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NUTRIENT COMPOSITION IN NON-ALCOHOLIC FATTY LIVER DISEASE— A REVIEW

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Non-Alcoholic Fatty Liver Disease (NAFLD) is the most prevalent non communicable disease arising due to obesity globally. Hepatic fat deposition is a consequence of excessive caloric intake due to imbalanced lifestyle factors of which diet and physical activity are responsible in a major way. NAFLD is a reversible condition which, with early treatment can prevent liver related mortality. There is no medicinal treatment for NAFLD, thus lifestyle management though diet modification and physical activity is the line of treatment. The quality of diet is more important than the quantity. This review compiles the previous years, evidence based research studies in humans and highlights the macronutrients including carbohydrates, proteins, fats and micronutrients in the management of NAFLD since modifying them even without weight loss can prove beneficial to NAFLD patients. Simple carbohydrates, saturated fats, cholesterol increase the fat content in liver. PUFA particularly n3 fatty acids, MUFA, fibre and antioxidants like vitamin E and C, have been studied to play a protective role. Research is ongoing for supplementation of n3 fatty acids and antioxidants like vitamin E, C and D for NAFLD. Sodium restriction is beneficial in NAFLD, but more evidence based studies are required to arrive at recommendations.

Keywords: NAFLD, Nutrition, Diet, Energy, Macronutrients, Micronutrients

INTRODUCTION

Non-Alcoholic Fatty Liver Disease (NAFLD) is an alarming and upcoming cause of liver related disorders globally.[1] The prevalence has been reported to be 25-45% worldwide.[2] In NAFLD there is increased accumulation of fat in liver in persons who are not consuming alcoholic beverages in excess (usually <20 g/d for women and <30 g/d for men).[3] NAFLD is a spectrum of disease condition with hepatic steatosis at one end, considered to be benign, which can progress to a more severe form, nonalcoholic steatohepatitis (NASH), which can further advance to liver cirrhosis and hepatocellular carcinoma (HCC). It is associated with higher risk of liver related Cardiovascular Disease (CVD), and overall mortality.[4] Diet related and lifestyle factors may influence NAFLD progression in a major way. NAFLD patients also manifest excess body weight, diabetes, dyslipidemia and hypertension.[5,6]

METHODS

The relevant published papers in English language were searched through an electronic database search using PubMed and Google scholar from 2004 till Mid 2017. Research articles including Dietary and Nutrient intake, anthropometry and biochemical aspects of NAFLD studies were included in the search. Studies on paediatric population were not included. Detailed referencing was done from original articles to seek clarity in ideas from the point of view of publication.

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The following keywords have been used during the search:

NAFLD, NASH, nutrition, diet, energy, macronutrients, micronutrients, carbohydrate, fat and protein.

RESULTS AND DISCUSSION

Five study categories included Role of Energy, Carbohyderates, Proteins, Fats and Micronutrients in NAFLD. 270 research articles with relevant captions and abstracts were studied .Detailed text of complete article of 137 articles including crosssectional studies RCTs, case control studies and other studies of adult patients were referred for including the concepts.

Role of Energy Restriction

Several studies have reported an increased caloric consumption in NAFLD subjects. Musso et al, in a systematic review and meta analysis of RCTs suggested that weight loss is safe for liver and protective for cardiometabolic health in NAFLD patients.[7] A weight reduction of more than 5% improves visceral fat and decreases liver enzymes[8] and more than 7% of weight loss improves liver histology in NASH.[9] According to the American Gastoenterological Association (AGA), loss of 3-5% of baseline weight is important to improve hepatic fat. When necroinflammation is present a more substantial loss of more than 10%, may be necessary.[10]

Similar improvements in cardiometabolic variables have been reported with hypocaloric diets.[11,12] Diet induced weight loss resulted in regression of fibrosis.[13,14]

Daily calorie reduction by 500 to 1000 Kcals/day lead to a weight loss of 0.5 to 1 kg/week, since losing weight rapidly may be deleterious for NAFLD patients.[15,16]

Non randomized studies have demonstrated that subjects who followed balanced diets with gradual weight reduction lead to decrease in hepatic fat, inflammation and NASH score.[17,18]

Macronutrient Composition

Manipulation of either macronutrients or micronutrient content can influence Insulin Resistance (IR), serum lipids, inflammation and hypertension irrespective of weight loss in NAFLD progression.[19,20,21] More important than the total caloric consumption is the macronutrient composition of the diet.[22] Carbohydrates, proteins and fat are involved with progression and treatment of NAFLD.[23]

Carbohydrates

The percent calories of carbohydrate coming from the diet and the Glycemic Index (GI) of food stuffs are likely to effect NAFLD.[24] Use of simple carbohydrates is on the rise leading to metabolic disorders.[25] Carbohydrate rich diets can raise blood glucose, insulin and triglycerides levels even under isocaloric conditions which can deteriorate NAFLD patients condition clinically.[26,27] A high-carbohydrate, low fat diet initiates the fatty liver development via excess denovo synthesis of fatty acid.[28] A significantly increased intake of carbohydrates from the diet (51% vs. 45% of total calories) and decreased intake of fat from the diet (34% vs. 40% of total calories) was reported to have an increased histological severity and a significantly high HOMA Index.[29] NAFLD patients consuming >54% of energy from carbohydrates compared with those consuming $\leq$35% had a significantly higher odds of liver inflammation.[30,31]

As compared to the above quoted studies, studies undertaken with a carbohydrate-restricted diet showed a greater decrease of liver enzymes and hepatic triglycerides. Ryan and colleagues randomized NAFLD patients to low calorie diets with either high carbohydrate-60% and low fat-25% or with low carbohydrate-40% and high fat-45% composition, with proteins as 15% of total calories in both and of equal energy deficit (750 kcal/day) for 16 weeks. Inspite of weight loss being equal, patients with decreased intakes of carbohydrate had lower levels of Alanine Amino Transferase (ALT), compared to patients with increased intake of carbohydrate and low-fat diets, implying that low carbohydrate, hypocaloric diets are of benefit to NAFLD patients, independent of weight loss.[32] Browning et al compared NAFLD patients on energy-restricted (1,200 to 1,500 kcal/day) diet with NAFLD patients following a carbohydrate-restricted diet less than 20 g/day. The weight loss was same in both the groups. A reduction in hepatic triglyceride level was observed in patients on a low carbohydrate diet (55 % vs 28%) ($P<0.008$).[33] A similar study reported a reduction in fat content, fibrosis, inflammation of liver and a weight loss after six months in NAFLD patients who were on a carbohydrate restricted diet of less than 20 gms per day.[34]

Intrahepatic lipid content decreased more with a low carbohydrate diet (less than 50 gms/day) compared to a high carbohydrate (more than 180 grams/day) hypocaloric diet, despite same weight loss of 7%.[35] Studies with low carbohydrate ketogenic diets lowered the liver volume more

than hypocaloric diets possibly due to the fact that low carbohydrate diets deplete liver glycogen rapidly.[36]

In a long duration RCT improvements in intrahepatic lipid content in both groups consisting of either low fat hypocaloric diet (<20% of total calories) or low carbohydrate hypocaloric diet (<90 grams of CHO and >30% calories of fat per day) without any significant difference was demonstrated.[37]

There is an increased consumption of highly processed food products often rich in sucrose and fructose which raises the liver enzymes and is implicated in MS.[38,39,40] Fructose metabolism decreases lipid oxidation, increases lipogenesis, gut permeability, free Radical Oxygen Species (ROS) production, bacterial overgrowth and serum lipopolysaccharide levels.[41,42]

Toshimitsu et al reported that in NASH patients a higher consumption of simple and total carbohydrates was found compared to those with simple steatosis.[43] Data from Framingham longitudinal study by Dhingra *et al.* projected that soft drink consumption of one or more drinks per day increases risk of Obesity and MS.[44] According to published studies there was a high fructose consumption in NAFLD patients, despite no difference in total carbohydrate consumption compared with controls.[45,46,47] The intake of 7 or more sugar sweetened drinks per week was associated with significantly higher fibrosis, hepatic inflammation and ballooning in 427 NAFLD patients.[48] Maersk *et al.* demonstrated in a RCT that when four test drinks (skimmed milk, regular cola, water and diet cola were administered as one litre per day for a period of 6 months ,the hepatic fat was significantly higher in the regular cola group compared to the other 3 groups.[49]

The use of complex carbohydrates, containing dietary fibers and antioxidants have proven beneficial in retarding NAFLD progression.[50,51] The additional benefits of using whole grains as reported by various studies were improvement of dyslipidemia, obesity and MS; decrease in visceral fat, fasting glucose and fasting insulin.[52-55]

Solomon *et al.* reported that a low-GI diet alone does not improve hepatic insulin sensitivity but along with exercise it does reduce post-prandial hyperinsulinemia.[56] A modified Mediterranean diet of low carbohydrate and low GI is associated with greatest reduction in ALT levels by 35% ($P<0.05$).[57] An association between high GI food intake and the presence of liver steatosis has been reported in crosssectional studies.[58-60]

Loria et al stated that the current recommendations of many scientific associations indicate a carbohydrate intake >50% of the total energy and choosing whole grain and low-glycemic index foods.[61]

The American Dietetics Association (ADA) recommends increased intake of complex carbohydrates for example the ones found in whole grains, pulses and legumes, vegetables and fruits and decrease intake of simple or refined carbohydrates.[62-64]

Proteins

Leclercq et al states that for the influx of crucial amino acids and for hepatocytes to regenerate, proteins are required. This prevents the excessive deposition of fat within hepatocytes.[65] The percentage of calories from proteins is generally not altered in NAFLD patients although Zelber-Sagi and colleagues reported increased consumption of meat protein.[66]

Studies report that protein deficiency or malnutrition can lead to formation of fatty liver.[67,68] Various studies have shown beneficial effects of increased intake of proteins which may improve loss of weight and glycemic control in Insulin Resistant (IR) patients and negate the effects of a high fat diet on intrahepatocellular lipids.[69-71] A study by Duarte et al in Brazilian subjects revealed that hypocaloric, high protein diets of 35% of mixed animal and vegetable protein was associated with improvement in clinical and biochemical markers in NAFLD independent of decrease in BMI or body fat mass.[72] Arciero et al , in his study reported a beneficial role of proteins in reducing body fat content and CVD development, when proteins constituted 40% of total calories compared to a diet when proteins constituted 15% of the total calories. A moderate protein intake of 25% of total calories was beneficial for body composition and glycemic response in overweight individuals without any side effects.[73]

Associations between consumption of red meat and NAFLD have been studied.[74,75] Animal data suggest that soy protein may reduce hepatic lipogenesis and improve insulin sensitivity.[76-78] In a parallel randomized trial, the low carbohydrate and low calorie soya rich diet reduced the liver enzymes significantly.[79] Presently there are no evidence based studies to state the impact of dietary protein on NAFLD and following the ADA guidelines which are based

on Recommended Dietary Allowances (RDA) seems appropriate.[62-64]

Fats

Western diets and over ingestion of fats are causative factors for IR and impaired metabolism of lipids leading to NAFLD formation.[5,24,58] Studies reported in NASH patients revealed a high intake of fat (21% to 37% of total calories) which was an independent nutritional risk factor for progression of NAFLD (odds ratio [OR] = 2.51).[80,81] The reduction of calories from fat (27% to 19%) for 6 months decreased the liver enzymes significantly.[82] Moderate weight reduction of 8% resulted in reversal of liver fat by 81%, IR and hyperglycemia on administration of a low calorie diet with 3% fat to NAFLD patients with Type 2 Diabetes over a maximum period of 16 weeks.[83]

Saturated Fatty Acids (SFA)

The lipid and glucose homeostasis can be adversely affected by Saturated fatty acids leading to development of MS and NAFLD.[84] Studies have reported that NAFLD patients consume less of polyunsaturated fatty acid (PUFA) omega 3 and more of SFA.[43,45,85]

In a double blind RCT trials by Lefevre et al , of the two reduced-fat diets (30% fat of which 9% SFA or 25% fat of which 6% SFA) compared with a control (38% fat of which 14% SFA) in healthy men, both low-fat diets decreased LDL-c levels and HDL-c levels. After a 6-week intervention, the triglyceride levels increased. This suggested that although reduced SFA intake of 10% might benefit NAFLD patients, intakes of ≤6% may produce counterproductive effects on lipid levels of plasma, especially triglycerides.[86]

McCarthy and Rinellas review summarized the SFA to be in range of 6-10% for NAFLD patients.[5]

Various studies on excess dietary cholesterol intake have been reported to be an important cause of NAFLD.[7,85,87] In a study on Japanese non obese NAFLD patients who consumed higher cholesterol and lower PUFA than obese NAFLD patients implying that the altered PUFA and Cholesterol intakes may be linked to NAFLD progression in non obese patients.[88] Although studies show that high cholesterol intake is responsible for NAFLD, in view of the current dietary guidelines for cholesterol from USDA (2015) the requirements needs to be revisited.[89]

Monounsaturated Fatty Acids (MUFA)

Compared with high-carbohydrate diets, diets high in MUFA may be preferable if they are not coupled with increased energy intake or contain higher quantities of cholesterol.

A randomized study by Bozzetto et al, on 45 patients with diabetes comparing a high carbohydrate/low-GI/high-fiber diet (carbohydrate 52% of total calorie intake and 28 gms of fiber) with a high MUFA diet (28% of total calorie intake) for 8 weeks, demonstrated a significant greater steatosis reduction in the high MUFA diet group (27% vs 5% $p<0.05$).[90]

Olive oil rich in MUFA, was found to benefit subjects of Metabolic Syndrome in their lipid profiles by decreasing the triglyceride levels and improving the glycemic response in subjects with IR.[91,92] In an intervention study with olive and canola oil compared with other vegetable refined oils, a significant reduction in BMI, improvement in lipid profile, liver span and grading of fatty liver with MUFA sources was reported.[93]

Evidence supports the benefits of a Mediterranean diet for patients with the metabolic syndrome, through improving insulin sensitivity and reducing cardiovascular risk, both of which would be beneficial to patients with NAFLD.[94-97]

Significant decrease in liver fat and metabolic profile have been reported on adhering to the Mediterranean diets.[98-100]

Polyunsaturated Fatty Acids (PUFA)

PUFA deficiency can influence the onset and progression of NAFLD.[101] The disturbance in omega-3: omega-6 ratio has been reported in NAFLD patients.[102,103] Omega 6 fatty acids in excess amounts have been studied to induce proinflammatory effects in liver.[104]

Various studies report that, n-3 PUFA supplementation is likely to be beneficial. Treatment with 15 ml per day of n3 fatty acids resulted in lowering of liver enzymes in NAFLD patients who were having hypertriglyceridemia; hepatic steatosis was resolved in 35% of the patients.[105,106]

A RCT investigated the use of 2 gms/day of seal oils in Chinese patients who were hyperlipidemic. The serum lipid and ALT levels were found to be improved.[107]

Human clinical trails demonstrated that prolonged omega 3 PUFA supplementation of 1 to 2.7 g/day for 6 to12 months ameliorates hepatic steatosis and lowers the liver enzymes, fasting blood glucose levels and serum TG in NAFLD patients.[108,109] However, 4g/day of marine omega-3 supplementation in the form of capsules or oil showed a

marked reduction of liver fat with no significant effect on serum aminotransferases levels.[110] Highly purified EPA when administered for a period of one year at a dose of 2.7 grams per day improved the liver enzymes, hepatic steatosis, fibrosis and decreased the hepatic inflammation in NASH patients due to its antioxidative and antiinflammatory properties.[111] A dose of 3 gms per day of n3 PUFA was associated with decreased hepatic fat, independent of weight loss.[112]

EPA from diet and along with DHA could be nutrients that could help in prevention of NAFLD in population based study from Japan.[113]

Trans Fats (TFA)

While no human studies have been reported on TFA and NAFLD/NASH, animal studies show association of increased TFA consumption from oxidized oils and liver inflammation.[114,115]

Table 1: Summary of Nutrition Guidelines and Recommendations for NAFLD

	AASLD, ACG, AGA (10)	ADA (62-64)	McCarthy and Rinella (5)
Weight loss	Loss of 3-5 % of baseline weight appears to improve steatosis. Upto 10% weight loss may be required to improve necroinflammation, through hypocaloric diet or increase in physical activity	Low carbohydrate or low fat diet, restricted in calories, may be effective for short term for upto 1 year	5-10% body weight loss over 1 year, is the initial goal. Maintenance of weight loss and IBW, is long term goal
Energy	Low caloric diet alone or in combination with physical activity	Low caloric diet, based on persons requirements	1200-1500 Kcals/day
Carbohydrates	Not specified	Whole grains should be half of total grain intake. Fiber intake of 14 gms/1000 Kcals	≥50% as whole grain. Avoid HFCS
Protein	Not specified	Insufficient evidence 15-20% of RDA	Lean meat or vegetable protein
Total Fat	Not specified	Varies with diet, low carbohydrate or low fat diet for loss of weight	<35% of total energy
Saturated Fat	Not specified	<7% of total Energy	<7% of total Energy
Trans Fat	Not specified	As minimum as possible	As minimum as possible
Unsaturated Fatty Acids	May be considered as the first agent for treatment of hypertriglyceridemia in NAFLD patients	2 or more servings of fatty fish/week	1 gm of Fish oil/day (EPA+DHA). MUFA-Upto 25 percent
Cholesterol	Not specified	<200 mg/day	Not specified
Micronutrients	800 IU/day of Vitamin E in non diabetic adults with biopsy proven NASH	No clear evidence	800 IU/day Vitamin E
Sodium	Not Specified	<2300 mg/day in hypertensive and normotensive individuals. <2000 mgs/day in Diabetics and Heart failure patients	Not Specified

Note: Abbreviations: AASLD = American Association for study of Liver Diseases; ACG = American College of Gastroenterology; AGA = American Gastroenterological Association; ADA = American Diabetes Association; NAFLD = Non-alcoholic fatty liver disease; NASH = Nonalcoholic Steatohepatitis; MUFA = Monounsaturated fatty acid; EPA = Eicosapentanoic Acid; DHA = Docosahexanoic acid; mg = milligrams; IU = International Units; HFCS = High Fructose Corn Syrup.

In view of the deleterious effects of trans fats the use of packaged and processed foods should be avoided as part of dietary recommendations for NAFLD.[6]

The ADAs recommendations for increased MUFAs and n3 PUFAs consumption and decreased consumption of Saturated Fats and Trans fats seems appropriate.[62-64]

Micronutrients in NAFLD

Vitamin E

Vitamin E is the best-studied antioxidant for the treatment of NAFLD.[116] Studies in NASH and NAFLD patients have reported a decreased consumption of Vitamin E as compared to controls.[85,117] The requirement of Vitamin E is increased to decrease the oxidative stress in NAFLD and NASH patients. Vitamin E improves aminotransferases and histological markers in NASH subjects. Studies show mixed results on effect of Vitamin E on liver fibrosis.[118,119] Sanyal and colleagues, reported 96 weeks of administration of 800 IU/day of vitamin E, with improvement in histology of liver compared to placebo. Vitamin E was found to improve the NAFLD activity score, despite not improving insulin resistance.[120] Various studies have shown marked improvements in fatty liver with doses of 800 IU/day and 1,000 IU/day.[121-123] Caution needs to be exercised in prescribing Vitamin E as it is associated with overall increased cardiovascular mortality.[124-126] Klein *et al.* studied the association of prostrate cancer with Vitamin E administration.[127]

The AASLD guidelines states that Vitamin E should be considered as pharmocological therapy to non-diabetic adult patients (biopsy proven NASH) when prescribed, at a dose of 800 IU/d on daily basis.[10] In patients with impaired fasting glucose or with fibrosis, 300 mg/d supplementation of vitamin E has been reported to be effective and safe.[128-130]

Studies have looked at the combination of vitamins C and E.[131] Fibrosis improved to a significant degree in those treated with vitamins C and E however there were no improvements in inflammation/necrosis scores or ALT levels with vitamin E and C supplementation.[132] Caution has to be exercised with prescription of Vitamin E supplements.

Vitamin D

Studies report that Vitamin D deficiency can cause oxidative stress and can result in MS, IR and NAFLD.[133-136] An association of low levels of serum Vitamin D3 concentrations and histology of liver was reported NAFLD subjects by Targher *et al.*[137] Presently more studies are needed to be undertaken to draw a conclusive statement about the potential role of Vitamin D.

The Summary of the Nutrition Guidelines and Recommendations for NAFLD are given in Table 1.

CONCLUSION

NAFLD is a noncommunicable chronic disease and is posing an ever-increasing health burden. Lifestyle intervention is presently the mainstay of therapy. The nutrients in the diet and their composition can impact and decrease the fat and inflammation in the liver. The evidenced-based guidelines provided by American Dietetic Association are reasonable for the nutritional management of NAFLD along with its associated comorbidities. Dietary modification such as restriction of calories along with refined carbohydrate and fat restriction may help in improvement of liver enzymes, metabolic risk factors and hepatic steatosis. Added sugars and refined carbohydrates should be reduced and fiber intake should be encouraged in the diet. Diets high in lean protein, n-3 PUFA, MUFA and fiber and low in SFA and TFA content have been studied to benefit the NAFLD patients. The components of the Meditarranean diet have proven benefits and can guide patients to make healthy choices.Dietary guidelines for NAFLD patients should be recommended based on sound dietary intervention trials.

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