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ROLE OF NUTRIENTS IN NON-ALCOHOLIC FATTY LIVER DISEASE

Clinical Research

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ABSTRACT

Introduction: Non-alcoholic fatty liver disease (NAFLD) is a liver disorder that refers to a group of conditions where there is accumulation of excess fat in the liver of people who drink little to no alcohol.

The most common form of NAFLD is a non serious condition called fatty liver (Naim Alkhouri, MD, et al. 2012). In NAFLD, simple fatty infiltration of the liver or hepatic steatosis (fat content exceeds 5% of liver volume) without any evidence of hepatocellular injury in the form of ballooning of hepatocytes or no evidence of fibrosis. The risk of developing cirrhosis and liver failure is minimal but due to its high prevalence it none the less represents an important cause of cirrhosis (Dr. James Mc Morran, et al. 2016). Cirrhosis occurs when the liver sustains substantial damage, and the liver cells are gradually replaced by scar tissue, which results in the inability of the liver to work properly. Some patients who develop cirrhosis may eventually require a liver transplant (surgery to remove the damaged liver and replace it with a new liver) (Marsha H. Kay, MD, et al. 2012).

KEYWORDS

Non Alcoholic Fatty Liver Disease, Liver cirrhosis, Steatohepatitis, Diet, Diabeties, Macro nutrients, Micronutrients, Physical activity.

INCIDENCE AND PREVALENCE

Prevalence of the disease is estimated to be around 9-32% in Indian population, with the higher incidence rate amongst obese and diabetic patients. Prevalence of disease is comparatively higher in females than in males (Kalra S, et al. 2013). Whereas, Global prevalence of NAFLD is 25.24% with maximum prevalence in middle East and South America and lowest in Africa.

Aetiology

NAFLD is part of the metabolic syndrome characterized by diabetes, or pre-diabetes (insulin resistance), being overweight or obese, elevated blood lipids such as cholesterol and triglycerides, as well as high blood pressure liver (*Naim Alkhouri, MD, et al.2012).*

Less common causes include: (Saurabh sethi, MD et al. 2019)

- *Pregnancy*
- Rapid weight loss
- Some types of infections, such as hepatitis C
- Side effects from some types of medications, such as methotrexate (Trexall), Tamoxifen (Nolvadex), Amiodorone (Pacerone) and Valproic acid (Depakote)
- Exposure to certain toxins

Risk factors associated with NAFLD

Conditions with associated association	Conditions with emerging association
Obesity	Polycystic ovary syndrome
Type-2 diabetes mellitus	Hypothyroidism
Metabolic syndrome	Obstructive sleep apnea
Dyslipidemia	Hypopitutarism
Gall bladder disease	Hypogonadism , Pancreato-duodenal-resection

Source: *Chalasani et al, 2012; Conlon et al, 2013*

Obesity has the most correlation with non-alcoholic fatty liver. Therefore, to modify the lifestyle is the first line treatment for non-alcoholic fatty liver. Managing the non-alcoholic fatty liver includes gradually decreasing the weight and increasing the physical activity (*Chalasani et al, 2012*).

Studies did not determine which material or micronutrients in the diet potentially increase the risk of developing Non-alcoholic fatty liver disease. To change the diet composition without decreasing weight will be difficult in long term. To change the diet composition without decreasing the rate of calorie will be a practical and realistic variation for treatment of non alcoholic fatty liver. Therefore, it is very important to evaluate the relationship between particular nutrient and compounds of diet to treat non alcoholic fatty liver.

CARBOHYDRATES

Fructose is a monosaccharide It is a sweet tasting sugar and found naturally in fruits and some vegetables. Fructose is sweeter than either glucose or sucrose (*Moeller SM et al, 2009*). High Fructose Corn Syrups (HFCS) are the principal sources of fructose which are found in soft drinks and pre-packaged foods. The most common form of HFCS is HFCS 55, which has 55% fructose compared to sucrose which is 50% fructose. Several meta-analyses suggested that the consumption of sugar-sweetened beverages is related to the risk of metabolic syndrome; increased triglycerides (TG) levels, stimulated DNL and increased visceral fat. Consumption of increased amount of sugar sweetened beverages and pre-packaged foods is related to the risk of metabolic syndrome, High fructose corn syrup (HFCS) stimulates de novo lipogenesis and finally development of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatosis (NASH) (*Lim JS, Mietus-Synder M et al,2010*).

Fructose is an intermediary in the metabolism of glucose. Fructose is poorly absorbed from the Gastro-intestinal tract by the glucose type-5 (GLUT-5) transporter. Glucose is transported into cells by GLUT-4, an insulin-dependent transport system. Fructose is almost entirely cleared by the liver. Hepatic metabolism of fructose induces de novo lipogenesis. Fructose phosphorylation in the liver consumes ATP. Consequently, the accumulated ADP serves as substrate for uric acid formation (*Eva Juarez-Hermandez et al, 2016*).

Fructose either from sucrose or from HFCS initiates liver dysfunction and the metabolic syndrome. Fructose can induce NAFLD by its ability to act as an up regulated substrate for DNL and by bypassing the major rate-limiting step of glycolysis at phosphofructokinase. Continuous fructose ingestion may cause a metabolic burden on the liver through the induction of fructokinase and fatty synthase **(***Metin Basaranoglu et al, 2015*).

FATS

Specific types of fat 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. Saturated fats could be important in the pathophysiology of NAFLD. Hyper caloric and high fats diet is associated with increased Intra Hepatic Triglyceride. Oleic acid is consumed as the main source of MUFA in the diet (*Eva Juarez-Hermandez et al, 2016*). Olive oil is the most important source of oleic acid (other sources are avocado and seeds). MUFA decreases the blood lipid indices, and it reduces the ratio of low-density lipoprotein (LDL) and total cholesterol to high-density lipoprotein (HDL) as well. Trans-fatty acids are unsaturated fatty acids that are produced through the process of hydrogenation to make partially hydrogenated oils. Trans-fatty acids have been associated with cardiovascular disease and

diabetes. High-fat diet increases liver lipid peroxidation and decreases hepatic antioxidant enzyme activities (superoxide dismutase, catalase and glutathione peroxidase). The intake of oxidized oil leads to higher levels of lipid peroxidation and a lower concentration of plasma antioxidants. There exists a strong relationship between the consumption of TFA in the oxidized oils and lipid peroxidation and non- alcoholic fatty liver disease (NAFLD) (*Lim JS, Mietus-Synder M et al, 2010*). The extent of the peroxidative events in liver differs depending on the fat source which means higher TFA levels may represent a direct source of oxidative stress for the organism.Studies prove that there is a direct effect of TFA on NAFLD (*Eva Juarez-Hermandez et al, 2016*).

CHOLESTEROL

In humans, cholesterol is absorbed from the diet and synthesized by cells in various tissues. the dietary cholesterol aggregates into micelles with biliary cholesterol (800–1300 mg/day) in the duodenum. Physiologically, approximately 50% of the cholesterol is absorbed in the jejunum (*Munechika Enjoji et al, 2012*). The cholesterol is then transported to the liver in the form of chylomicrons and chylomicron remnants. NPC1L1, which may facilitate the hepatic accumulation of cholesterol, is expressed on the canalicular membrane of hepatocytes in humans. The main metabolic pathways of cholesterol in hepatocytes include (1) cholesterol de novo synthesis (acetyl-CoA-mevalonate-cholesterol pathway); (2) cholesterol uptake in the form of LDL and chylomicron remnants; (3) cholesterol excretion into the blood in the form of VLDL; (4) cholesterol excretion and uptake through bile; (5) synthesis of bile acids and their excretion. Under normal conditions, these pathways interact with each other to maintain cholesterol levels within a specific range (*Munechika Enjoji et al, 2012*). However, in NAFLD patients, these systems are highly disorganized. High levels of LDL cholesterol increase the risk of fatty deposits on vessels that bring blood to the heart. Too-low levels of HDL cholesterol suggest the body may not be able to clear plaques and other fatty deposits from the body. Both conditions create a risk for heart disease and heart attack (*E Rusu et al, 2015*).

MICRONUTRIENTS:

Micronutrients include electrolytes, minerals, vitamins and carotenoids and are required in micro or milligram quantities for cellular metabolism. The liver plays an important role in micronutrient metabolism and this metabolism is often altered in chronic liver diseases (*Octavia Pickett-Blakely et al, 2018*).

Electrolytes (sodium, Chloride, and potassium) and minerals (calcium, phosphorous, zinc etc.,) are inorganic compounds required for tissue culture, pH regulation, neuronal signaling, muscle contraction, and enzymatic activities. However, the role of electrolyte homeostasis is not well in NAFLD (*Choi Y et al, 2016*). Several minerals, vitamins and carotenoids contribute to the pathogenesis of NAFLD (*Kwok RM et al, 2013*).

Vitamins are organic compounds that regulate cellular growth and metabolism, and their solubility into either lipids or water determines the mechanisms by which they are absorbed, transported, stored, and excreted (*Liyu Yet al, 2015*). After small intestinal absorption, fat-soluble vitamins (vitamins A, D, E, and K) are transported through the lymphatic system via chylomicrons and stored in liver and adipose tissues, whereas water-soluble vitamins (thiamin, riboflavin, niacin, vitamin B_6, folate, vitamin B_{12}, pantothenic acid, biotin, and vitamin C) enter the bloodstream, existing only in trace amounts in tissues before being excreted in urine. These differences in tissue reserves between fat- and water-soluble vitamins translate to differences in daily consumption requirements to maintain physiologic levels. Namely, daily intake of fat-soluble vitamins is not required whereas daily consumption of water-soluble vitamins is essential (*Ganji SH et al, 2009*).

Carotenoids are a large class of phytochemicals with anti-oxidant and anti-inflammatory activity. This class includes carotenes (eg, α-carotene, β-carotene, and lycopene) and xanthophylls (eg, lutein, zeaxanthin, β-cryptoxanthin, and astaxanthin) (*Erhardt A et al, 2011*). They largely are found in fruits and vegetables, but also are found in smaller concentrations in poultry. Because several carotenoids can be converted to vitamin A, carotenoids have additional roles in cellular development, growth, and differentiation. The majority of this conversion occurs in the intestine and is impaired in obese individuals, thus linking carotenoid metabolism indirectly with NAFLD pathogenesis (*Nagata N et al, 2015*).

Zinc deficiency may augment oxidative stress in NAFLD, a related condition of hepatic lipid dysregulation (*Carr RM et al, 2015*). Zinc reduces hepatic triglyceride accumulation and oxidative stress through enhanced very low density lipoprotein secretion and peroxisome proliferator activated receptor-α and hepatocyte nuclear factor-4α–mediated augmentation of fatty acid oxidation. In addition to the putative effects on oxidative stress, zinc deficiency also may exacerbate NAFLD fibrosis and cirrhosis (*Mousavi SN et al, 2018*).

The liver has a critical role in **copper** metabolism. Copper has its effects on the liver including on anti-oxidant and cellular respiratory systems. In the liver, copper is a co-factor for several anti-oxidant enzymes (*Aigner E et al, 2018*). Copper deficiency in NAFLD patients may exacerbate oxidative stress and lipotoxicity from both impaired mitochondrial function and up-regulation of triglyceride synthetic pathways. Low hepatic copper is associated with more advanced liver disease, systemic metabolic disease, and diabetic status (*Aigner E et al, 2018*).

The earlier-mentioned minerals have been implicated in NAFLD pathogenesis largely owing to serum and/or hepatic deficiencies, however, the contribution of **iron** to NAFLD is most widely accepted to be owing to iron excess. Excess iron correlates with hepatic lipid peroxidation and NAFLD severity (*V Nathan Subramaniam et al, 2016*). The iron regulatory protein hepcidin is a hormone produced by the liver that regulates iron absorption from enterocytes by causing internalization of the basal membrane iron transporter ferroportin. Ferroportin is expressed in multiple issues but the enterocyte ferroportin is considered the major driver of iron hemostasis. Hepcidin, ferroportin, ferritin (the storage form of iron), and iron itself all have been associated with hepatic injury in NAFLD (*Ryan JD et al, 2018*).

PHYSICALACTIVITY

Physical activity also helps in improving insulin resistance, a common finding in people with NAFLD. Insulin resistance is a condition which causes impaired uptake of glucose by mainly the muscle and fat tissues of the body (*Neha pahariya agarwal et al, 2017*). Liver glucose uptake is not dependent on the insulin like the other tissues of the body thereby leading to an increased uptake of glucose by the liver cells from the blood stream. This excess glucose is then converted to fats and stored within the liver leading to accumulation of fat within the liver. Daily walking for about 30-45minutes is encouraged to deal with the condition (*Romero-Gomez M et al, 2017*).

CONCLUSION

Lifestyle modifications offer simple therapeutic targets for NAFLD. Cognitive nutritional support, which is aimed at reducing calorie-intake and avoiding overeating, should be developed alongside pharmaceutical treatments to prevent the disease progression to cirrhosis and HCC (*Chalasani et al, 2012*). Excess cholesterol intake, in particular, is a major stimulant for the development of fatty liver. The accumulation of cholesterol rather than triglycerides may play a critical role in the progression from simple steatosis to steatohepatitis. Accordingly, strategies targeting cholesterol accumulation offer basic therapeutic approaches for NAFLD patients, and cholesterol management therapy seems to represent a promising treatment for NAFLD. The potential clinical benefit of cholesterol management for treating NAFLD with respect to hepatic steatosis and injury should be estimated in appropriately designed trials (*Munechika enjoi et al, 2012*).

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