat content

Short-term postprandial effects on IHCLs were assessed by Szczepaniak *et al.* [8]. After an overnight

fast, the IHCLs of eight subjects were measured by magnetic resonance spectroscopy. Subjects then consumed a high-fat meal providing 50 g of fat. Four hours after the meal, measurements were repeated. No changes were observed.

Westerbacka *et al.* [22] have studied the effects of the amount of fat in the diet on liver steatosis, as measured with magnetic resonance proton spectroscopy. For this, 10 normal, obese women received for 2 weeks a low-fat diet, in which 16% of total energy intake (En%) was provided by fat, or a high-fat diet (56 En%) in randomized order using a crossover design. On the low-fat diet, the intakes of saturated, monounsaturated, and polyunsaturated fatty acids were decreased. This makes it impossible to attribute the effects observed to one single class of fatty acids. Before the start of the experimental periods, liver fat content was on average 10% and decreased to 8% on the low-fat diet and increased to 13.5% on the high-fat diet. On the high-fat diet, fasting serum insulin concentrations were also increased, while no effects on plasma glucose concentrations were observed, suggesting the development of insulin resistance. Surprisingly, the expected effects of the huge changes in total fat and fatty acid intake on the serum lipid or lipoprotein profile were not observed.

Fish oils

As for total fat intake, the effects of individual fatty acids on improving NAFLD have hardly been studied. Good candidates are of course the highly unsaturated fish oils, which are thought to improve insulin sensitivity [23]. Capanni *et al.* [24] therefore fed for 1 year 42 patients with NAFLD 1 g of fish oil daily. Fourteen patients who were not willing to swallow the fish oil capsules were used as controls. Thus, it was a nonblinded, nonrandomized study. After the intervention period, no liver steatosis as measured by ultrasonography could be demonstrated in 24% of the patients in the fish oil group, whereas no changes were observed in the control group. Liver enzyme levels and serum triacylglycerol and glucose concentrations were also improved. Preliminary results of a study that has been published as an abstract only also suggest that a daily supplement of 2 g of fish oil for 6 months resulted in regression of steatosis as determined by ultrasonography [25].

Vitamin E

In an earlier open-label pilot study, it was suggested that a daily supplement of 100 mg α-tocopherol three times a day for 1 year may have a beneficial effect on NAFLD in patients with NASH [26]. A later study [27] also examined the potential beneficial effects of vitamin E. In that study, 28 children with obesity-related hypertransaminasaemia and increased IHCLs were randomly assigned to receive placebo pills or pills filled with α-tocopherol acetate. For the first 2 months, 400 mg/day was given and for the next 3 months 100 mg/day. In addition, all children were prescribed a balanced low-energy diet and a moderate daily exercise programme. No differences between the treatment groups were found in IHCLs at ultrasonography [27].

Multidisciplinary intervention programmes

Huang *et al.* [28] studied the effects of a recommended diet combined with an increase in physical activity on the progression of NASH. Sixteen patients completed the 12-month study, of which 15 underwent repeated liver biopsies. Compared with patients with unchanged histologic scores, patients with improved scores had significantly greater reductions in body weight.

In a nonplacebo-controlled study, de Piano *et al.* [29] studied the effects of a multidisciplinary programme on the dietary and metabolic profiles of 43 nonobese adolescents, aged between 15 and 19 years. Thirteen participants had NAFLD as diagnosed by ultrasonography. Before and after a 12-week intervention programme blood samples were taken. The intervention programme consisted of an aerobic training programme and a dietary programme. After the intervention, the number of subjects with NAFLD had decreased. Unfortunately, no detailed information was given on the dietary intervention programme. In addition, it was mentioned that energy and cholesterol intake had decreased in the NAFLD group, but no between-group comparisons were made. In a pilot study with 10 subjects, Hollingsworth *et al.* [30] showed that a diet that provided less than 20 g daily of carbohydrate reduced hepatic fat content as measured with MRI within 10 days. All subjects also lost weight (3 kg), which did not however correlate with changes in hepatic fat loss.

Summary

The number of randomized intervention studies to examine relationships between NAFLD and dietary macronutrient composition is limited. There is evidence to support a role for weight loss. The role of decreasing total fat intake and increasing the intake of fish oils in the treatment of NAFLD is weaker.

Conclusion

NAFLD is a common and potentially serious form of chronic liver disease that occurs in patients who do not abuse alcohol. Therefore, there is an urgent need for evidence-based dietary guidelines to prevent or even to treat NAFLD. Surprisingly, only little is known about the effects of decreasing energy intake and dietary macronutrient composition on the development and treatment of NASH. The cross- sectional epidemiological studies did not give consistent results, which are in addition prone to bias. Many of the intervention studies were

not randomized and conclusions were sometimes based on within-group comparisons instead of between-group comparisons. There is evidence, however, to support a role for weight loss. Some studies also suggested that decreasing total fat intake and increasing the intake of fish oils may be beneficial in the treatment of NAFLD. Clearly, however, more rigorously conducted, randomized controlled trials using realistic dietary intakes are needed in this area.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 88).

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