MINIREVIEWS

Role of diet on non-alcoholic fatty liver disease: An updated narrative review

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Abstract

The purpose of this article review is to update what is known about the role of diet on non-alcoholic fatty liver disease (NAFLD). NAFLD is the most common cause of chronic liver disease in the developed world and is considered to be a spectrum, ranging from fatty infiltration of the liver alone (steatosis), which may lead to fatty infiltration with inflammation known as non alcoholic steatohepatitis While the majority of individuals with risk factors like obesity and insulin resistance have steatosis, only few people may develop steatohepatitis. Current treatment relies on weight loss and exercise, although various insulin-sensitizing medications appear promising. Weight loss alone by dietary changes has been shown to lead to histological improvement in fatty liver making nutrition therapy to become a cornerstone of treatment for NAFLD. Supplementation of vitamin E, C and omega 3 fatty acids are under consideration with some conflicting data. Moreover, research has been showed that saturated fat, trans-fatty acid, carbohydrate, and simple sugars (fructose and sucrose) may play significant role in the intrahepatic fat accumulation. However, true associations with specific nutrients yet to be clarified.

Key words: Diet; Non-alcoholic fatty acids; Fatty acids; Obesity; Insulin resistance

Core tip: The beneficial effects of weight loss and exercise have been well documented by many authors in reducing the steatosis, inflammation and fibrosis. Vitamin E can also be used with safety in adults only with biopsy proven non alcoholic steatohepatitis. Consumption of high fructose syrup to the development of non-alcoholic fatty liver disease is still under debate. The data for vitamin C shows no clear effect while the supplementation of n-3 fatty acids and probiotics is still conflicting but shows promise.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), the spectrum of hepatic disorders embracing uncomplicated fatty liver and nonalcoholic steatohepatitis (NASH) is associated with features of metabolic syndrome (MS) and several hepatic and extra-hepatic complications[1]. Medications such as tamoxifen, methotrexate and corticosteroids may be considered as a secondary causes of MAFLD, rarely though. Additionally, rapid weight loss, total parental nutrition and lipodystrophy may also aggravate fatty liver disease. NAFLD may also progressed to non-alcoholic steatohepatitis, a term that includes symptoms of hepatocellular damage plus inflammation and/or fibrosis[2]. The diagnosis of NAFLD remains under-recognized, as most patients are asymptomatic until late stages of disease. Liver biopsy is the gold standard in diagnosing NAFLD and the most accurate tool for grading fibrosis however is invasive and carries the risk of complications[1]. Although literature information is emerging, it is not clear what type of diet is more likely to cause fatty liver. Since it is very difficult to reduce and maintain weight loss, it looks more feasible for someone to change the dietary composition of a particular diet as a more realistic method to treat NAFLD without the need of decreasing in Kcal intake. Therefore, it is more important to look for associations between NAFLD and specific nutrients.

EPIDEMIOLOGY

Excessive fat deposition in the liver is seen in about thirty percent (30%) of the adult general population. NAFLD is very common in the general population and may effects form children to elderly[3]. This increase in the prevalence of NAFLD is possibly due to the fact that the obesity rates have been also increased the last 2 decades[3].

The prevalence of non-alcoholic fatty liver disease ranges from 9% to 36.9% of the population in different parts of the world[4-6].

Approximately 20% of the United States population suffers from non-alcoholic fatty liver, and the prevalence of this condition is increasing[7]. NAFLD is also high in elderly people. A chinese case-control study examined 4226 adults above 60 years of age from a previous cohort investigated and compared them to 3145 randomly selected younger controls (< 60 years) from the same cohort. NAFDL was higher in the elderly (26.7%) than in the non-elderly (22.8%) and similar in the elderly between men and women (26.6% *vs* 27.0%, $P > 0.05$)[8]. Similar results presented by a cross-sectional study of 6905 nonobese (BMI < 25) subjects. Risk factors for the development of NAFLD were assessed in a subsequent prospective study in NAFLD-free individuals at baseline, 494 of who had developed NAFLD during the 5-year follow-up. Prevalence of NAFL was found to be 7.27%[9].

PATHOGENESIS

Even though the pathogenesis of nonalcoholic fatty liver disease is not clear yet, the most important factor of the development of NAFLD is insulin resistance. Insulin résistance increase fat breakdown from adipose tissue, which in turn, increases circulating free fatty acids having as a final result the retention of lipids within the liver, called steatosis[10]. De novo synthesis of fatty acids is also regulated by hyperinsulinemia and hyperglycemia. This is a result of transcription factors such as sterol regulatory binding protein-1c and carbohydrate response element binding protein[11]. Then, the mitochondrial-oxidation system is overloaded by the extra amount of fatty acids leading to the accumulation of free fatty acid within the hepatocytes. Finally, production of free oxygen radicals is generated by the cytochrome P450 4A and 2E1 isoenzymes-lypoxygenases[12].

Age- related data even though still undefined might reveal some connection of alterations in cholesterol synthesis in patients with NAFLD[13]. Finally this lipid peroxidation leads to the release of malondial-dehyde and 4-hydroxynonenal, which causes cell death and protein cross-linkage, resulting in the formation of Mallory's hyaline in the hepatocyte[14]. They also activate stellate cells, which lead to collagen synthesis and fibrosis[15]. Altered distribution of inflammatory cytokines in the different body compartments may further contribute to worsening NAFLD course in the elderly[16].

HISTOLOGY

Recently, information from consensus conference defined NASH as steatosis that includes hepatocellular ballooning plus lobular inflammation. However, in the absence of inflammation, subjects with steatosis in conjunction with peri-cellular fibrosis may also considered to present NASH[2]. This histological distinction between NASH and simple steatosis, yet to be clarified. Histologically, a minimum of 5% steatosis is required to confirm NAFLD. The histologic features of steatohepatitis, which include steatosis, inflammation, ballooning hepatocyte necrosis, are similar to those of alcoholic liver disease. A new development system for grading and staging was recently developed by Alkhouri *et al*[17]. The diagnosis of NASH was based on Brunt's criteria. Histological features were scored: steatosis (0-3), lobular inflammation (0-3), ballooning (0-2), and PI (0-2). The new score was called the Pediatric NAFLD Histological Score or PNHS and was found to have excellent correlation with NASH.

DIAGNOSIS

Even though significant liver disease can exist with normal levels of transaminases, increased levels of

the hepatic enzymes aspartate aminotransferase and alanine aminotransferase (ALT) are usually very good predictors of the presence of NAFLD and NASH. Serum ALT levels can be found up to 10 times higher than normal in general population with fatty liver disease[18-21]. The last few years, different non-invasive tests have been developed to estimate liver fibrosis (FibroTest)[22] and simple steatosis (SteatoTest)[23]. However, both of them have not been widely adopted[24].

Histological examination of biopsy samples can assess the presence of necro-inflammation and fibrosis[25,26], and can differentiate between macro- and micro-vesicular steatosis, thus it remains the reference standard for the grading and staging of NAFLD[27]. However, it is subject to sampling error due to histological heterogeneity[28,29] scoring is semi-quantitative, limiting its ability to detect modest changes, and scoring systems vary between reports precluding direct comparisons. Ultrasound provides semi-quantitative estimates of hepatic steatosis based on diffuse increases in echogenicity[30]. Reported sensitivity and specificity vary between 60%-94% and 66%-95%, respectively[30]. Even though it is important to diagnose NAFLD, special attention must be give when it comes for the diagnosis of NASH. Symptoms and physical examination may not be enough while presence of MS most of the times will reveal the presence of NASH. Increased liver enzymes have been found to highly related with NASH, however, may not be reliable[31]. Lately, it has come to the literature a new model namely the fragment of keratin 18 (CK18), which is for now, the best marker for detecting NASH, however showed lower accuracy with sensitivity (60%)[32].

TREATMENT

Drug management
Improvement of insulin sensitivity remains the main strategic treatment for NAFLD as well as the modification of all others underlying metabolic risk factors. One of the most common drugs, metformin, it has been used to reduce hyperinsulinemia and to improve insulin resistance. Data for mice studies has been shown to reverse fatty liver in obese, leptin deficient mice[33]. Moreover, a trial using adults who underwent a therapy of 4 mo with metformin demonstrated significant reduction in serum ALT[34]. Nobili *et al*[35] found that metformin was no more effective than lifestyle interventions improving liver enzymes or histology. Additionally, other studies have also failed to prove benefits of using metformin to improve liver histology[36]. Another agent, pioglitazone was found in a metanalysis[37] of reducing liver enzymes and inflammation and benefit of metabolism of glucose, however, the review failed to reveal an improvement of liver fibrosis. Statins are also a promising drug agent; two large studies examine the effect of statins in cardiovascular disease. The authors showed that NAFLD patients with high liver enzymes had lower cardiovascular events compared to patients with normal liver enzymes[38,39]. These results are very encouraging of using statins as a treatment for NAFLD patients with high liver enzymes. Losartan, which is also used in NAFLD patients as a anti-hypertensive drug, has been found to decrease liver fibrosis[40]. Finally, Telmisartan *et al*[41] has been found to reduce insulin resistance and fat deposition in the liver and seems to be looks even more promising in the near future.

Dietary modifications and exercise
One of the most effective method of treating NAFLD is weight loss and exercise together. In a recent review by Schwenger *et al*[42], the authors summarized the effects of weight loss and exercise intervention studies in obese patients with NAFLD. A randomized controlled trial conducted by Promrat *et al*[43] used a combination of diet, physical activity and behavior modification to trigger 7%-10% weight loss in obese NASH patients. Those who achieved a minimum of 7% weight loss had improvements in their liver histology. A similar study used NAFLD patients with elevated liver enzymes and central obesity to assess the effectiveness of lifestyle interventions. Patients were randomly assigned to either low (3 sessions/4 wk) or moderate (6 sessions/10 wk) physical activity intensity groups and were compared to a control group. The lifestyle interventions included physical activity and dietary guidance as well as behavior modification. The authors found that there was a decrease in aminotransferases, which was greater in the group with the moderate-intensity lifestyle compared to the control one[44].

Exercise alone has been also found to have positive results. Hallsworth *et al*[45] found that after 8 wk (3 times per week lasting 45-60 min) of resistance based exercise resulted in a reduction of liver lipids, and improvements of lipid oxidation, glucose control and insulin resistance.

Additionally a recent review conducted by Thoma *et al*[46] analyzed 23 studies using diet modification, physical activity, or a combination of both. He concluded that lifestyle modifications that led to weight reduction and/or increased physical activity greatly reduced liver fat and improved insulin sensitivity. More recently a study led by Montesi *et al*[47] found that intensive psychological counseling for physical activity improves physical fitness and liver fat independent of weight loss. Similar effects have been also verified by a recent meta-analysis study[48].

Dietary changes for 1-3 mo have shown to reduce liver enzymes and even normalize them (Table 1)[49-55].

Many study in adults[50,55,56] and children[56] have shown improvement in the histological profile that underwent a weight loss program. The type of weight loss with a traditional low fat diet or calorie restriction is still debatable. All of these studies though, have

Table 1 Nutritional recommendations for non-alcoholic fatty liver disease
Diet trials in NAFLD
Decrease of about 600-800 kcal per day[49]
Based on IBW, a reduction of caloric intake to < 25 kcals/kg per day[50]
Reduction of total fat intake of < 30% of energy intake with no more of 10% of saturated fatty acids[51-53]
Reduction of total Kcal per day of < 30 kcal/kg[54]
A diet low in calories and carbohydrates of 40%-45%[55]

NAFLD: Non-alcoholic fatty liver disease.

failed to examine any decrease of NAFLD as the final result[57-59]. However, the main outcome from these studies was that a reduction of total body weight between 5%-10% would have the most benefits to these patients. This probably verify the theory where the amount of fat that is delivered to the liver may play very important role in the lipid metabolism as well to the total real weight loss itself[55]. Therefore, it is important for dietitians and other health professionals to direct the patients with NAFLD to lose weight, as this interventions therapy seems to offer the most advantages. Rapid weight loss of more than 1.6 kg/wk has been also found in studies[60] to cause deterioration of the inflammation in people with NAFLD and may increase the progression pace of the disease by promoting increase of fatty breakdown from fatty tissue and increasing transport to the liver. Patel *et al*[61] observed that a reduction in BMI of at least 5% is associated with a significant decrease in liver fat and volume in patients with biopsy-proven NASH. Even for the normal weight people, losing weight has an effect on the improvement of non-alcoholic fatty liver disease. A Korean study of 180 subjects, compared with the stable group, the loss group showed an almost 19-fold increase in the odds of disappearance of non-alcoholic fatty liver disease[62].

Even though factors that determine the severity of NAFLD are still unclear in some studies[63], the exercise component is a recommended treatment. Physical activity intensity and histological severity of NAFLD were evaluated in 813 adults (males = 302, females = 511). Moderate-intensity exercise and total exercise per week was associated with decreased levels of NASH or stage of fibrosis. In the same study vigorous exercise was relate with beneficial results in subjects with NAFLD. The authors concluded that intensity of exercise may be more important than duration or total volume. Resistance training (RT) has been also found to be beneficial recently. Three months of RT improves hepatic fat content accompanied by favorable changes in body composition and ferritin and may serve as a complement to treatment of NAFLD[64]. In addition, intensive psychological counseling for PA produces hepatic effects the same as standard cognitive behavior counseling, improving physical fitness and liver fat independent of weight loss. Strategies promoting exercise are effective in motivated patients,

particularly in lean NAFLD patients where large weight loss cannot be systematically pursued[47,65].

OTHER NUTRIENTS

Vitamin C
Vitamin C and E together with weight loss or without has been also examined in children with fatty liver disease. The authors concluded that significant histologic improvements (degree of steatosis, inflammation and ballooning degeneration) were produced by a weight loss of around 5 kg. However, the study failed to prove and beneficial effects of Vitamin C and E on weight loss[56]. Data for Vitamin C and its effects on NAFLD shows no clear beneficial effects. The statement of the most recent consensus was that vitamin C is not recommended for patients with NAFLD outside the context of research protocols[66].

Vitamin E
Oxidative stress and depletion of endogenous antioxidants are important in the pathogenesis of disease progression in NASH. Many drugs with antioxidant features were tried in studies for the treatment of NASH with variable conclusions. Vitamin E (a-tocopherol) is a well-known antioxidant and this feature is the best studied of its many other biological functions. The largest randomized controlled study on vitamin E, the PIVENS trial, demonstrated a greater histological improvement in inflammation in non-diabetic patients with biopsy-proven NASH compared with the placebo and pioglitazone groups. However, only 42% of patients receiving high dose vitamin E (800 IU/d) for 96 wk achieved an improvement in histological parameters compared with 19% in placebo-treated patients[67]. Recently, the Nonalcoholic Steatohepatitis Clinical Research Network conducted a multicenter study comparing metformin and vitamin E in 173 pediatric patients with NAFLD, who were followed up for 96 wk and underwent a post-treatment biopsy (the TONIC study). This study did not show significant benefits of vitamin E for aminotransferase levels; however, it did show differences in the histological characteristics (ballooning and NAFLD activity score) of the liver biopsy performed at 96 wk[68]. Several concerns have been raised regarding an increase in all-cause mortality with the long-term use of vitamin E[69]. Thus, the statement of the consensus was that the use of vitamin E is well supported for nondiabetic adults with biopsy-proven NASH[66].

n-3 fatty acids
A decrease rate in the development of NASH has been demonstrated by a diet high in n-3 PUFA in animal studies[70]. This is possibly due to the fact that n-3 PUFAs have the ability to regulate lipid processing to the liver by reducing oxidative stress and liver inflammation[70].

Capanni *et al*[71] examined the effects of n-3 PUFA

in non-alcoholic fatty liver disease in 42 patients who received 1 gm n-3 PUFA per day for 1 year. Both liver enzymes as well as ultrasound results were improved. A 53% reduction in NAFLD was also observed in 134 patients who received 2 gm of n-3 PUFA three times per day compared with a 35% reduction of NAFLD group who follow a diet low in kcal, respectively[72]. Other similar studies using n-3 PUFA to treat NAFLD have shown pararell results when used aminotransferases and ultrasound to asses fatty liver[73,74]. A recent systematic review and meta-analysis[75] found significant heterogeneity between these studies and concluded that although omega-3 PUFA supplementation may decrease liver fat (with no effects on aminotransferase levels), the optimal dose has not been established. Additional trials are needed to support the routine use of omega-3 PUFA in patients with NAFLD. To date, there is insufficient evidence to support the routine use of omega-3 PUFA supplementation in patients with NAFLD[66].

Fructose

The most common sugar found in fruit and soft drinks is high fructose corn syrup (HFCS). Sucrose is 50% fructose and 50% glucose. In a recent study that included health people the authors demonstrated an increase of liver enzymes of those subjects consuming ¼ of total calories per day in the form of sucrose[76]. In another similar study patients with fatty liver found to have twice the consumption of high fructose syrup compare with those without fatty liver disease (365 kcal *vs* 170 kcal)[77].

In another study, patients that consumed a diet high in calories and fructose were found to have an increase in hepatic fat deposition compared to the normal group[78]. Most recently, Sullivan *et al*[79] showed that children with NAFLD absorbed and metabolized fructose more effectively than lean subjects. Fructose ingestion was associated with an exacerbated metabolic profile[79]. In a 4-wk randomized, controlled, double-blinded beverage intervention study, Jin *et al*[80] demonstrated that reduction of dietary fructose in Hispanic-American adolescents with NAFLD improved several important factors related to cardiovascular disease risk, including adipose insulin sensitivity, high sensitivity C-reactive protein and low-density lipoprotein oxidation. On the other side a recent study by Kanerva *et al*[81] found that high fructose intake was inversely associated with risk of NAFLD in older Finnish adult. A latest meta-analysis of 21 intervention studies concluded that there was insufficient evidence to draw a conclusion for effects of HFCS or sucrose on NAFLD[82].

Prebiotics and probiotics

Dietary prebiotic consumption, which modulates gut microbiota[83] although associated with subjective satiety, reduced postprandial glucose and insulin concentrations and exhibits inconsistent results regarding total energy intake, body weight, gut peptides, insulin sensitivity, serum lipids, inflammatory markers and immune function[84]. Despite the positive results in animals[85], data of probiotics on metabolic effect in humans is still conflicting. Further studies are needed to identify strategies to target gut microbiota composition as an innovative NAFLD treatment in humans.

CONCLUSION

NAFLD is one of the major causes of liver diseases in the world. As the disease progresses from simple steatosis to steatohepatitis, and finally, cirrhosis should alarm health professionals to look over in order to avoid high mortality rates that have been found to related with the disease. The treatment should lie on the management of the "insulin resistance-metabolic syndrome" and not in fatty liver disease itself. The significant recognition of the disease will involve a challenge in educating people as well in the initiation of the appropriate interventions. Weight loss and exercise has been proven in reducing the steatosis inflammation and reversion of fibrosis in some cases. Vitamin E can also be used with safety in adults only with biopsy proven NASH. Consumption of high fructose syrup to the development of NAFLD is still under debate. The data for vitamin C shows no clear effect while the supplementation of n-3 FA and probiotics is still conflicting but shows promise.

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