

NAFLD and It's Association with Vitamin D

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ABSTRACT: Non alcoholic fatty liver disorder (NAFLD), as the name suggest is the accumulation of fat content in the liver due to reasons other than consumption of alcohol. Under NAFLD we can find a range of diseases, Non Alcoholic Steatohepatitis (NASH) being the most prominent one. It is a scenario where the inflammation maybe a result of response to stress that may lead to accumulation of lipid in the liver.

One of the main causes of NAFLD is the deficiency of Vitamin D. Vitamin D can either be obtained exogenously by exposure to sunlight or endogenously by diet metabolism in the liver. Recent studies provides evidence that even when exposed to adequate sunlight, the amount of Vitamin D acquired has not been able to meet the requirement of the body, without supplementation. Low Vitamin D levels are associated with high prevalence of NAFLD. Its deficiency and insufficiency has led to a systemic increase in inflammation. The precise role of Vitamin D in NAFLD is not completely known but its association with innate and adaptive immunity and its anti proliferative effect explains its significance in such diseases.

KEYWORDS: Non alcoholic steatohepatitis, steatosis, inflammation, dehydrocholesterol

I. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has become the most common form of chronic liver disease in Western countries with a prevalence as high as 30%, already exceeding viral hepatitis and alcoholic fatty liver disease.(1) NAFLD is defined as a state of accumulation of fat in the liver in the absence of excessive alcohol consumption. NAFLD has become the most common cause of liver disease. It comprises of a wide spectrum of liver damage ranging from simple steatosis to steatohepatitis , to fibrosis and cirrhosis that can progress to liver failure and hepatocellular carcinoma. This disease can be classified as non alcoholic fatty liver (NAFL) and non alcoholic steatohepatitis (NASH).(2) It is frequently associated with abnormal obesity, insulin resistance, type 2 diabetes, and its pathogenesis is closely associated to the metabolic syndrome.

Vitamin D deficiency, is also linked with obesity, hence often found to co-exist with NAFLD. Vitamin D is a secosteroid hormone whose main function is calcium and phosphate balance. This fat soluble vitamin is found to be in a few foods and is produced exogenously when ultraviolet rays comes in contact with the skin and trigger its synthesis. Vitamin D has its action for immune modulation, cell differentiation and proliferation, and inflammation regulation. Its deficiency has become one of the most prevalent micro nutrient deficiency. The aim of this review is to systematically quantify the association between Vitamin D levels and NAFLD. We hypothesize that low Vitamin D levels were associated with higher prevalence of NAFLD.

II. NAFLD

Non alcoholic fatty liver disease is a kind of chronic hepatitis that affects a wide range of individuals. NAFLD mainly includes obesity, impaired insulin sensitivity and dyslipidemia. Important feature of NAFLD includes steatosis, inflammation, hepatocellular ballooning and fibrosis. There are two types of NAFLD, non alcoholic fatty liver(NAFL) , and non alcoholic steatohepatitis(NASH). In NAFL hepatocellular injury is absent whereas NASH involves the presence of inflammation with hepatocyte damage with or without fibrosis.(3) Therefore NASH could reflect a disease where inflammation is followed by steatosis. The natural history of NAFLD is not completely understood and hence it is not known why certain patient progress towards inflammation and fibrosis.

Fatty liver is the result of accumulation of various lipids, several mechanism may lead to fatty liver, which are as follows: a) increased free fatty acid supply due to increased lipolysis from both visceral/subcutaneous adipose tissue and increased uptake of dietary fat, b) decreased free fatty oxidation, c)increased de novo hepatic lipogenesis(DNL), d)

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decreased hepatic, very low density lipoprotein(5). Inflammation results in a stress response of hepatocyte which may lead to lipid accumulation and therefore may precede steatosis in NASH. Non alcoholic steatohepatitis, NASH causes inflammation and fibrosis and may also involve in cirrhosis, and liver failure in 20-25% of affected subjects. NAFLD is considered one of the leading causes of cryptogenic cirrhosis.(4)

NAFLD is defined as excessive accumulation of fats, which is accompanied by increased enzyme levels in the liver in the absence of significant alcohol consumption. A healthy liver should contain little or no fat, but it is observed in the Western countries that in majority of people, early stages of NAFLD has been diagnosed. Early stage NAFLD doesn't usually cause any harm, but it can lead to serious liver damage, including cirrhosis, if it gets worse. Having high levels of fat in the liver is associated with increased risk of problems such as diabetes, heart attacks and strokes. NAFLD usually develops in four main stages. The main stages are :

- ❖ Simple fatty liver(steatosis)- a largely harmless accumulation of fat in the liver cells.
- ❖ Non alcoholic steatohepatitis(NASH)- a serious form of NAFLD where the liver becomes inflamed.
- ❖ Fibrosis- in this stage, persistent inflammation causes scar tissue around the liver and near by blood vessels.
- ❖ Cirrhosis- this is the most severe stage which occurs after years of inflammation, where the liver shrinks and becomes scarred and lumpy, which leads to permanent liver failure and liver cancer.

The symptoms of NAFLD are not so prominent in the early stages, but in later stages, the symptoms are gradually seen. People with NASH or fibrosis may experience an aching pain in top right of the abdomen, fatigue, weakness and unexplained weight loss. If cirrhosis develops, one may get more severe symptoms such as jaundice, itchy skin and swelling in various parts of the body. (5)

III. VITAMIN D AND ITS SYNTHESIS

Vitamin D is a fat soluble vitamin. Two of its predominant types are Vitamin D2 (exogenously) and Vitamin D3 (endogenously). Vitamin D2 is usually provided to the body in the form of dietary supplements as it is not present in the required quantities in the food that we consume. The primary source of Vitamin D is in the form of Vitamin D3. Pre Vitamin D3 is synthesized in the dermal region of the skin by UV radiations from the sunlight from 7 dehydrocholesterol which is converted to Vitamin D3(cholecalciferol). (6)

Dietary vitamin D2 is absorbed by the small intestine and incorporated into chylomicrons where it is transported to liver and to Vitamin D binding proteins. The synthesis of 1,25(OH)₂D is tightly regulated by synthesis activity of 1α hydroxylase and catabolic activity of 24 hydroxylase which catabolises 1,25(OH)₂D to water soluble and biologically inactive calcitric acid which is then excreted in the bile. Parathyroid hormone, 1,25(OH)₂D and fibroblast growth factor 23 are the main regulator of these enzymes. 1,25(OH)₂D decreases its own synthesis through negative feedback but also by way of inhibition of parathyroid hormone which is the main stimulus of 1α hydroxylases transcription. Fibroblast growth factor 23 acts on the kidney to suppress renal expression of 1-α hydroxylase and to promote 24 hydroxylase activity which result in reduced production of 1,25(OH)₂D.

In liver, Vitamin D from both skin and diet is then metabolized by 25-hydroxylase to 25-hydroxyvitamin D, which is the major circulating metabolite and most widely used indicator of vitamin stores. 25 hydroxyvitamin is transported to the kidney where it undergoes hydroxylation by 1α-hydroxylase to the biologically active form 1,25-dihydroxy (1,25(OH)₂D) Vitamin D. Finally via binding to Vitamin D receptor, 1,25-dihydroxy Vitamin D is able to exert its biological action(7)

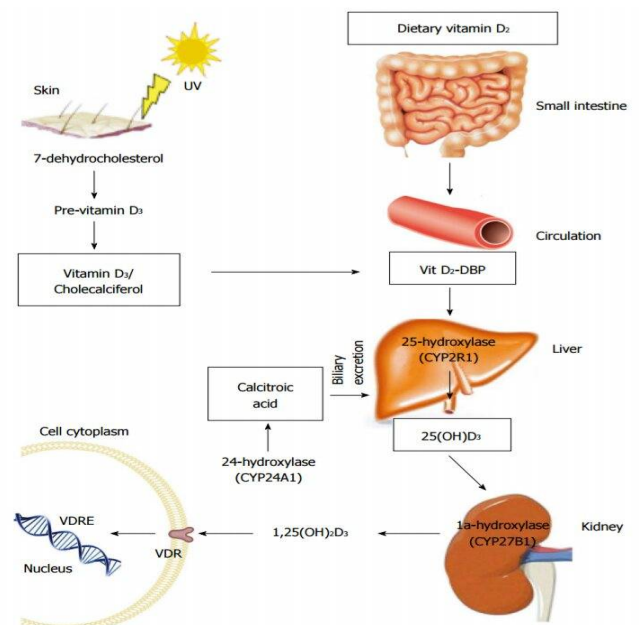


Figure 1 Vitamin D synthesis and metabolism. DBP: D binding protein. VDRE: Vitamin D response element.

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IV. ASSOCIATION BETWEEN VITMIN D AND NAFLD/NASH

The aim of this study is to describe the association between the level of Vitamin D as measured by serum 25-hydroxy Vitamin D with NAFLD and NASH. Vitamin D through the Vitamin D nuclear receptor (VDR) plays a key role in mineral ion homeostasis. The most widely known physiological function of 1,25(OH)₂D is to regulate mineral and skeletal homeostasis. The appropriate level of circulating 25(OH)D required for good health. Vitamin D is argued by many to have potential extra health effects impacting energy balance and possibly reducing inflammation. Vitamin D is a key modulator of immune function and inflammation. Inadequate Vitamin D status is common in many parts of the world and is associated with many diseases like obesity and chorionic related diseases. Current evidence suggests that the circulating level of 25(OH)D maybe crucial for the optimal anti-inflammatory response of human monocytes. The active metabolite of Vitamin D has an anti-inflammatory effect on inflammatory profile of monocyte downregulating the expression and production of several pro-inflammatory cytokines. some immediate Vitamin D action occurs in the cell that possess membrane Vitamin D receptor (VDR).(8) VDR may be involved in metabolic diseases.

The hepatic component of the metabolic syndrome is considered to be the accumulation of fat in hepatocytes. Although the main function of Vitamin D is to regulate bone metabolism, Vitamin D levels have been additionally associated with obesity, inflammation, and immune function. Vitamin D administration decreases free fatty acid, flux regulation form periphery to the liver. Its deficiency may promote fat deposition into hepatocytes. Vitamin D directly regulates the metabolism of FFA by means of its action on peroxisomes proliferator- activated receptor gamma. Improving FFA induced insulin resistance in vitro. Hence under the condition of Vitamin D deficiency, the increased FFA flow in the blood stream may promote fat storage into the liver and facilitate the development of NAFLD. Vitamin D deficiency may promote development of NAFLD through increased inflammation. Chorionic inflammation is considered a key factor in NAFLD progression. It has been studied that increased visceral adiposity promotes release of both free fatty acid and pro inflammatory cytokines. In turn this causes activation of inflammation with in the liver possibly via increased nuclear factor k-beta. Low serum 25(OH)D levels are associated with higher circulating markers of inflammation.(9) As a result, hepatic steatosis resulting from accumulation of free fatty acid is associated with the state of chorionic hepatic inflammation, an important mediator in this process is nuclear factor k-beta which functions as pro-inflammatory.

V. CONCLUSION

Low Vitamin D levels are associated with presence of NAFLD. Studies have suggested that low Vitamin D levels associated with NAFLD are independent of age, sex, race, seasons of measurement, BMI, history of diabetes, renal disease, peripheral vascular disease, liver diseases and hypertension. The metabolic anti-inflammatory and anti-fibrotic properties of vitamin D provide plausible mechanisms by which vitamin D may impact on various steps of disease progression and severity.

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