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Vitamin D as a Modifiable Risk Factor for NAFLD in T2DM patients

Kiran Akhtar[1], Mariam Aftab[2], Farah Naz Tahir[3], Laiba Hamid[4], Mishal Rizwan[5], Zahra Farooq[6], Aliza Ahsan[7], Haris Bin Khalid[8], Kainat Amir[9], Khushnaseeb Aziz[10]

Affiliations:
[1] 4th year MBBS Student, Central Park Medical College, Lahore. kiranakhtar500@gmail.com.
[2] MBBS 4th year student, Central Park Medical College, Lahore. mariamaftabgem0@gmail.com.
[3] MBBS, MPhil, PhD, Associate Professor of Biochemistry, MIMDC. tahirnazfarah@gmail.com
[4] 4th year MBBS Student, Central Park Medical College, Lahore. laibaahamid21@gmail.com.
[5] 4th year MBBS Student, Central Park Medical College, Lahore. mishalrizwan987@gmail.com.
[6] 4th year MBBS Student, Central Park Medical College, Lahore. zahrafarooq787@gmail.com.
[7] MBBS 4th year student, Rahbar Medical and Dental College. Alizaahsan251@gmail.com.
[8] 4th year MBBS Student, Central Park Medical College. harisbinkhalid121@gmail.com.
[9] 4th year MBBS Student, Central Park Medical College, Lahore. Kainatamir79@gmail.com.
[10] 4th year MBBS Student, Central Park Medical College, Lahore. Khushnaseebaziz@icloud.com.

Abstract : To investigate the role of vitamin D as a modifiable risk factor for NAFLD in type 2 diabetes mellitus patients, exploring its potential impact on NAFLD development, progression, and management. Overall 200 patients with TD2M hospitalized to Central Park Teaching Hospital (CPTH) and Lahore General Hospital (LGH) were selected as the subjects for an observational cross sectional study. On the basis of 1999 WHO diagnostic and classification criteria patients were divided into vitamin deficient (20ng/ml) groups. Serum 25(OH)D, Liver function tests(LFTS) and HBA1c of these patients were measured. T-test, Chi square test were used in comparison of the two groups. The correlation between Vitamin D and NAFLD presence/severity was analyzed using correlation and regression analysis, controlling for potential confounders. A significant inverse correlation between vitamin D levels and NAFLD severity and progress in TD2M patients was found. TD2M patients with NAFLD had lower vitamin D levels (15.89 ng/ mL) compared to those without NAFLD (18.27 ng/mL, p23kg/m2, age 7%, without hypertension, TG>1.7mmol/l, HDL>1mmol/l in men and >1.3mmol/l in women). This study suggested that low vitamin D levels are inversely associated with the prevalence of NAFLD and hepatic fibrosis in

T2DM patients particularly in those with BMI>23kg/m2 and that it is significant to maintain optimal serum vitamin D level as well as BMI levels in T2DM patients.

Keywords : Vitamin D , NAFLD , T2DM , BMI and MESH.

Introduction :

Nonalcoholic fatty liver disease is among the leading causes of chronic liver disease around the globe. Despite the alarming rise in NAFLD cases, there remains a lack of population based epidemiological data at national and global level. Several meta-analyses have been conducted to bridge this gap. In these studies, the prevalence of NAFLD is estimated to be 32.4% [1]. NAFLD is a metabolic disorder that manifests as excess fatty accumulations in the hepatocytes leading to inflammation and subsequent cirrhosis. The morphology of NAFLD ranges from simple hepatic steatosis resulting from insulin resistance and nonalcoholic steatohepatitis, to which results from oxidative stress and chronic inflammation [2], this type is more at risk of giving rise to CLD and Hepatocellular carcinoma. As insulin resistance is the hallmark of diabetes mellitus and obesity, the prevalence of NAFLD reaches 54%-59.67% in patients suffering from type 2 diabetes mellitus [3] and 69.99% in overweight population [4].

The International diabetes foundation has claimed that the prevalence of diabetes mellitus in Pakistan is 33% and is on the rise [5]. Approximately half of these patients suffer from diabetes complicated with NAFLD of some stage, as mentioned earlier. The pathophysiology of NAFLD subsequent to Diabetes Mellitus revolves around insulin resistance that leads to impairment of glucose and lipid metabolic pathways in the hepatocytes [6] and can be attributed to one, increased dietary intake of fats, increased de novo lipogenesis and decreased hepatic triglyceride excretion, and two, oxidative stress, mitochondrial disruption and inflammation[7].

Insulin is a major governor of metabolism in hepatocytes, adipocytes and all the cells of body. It maintains homeostasis between gluconeogenesis and glucose utilization, lipolysis and fatty acid synthesis, proteolysis and protein synthesis. As resistance against its effect prevails, there is a increase in insulin secretion that generates a state of hyperinsulinemia. The free fatty acids derived in part from high calorie intake and obesity as well as adipocyte's resistance to insulin are transported to liver and bind to the sterol regulatory element binding protein, SREBP, a key factor

among others in lipogenesis, in hepatocytes to promote lipogenesis[8]. A state of increased serum FFAs, decreased lipolysis and increased lipogenesis is created, leading to increased hepatic FFAs. These free fatty acids exceed the hepatocytes ability to lipolyze via oxidation and generate oxidative stress on the hepatocytes and cause mitochondrial dysfunction. This lipo-toxicity triggers inflammation via formation of reactive oxygen species (ROS) and production of pro-inflammatory regulators[9]. The pro-inflammatory mediators are not only involved in progression of steatosis to steatohepatitis, but also further elevate IR. [8]

Vitamin D is a fat soluble vitamin that acts via vitamin D receptors, there are two forms of Vitamin D, cholecalciferol or D3 and ergocalciferol or D2 [10]. Vitamin D was previously known for its role in calcium and phosphate homeostasis, bone and skeletal development, but now it is implicated in many disorders owing to its anti-inflammatory via suppression of ROS, proapoptotic, antiangiogenic, and immunomodulatory role via its action on Toll like receptors, TLDRs [10]. Low levels of serum 25(OH)D levels are related to adverse health outcomes mainly diabetes mellitus, cardiovascular disorders, chronic liver disease, and cancer[3]. Moreover, vitamin d transporting globulin, also known as Gc globulin has anti-inflammatory features [10]. Pakistan has one of the highest prevalence of Vitamin D deficiency in Southeast Asia at 73% [11]

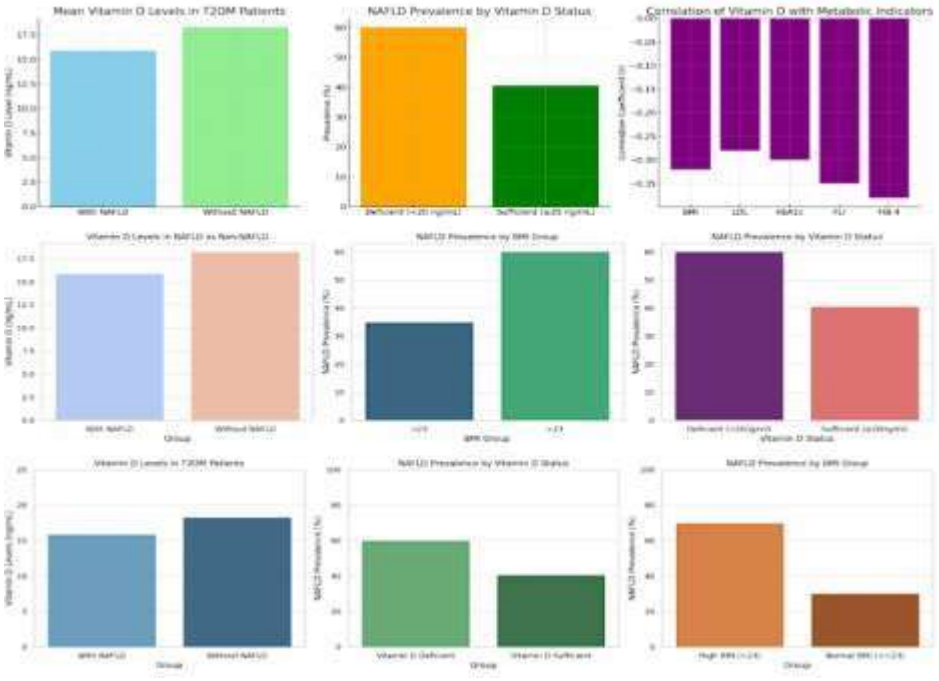
It has been proven in multiple studies that Vitamin D levels are negatively correlated to insulin resistance [12] and NAFLD progression, and vitamin D deficiency exacerbates the histologic features in NAFLD. Low vitamin D levels are found with high FLI/FIB-4 levels, indicators of extent of liver disease, further hinting at a negative correlation between Vitamin D and NAFLD [13]. Vitamin D has antifibrotic role via suppression of profibrotic mediators as well as inhibition of HSCs [10]. Studies on rats with NAFLD have shown that vitamin D supplementation ameliorates the disease [14].However, clinical data on vitamin D's independent association with NAFLD in T2DM patients is limited. This study aims to evaluate the relationship between Vitamin D status and NAFLD in Pakistani T2DM patients, focusing on its therapeutic potential.

Methodology :

A cross sectional and observational study was conducted for assessment of vitamin D as a modifiable risk factor for NAFLD in patients with type 2 diabetes mellitus (T2DM). It was an

independent assessment conducted by our team and evaluated against inclusion and exclusion criteria. About 200 patients with type 2 diabetes mellitus who were hospitalized in central park teaching hospital Lahore (CPTH) and Lahore general hospital (LGH) in collaboration with MIMDC were selected and the diagnosis was based on 1999 WHO diagnostic and classification criteria. Inclusion criteria was age above 18 years ,Type 2 diabetes mellitus confirmed according to 1999 WHO diagnostic criteria and ultrasound findings confirming the NAFLD. Exclusion criteria included alcohol consumers , Vitamin D supplementation in last 3 months, pregnant and lactating women, any autoimmune disorders, viral hepatitis ,any other liver disease and thyroid disorder. Further stratification was done on serum 2,5 hydroxy vitamin D levels as Vitamin D deficient (<20ng/ ml) and Vitamin D sufficient (≥20ng / ml). Samples that were taken included serum 25 (OH) D levels , liver function tests (AST, ALT ,gamma GGT and alp levels) and HbA1c. Statistical analysis were done by comparison of continuous variables between the groups using T – test. Categorical variables (e.g., prevalence of NAFLD) were compared using chi-square tests. Correlation and regression analyses for the assessment of the association between vitamin D levels and NAFLD presence, severity and adjustment for potential confounding variables (BMI, age, sex, lipid profile,HbA1c). Analysis of the subgroups by BMI, age, and gender to explore modification effect. Ethical considerations Informed consent was taken from every patient, confidentiality was maintained, approval from respective hospital was obtained and conducted in supervision of our supervisor.

Results



The bar graph illustrates a clear inverse relationship between serum Vitamin D levels and the presence of non-alcoholic fatty liver disease (NAFLD) in patients with type 2 diabetes mellitus (T2DM). Patients diagnosed with NAFLD exhibited significantly lower mean Vitamin D levels compared to their non-NAFLD counterparts. This trend supports the growing body of evidence suggesting that hypovitaminosis D may play a contributory role in the pathogenesis or progression of NAFLD among individuals with T2DM. The marked difference observed underscores the potential utility of monitoring and correcting Vitamin D deficiency as part of a comprehensive approach to managing liver health in diabetic populations.

Discussion: Vitamin D serves a variety of purposes in our bodies. Studies have proven that vitamin D has a key role in the regulation of oxidation, the production of pro-inflammatory cytokines, hepatocyte apoptosis, and even liver fibrosis[15,16,17]. Our research examines the several elements that demonstrate how vitamin D levels in the body may be a risk factor for non-alcoholic fatty liver disease (NAFLD) in individuals with type 2 diabetes. Although there is no direct "cause" of vitamin D deficiency by NAFLD (non-alcoholic fatty liver disease), there is a high correlation between the two, and multiple processes point to a reciprocal link. According to studies, patients with NAFLD frequently have lower vitamin D levels than people without the illness, particularly

those who are obese and have type 2 diabetes. Compared to healthy controls and either the diabetic or NAFLD-only groups, type 2 diabetic individuals with NAFLD have lower total vitamin D levels.

Total vitamin D level is negatively correlated with body mass index, waist circumference, total cholesterol, LDL, triglycerides, Fasting plasma glucose, glycosylated hemoglobin and degree of fatty liver index[22] . Several studies have highlighted the significant association between NAFLD and T2DM, describing a complex bidirectional link. By regulating the immune system, suppressing the expression of pro-fibrotic inflammatory mediators like platelet-derived growth factor (PDGF) and transforming growth factor β (TGF-β), and increasing the expression of collagen, α-smooth muscle actin, and tissue inhibitor of metalloproteinase-1, 25(OH)D activation has anti-inflammatory and anti-fibrotic effects in the liver. However, vitamin D loses its beneficial antifibrotic action once cirrhosis develops.

According to certain studies, 25(OH)D levels may decrease as NAFLD severity rises. It was discovered that there was a negative correlation between 25(OH)D and FIB4 and FLI. These findings indicate that a lack of 25(OH)D may accelerate the development of hepatic fibrosis in T2DM patients with NAFLD. Alfadda et al. investigated the prevalence of NAFLD in patients with T2DM using transient elastography and found that 80.8% of T2DM patients had steatosis, of which 82.3% had severe steatosis and 17.6% had mild to moderate steatosis.[18,19,20] A study shows NAFLD prevalence in T2DM patients with 25 (OH) D deficiency was higher than in those without 25 (OH) D deficiency, and the difference was statistically significant (60.1% vs 40.6%, $P<0.001$).[21] While many studies suggest an association between vitamin D deficiency and non-alcoholic fatty liver disease (NAFLD) in type 2 diabetes mellitus (T2DM) patients, some evidence indicates that this relationship may not be causal or clinically significant. For instance, a meta-analysis by Barchetta et al. (2017) in Nutrients reviewed multiple studies and concluded that although vitamin D levels are often lower in NAFLD patients, vitamin D supplementation does not consistently improve liver histology or metabolic parameters.

[23] Another study found that 12 weeks of vitamin D supplementation in T2DM patients with NAFLD did not significantly improve liver enzymes, insulin resistance, or lipid profile. These

findings suggest that vitamin D deficiency may be a coincidental comorbidity rather than a contributing factor to NAFLD in diabetic patients, and supplementation alone may not yield therapeutic benefits. Therefore, current evidence remains inconclusive, and more robust, long-term interventional studies are needed to determine the true nature of this relationship. [24]

Conclusion :

It is concluded that Vitamin D is negatively related to BMI, waist circumference, LDL, HbA1c, FLI and FIB-4. Low VIT d is a major risk factor of NAFDL and hepatic fibrosis in T2DM patients. Thus vit D is used as an independent predictor of hepatic fibrosis. Individuals with BMI>23kg/m2 are at more risk to NAFDL. So Vit d supplements are suggested to diabetic patients to improve its level. Thus, the clinicians should pay attention to vit d deficiency inT2DM with NAFLD, and be alert to the risk of progressive hepatic fibrosis in such patients.

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