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Implications of Diet on Nonalcoholic Fatty Liver Disease

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Abstract

Purpose of the Review—This review examines the effects of diet on nonalcoholic fatty liver disease (NAFLD). This includes the effects of calories, both in excess and restricted, as well as macronutrients.

Recent Findings—Recent findings suggest that short term hypercaloric feeding leads to increased intrahepatic triglyceride (IHTG), while short term hypocaloric feeding leads to decreased IHTG despite little change in total body weight, suggesting that ongoing excess caloric delivery directly contributes to the development of NAFLD. Weight loss with either low fat or low carbohydrate diets can improve IHTG, however specific macronutrients: fructose, *trans*-fatty acids, and saturated fat may contribute to increased IHTG independent of total calorie intake. N-3 polyunsaturated fatty acids and mono-unsaturated fatty acids may play a protective role in NAFLD. The mechanisms behind these effects are not fully understood.

Summary—Diet plays a role in the pathophysiology of NAFLD. It is reasonable to advise patients with NAFLD to reduce calorie intake with either low fat or low carbohydrate diets as well as limit intakes of fructose, *trans*-fatty acids, and saturated fat.

Keywords

NAFLD; hypocaloric diet; hypercaloric diet; fructose; *trans*-fat; saturated fat; n-3 polyunsaturated fat

Introduction

Nonalcoholic Fatty Liver Disease (NAFLD) is a spectrum of liver diseases associated with obesity, that include varying degrees of steatosis, inflammation, hepatocellular injury, and fibrosis. NAFLD is also associated with an increased risk of type 2 diabetes mellitus, coronary heart disease, hypertension, and dyslipidemia^{1, 2}. NAFLD is an important health problem not only for the morbidity associated with it, but also because of its prevalence: NAFLD, affects approximately 33% of the US adult population³, using a quantitative definition of >5.6% intrahepatic triglyceride (IHTG) based on magnetic resonance spectroscopy (MRS) imaging. Nonalcoholic steatohepatitis (NASH), part of the NAFLD spectrum, is a pattern of liver injury that is composed of several different histologic features and requires liver biopsy for diagnosis⁴. The risk of NAFLD and NASH clearly increases with increasing BMI: NAFLD and NASH are present in 65% and 20% of persons with Class I or II obesity (BMI 30–39.9kg/m²) and 85% and 40% in persons with a BMI ≥ 40 kg/m², respectively^{5, 6}. However, despite these definitions, metabolic abnormalities such as insulin resistance in liver, adipose tissue, and skeletal muscle are proportional to IHTG, without a definite cut-off between normal and not normal⁷.

The pathophysiology of NAFLD is not fully understood. Complex interactions exist between glucose, fatty acid, and lipoprotein metabolism in a variety of tissues including the

liver, adipose tissue, and skeletal muscle in the setting of systemic inflammation, altered cytokine production, and in many cases insulin resistance. It is unclear whether excess fat in the liver drives these metabolic derangements and inflammation or if NAFLD is a consequence of it. However, there must be an imbalance in the liver between free fatty acid (FFA) input and FFA output. This equation of fat in and fat out of the liver is likely influenced by environmental factors including diet.

Currently, few treatment options exist for NAFLD, but consensus statements agree that lifestyle modification including diet therapy is the cornerstone of therapy⁸. The purpose of this review is to examine the role of diet and nutrition in both the pathophysiology and management of NAFLD.

Caloric Intake

A number of studies have recently been published that investigate the effects of excess caloric intake, with varying macronutrient composition, on liver fat. Three studies increased calories by increasing fat content. The first study by Kechagias et al⁹ examined the effects of a 4 week hypercaloric diet approximately doubling the caloric intake from baseline on liver enzymes and IHTG by MRS in young healthy subjects compared with matched controls. The excess calories were provided by subjects eating at least 2 meals a day at fast-food restaurants, and the diet contained a higher percentage of calories as fat than the subjects' normal diet. No subjects had NAFLD on baseline MRS; however, after gaining 5–15% total body weight on the hypercaloric diet, IHTG increased from 1.1% to 2.8% with 2 subjects reaching IHTG levels >5.6%. In addition, serum ALT concentrations tripled during the hypercaloric feeding from 22 U/l to 69 U/l. Brons et al¹⁰ compared 26 young healthy male subjects in a randomized cross-over study with 5 days of hypercaloric feeding (50% more calories than baseline diet) or a control diet. Again, the hypercaloric diet had a higher percentage of calories from fat (60% vs 35%) than the control diet. Although fasting serum FFA, fasting triglycerides, and LDL concentrations were lower on the hypercaloric diet, there was a 26% increase in fasting hepatic glucose output and an almost two fold increase in the hepatic insulin resistance index (HISI). Insulin stimulated glucose disposal, measured by hyperinsulinemic euglycemic clamp testing, in skeletal muscle did not change with short term overfeeding. The third study by van der Meer et al studied 15 men before and after 3 days of supplementation with 280 grams of fat in the form of cream¹¹. IHTG content increased from baseline to day 3 and was associated with an increase in triglycerides and FFA.

Another study by Le et al¹² investigated the effects of 7 days hypercaloric feeding with high-fructose corn syrup (35% more calories than baseline diet) on healthy male offspring of patients with type 2 diabetes and 8 control subjects with no family history of type 2 diabetes. As with the Kechagias study, none of the participants had NAFLD based on MRS at baseline; however, the high fructose corn syrup diet increased IHTG by 76% in the control group and 79% in the offspring of diabetic patients. The offspring of diabetic patients also had an increase in serum very low-density lipoprotein (VLDL) concentrations; however, it is unclear if this was the result of increased secretion by the liver or decreased clearance in the peripheral tissues. Additionally, basal hepatic glucose production was increased on the hypercaloric diet but the HISI decreased. Lastly, a study by Bortolotti et al¹³ compared 4 days of hypercaloric high fat/high protein or hypercaloric high fat diets to an isocaloric control diet in 10 healthy young male volunteers in a randomized crossover study. Both hypercaloric diets increased IHTG compared with the control diet, although the increase was greater on the hypercaloric high fat diet.

Taken together, these data suggest that changes in IHTG in humans occur quickly with a range of excess calorie consumption even in healthy subjects, regardless of the macronutrients components of the diet and prior to significant weight gain. This is associated with insulin resistant glucose metabolism in the liver which appears to precede insulin resistance to glucose metabolism in skeletal muscle. The mechanisms behind these changes are unclear. While serum FFA concentrations are thought to promote increased IHTG, fasting serum FFA concentrations were not consistently elevated on hypercaloric diets. Furthermore, it is unclear how these diets affect inflammation in the liver as liver biopsies were not performed in any of the aforementioned studies.

Reducing caloric intake and weight loss have been shown to be effective therapies for overweight and obese patients with NAFLD. Recently, a concise review was published investigating the effects of lifestyle therapy including behavior modification and diet therapy with or without exercise on NAFLD¹⁴. Only 14 studies met the strict criteria of the lifestyle therapy intervention, but in those studies 5%–10% of initial body weight was lost. Substantial improvements were seen in liver enzymes, radiologic evidence of steatosis, insulin resistance, and liver histology in the studies where repeated liver biopsies were performed. More recent studies have continued to show a correlation of weight loss and decreased IHTG content with hypocaloric diets^{15–19}. These studies directly measured IHTG before and after hypocaloric diets, demonstrating a decrease in IHTG^{17, 19}. Reduced IHTG was associated with decreased hepatic FFA uptake as well as an improvement in insulin mediated suppression of hepatic glucose production¹⁹ and skeletal muscle insulin sensitivity^{15, 16}.

Based on the above data, it is clear that weight loss from reduced calorie intake with is effective in reducing IHTG. However similarly to the overfeeding studies, it is not clear whether this benefit is due to weight loss or ongoing negative caloric balance. Recent data, indicates that short-term calorie restriction decreases IHTG prior to significant weight loss²⁰. In the study by Kirk et al, subjects underwent MRS and hyperinsulinemic euglycemic clamps to determine insulin sensitivity in liver and skeletal muscle before and after 48 hours of calorie restriction (either low fat or low carbohydrate), and again after subjects achieved 7% weight loss. Both calorie restricted diets decreased IHTG within 48 hours, although the decrease in IHTG on the low carbohydrate diet was roughly 3 times the reduction with the low carbohydrate diet. Further reduction in IHTG, leading to equivalent reduction in IHTG, was seen with 7% weight loss. HOMA-IR, hepatic insulin sensitivity index and fasting serum insulin concentrations were also improved in both groups but showed more of an improvement in the low carbohydrate group. This is consistent with data from a prior study showing decreased IHTG by MRS on a short term low carbohydrate diet²¹. This data demonstrates that the liver rapidly responds to reduced calorie intake, suggesting that ongoing excess caloric delivery directly contributes to the development of NAFLD.

Macronutrients

Although total calorie intake potentially plays a role in both the pathophysiology and treatment of NAFLD, dietary macronutrient composition may also play a role. The next sections will discuss the independent effects of carbohydrate, fat, and protein intake on the pathophysiology and treatment of NAFLD.

Carbohydrates

Simple carbohydrates in the diet, in particular fructose, have been linked to NAFLD. Fructose is extensively metabolized by the liver and although it may cause less insulin secretion than glucose or sucrose, it may be more lipogenic²². Animal models have demonstrated increased IHTG in response to a high fructose diet^{23, 24}. Overfeeding with

fructose in humans has been shown to increase TG^{25, 26} and IHTG¹², but a recent meta-analysis of isocaloric fructose consumption found that only subjects with type 2 diabetes responded to increased fructose with increased triglyceride and lower HDL cholesterol²⁷. Moreover, recent epidemiologic studies in humans have shown a correlation between high fructose corn syrup consumption and NAFLD^{28–31}. Animal models suggest that fructose induces activity of peroxisome proliferator-activated receptor gamma co-activator (PGC-1 β), sterol regulatory element binding protein 1 c (SREBP-1c) (both directly and indirectly through PGC-1 β), and carbohydrate response element binding protein (ChREBP)^{32, 33}. Both SREBP-1c and ChREBP are transcription factors for proteins involved in lipogenesis³⁴ and their up regulation by fructose may increase de novo lipogenesis, contributing to IHTG.

Fiber, both insoluble and soluble, has been shown to be beneficial in diabetes and diabetes prevention by lowering postprandial glucose response and improving some lipid profiles³⁵. Few studies have been done in animals or humans regarding the effects of fiber on NAFLD. In an animal model, increased dietary fiber has shown to reduce IHTG³⁶. No randomized studies of fiber and NAFLD have been done in humans, and studies involving dietary recall in human subjects have yielded conflicting results in the correlation between fiber intake and NAFLD^{31, 37}.

Fat

The composition of dietary lipid may influence IHTG. It is important to remember; however, that low carbohydrate/high fat diets that result in reduced calorie intake with weight loss improve metabolic parameters^{38, 39}, reduce IHTG^{20, 21}, and improve liver histology^{40, 41}. As previously discussed, hypercaloric high fat diets have been associated with increased IHTG. One study in humans investigating the effects of an isocaloric high fat diet in post-menopausal women demonstrated an increase in IHTG⁴², and one recent study in rats also showed an increase in IHTG on a high fat isocaloric diet compared with a control chow diet⁴³. Furthermore, a study comparing diets of NAFLD patients with NASH patients found that patients with NASH consumed a higher percentage of calories from fat than those with steatosis alone, despite consuming fewer total calories⁴⁴.

Specific types of fat may play an important role in NAFLD pathophysiology in addition to the total fat content of the diet. Saturated fat has been linked with diabetes, cardiovascular disease and the metabolic syndrome^{45, 46}. Several pieces of evidence suggest that saturated fats could be important in the pathophysiology of NAFLD. Saturated fat has been implicated in up-regulation of PGC-1 β co-activation of SREBP⁴⁷, promotion of ER stress and inducing hepatocyte apoptosis^{48, 49}. Animal models have shown increased IHTG with high fat diets that were also high in saturated fat; however, many of these diets were hypercaloric. Therefore, it is difficult to ascertain the effects of saturated fats independent of total calories^{50–52}. The same is true for human studies, while saturated fat intake increased IHTG in the multiple studies^{9–11, 13}, these were in the setting of overfeeding, making the effect of saturated fat on IHTG difficult to interpret. Furthermore, dietary pattern studies have not shown a correlation between IHTG and saturated fat^{31, 37, 53}.

Trans-fatty acids are unsaturated fatty acids with at least one double bond in the trans configuration. They are rarely found in the food supply naturally, however they are produced through the process of hydrogenation to make partially hydrogenated oils. *Trans*-fatty acids have been associated with cardiovascular disease and diabetes⁵⁴. Recent animal studies have shown that low-fat diets with some of the fat replaced by *trans*-fatty acids leads to similar or increased IHTG as diets high in fat^{55, 56} or high-fructose corn syrup⁵². Human studies have not directly studied the effects of *trans*-fatty acids on IHTG. Therefore, their role in NAFLD in humans remains undetermined.

Polyunsaturated fatty acids and specifically the n-3 polyunsaturated fatty acids (PUFA), and mono-unsaturated fatty acids (MUFA) may play a protective role against increases in IHTG. N-3 Polyunsaturated fatty acids up regulate gene expression of proteins involved in fatty acid oxidation, while they decrease those involved in lipogenesis including SREBP-1⁵⁷. PUFA concentrations are lower in patients with NAFLD, and have a less favorable higher ratio of n-6 to n-3 PUFA⁵⁸. n-3 PUFA supplementation of 2g/day in patients with NAFLD decreased decrease in IHTG based on US after one year of treatment⁵⁹. Diets high in MUFA have been shown to improve serum lipid profiles associated with NAFLD⁶⁰. No studies have directly measured the effects of MUFA on NAFLD; however, one trial of MUFA demonstrated decreased abdominal fat deposition and improved insulin sensitivity, which are both conditions associated with NAFLD⁶¹.

Protein

Little is known of the effects of protein on NAFLD. Increased protein intake may be associated with improved insulin sensitivity in the insulin resistant subject⁶²; however, this data is confounded by the source of protein, which may contain other beneficial macronutrient components. As mentioned above, high protein intake reduced the increase in IHTG associated with high calorie/high fat feeding¹³; however meat, but not total protein was associated with NAFLD in one study of dietary intake in NAFLD³¹.

Conclusion

NAFLD is a liver disease with varying degrees of severity. It is associated with cardiovascular risk factors including diabetes, and affects almost 1/3 of the US population. Based on the data provided, even short term caloric restriction can rapidly improve, and hypercaloric feeding can rapidly worsen NAFLD and NAFLD-associated hyperlipidemia and insulin resistance. Both low carbohydrate and low-fat diets that cause weight loss are associated with decreases in IHTG and improved metabolic phenotype; however, the long-term effects of low carbohydrate diets are unknown. At this time it is reasonable to advise overweight patients to lose weight and to limit their intake of high fructose corn syrup, saturated fat and trans-fatty acids. Supplementation with n-3PUFA or fish containing high amounts of these fats, may reduced IHTG content and improve lipid profile in patients with NAFLD, but further studies are needed to verify these findings and determine appropriate doses

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