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DOES EMPIRICAL VITAMIN D REPLACEMENT IMPROVE LFTS IN PATIENT WITH NAFLED AND TYPE-II DM

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Abstract

Objective: *To observe the effects of vitamin D replacement in improving LFTs in patients with NAFLD and Type-II DM*
Study Design: *A single blind, prospective randomized trials*
Study Duration: *06 months*
Study Place: *Divisional Head Quarter Hospital Mirpur Azad Kashmir*
Methods: *Total 136 individuals were included in study, among them 86 were males and 50 were females. 02 groups were made with equal distribution of participants. Group A was given oral vitamin D tablet 20,000IU every week for 24 weeks and Group B was given placebo. LFTS, serum IGF and HBA1C was done before and after the oral vitamin D to look for the trend in improvement.*
Results: *Both group A and B were observed for 06 months, and pre vitamin D LFTs and HBA1c and IGF levels were done. The group A showed improving trend in ALT and AST following vitamin D therapy and serum IGF showed modest improvement. HBA1C also showed improvement in trend.*
Conclusion: *From our study, we can conclude that oral vitamin D therapy has beneficial effects in improving the liver function tests and glycaemic tolerance in patients with NAFLD and type II diabetes mellitus.*

INTRODUCTION

NAFLD stands for Non Alcholic Fatty Liver Disease, is a clinicopathological syndrome characterized by hepatic steatosis, excluding alcohol and other definite liver damage factors. The development of NAFLD is associated with lipid accumulation, oxidative stress, endoplasmic reticulum stress, and lipotoxicity.[1] Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease and is predicted to become the most common reason for liver transplantation by 2030.[2] NAFLD is multisystem disorder and has linkage with type 2 diabetes mellitus, cardiovascular diseases and chronic renal disease. The primary pathology in NAFLD affects liver hepatocytes by inducing microsteatosis and leading ultimately to cirrhosis and hepatic failure.[3] Global prevalence of NAFLD is 30%[4] and is ever increasing, and in Pakistan, its prevalence is 29% and its prevalence doubles in diabetic patients where it is around 58.7%.[5]

There is strong relationship between type 2 diabtes mellitus and NAFLD and both conditions act

synergistically as risk factor to increase cardio vascular disease probability. Further more it has been seen that anti diabetic drugs improve histological and biochemical features of NAFLD, further proving there co existing realtion.[6]

Vitamin D, a fat soluble vitamin and its active form 1a-25-dihydroxyvtamin D [1,25$(OH)_2$D] plays a key role in mineral metabolism, immune modulation, cell differentiation, bone maturation and in inflammation cascade.[7] Numerous publications have shown a strong association between Vitamin D deficiency and NAFLD and increase risk of metabolic syndrome.[8] It is proposed that supplimenatation with Vitamin D leads to improvement in insulin resistance and improvement of NAFLD.[9]

In our study we will also observe the effect of vitamin D supplementation on improving liver functional parameters in NAFLD and Type II diabetes mellitus patients.

Methodology:

After taking informed written consent from hospital ethical review committee, a single blind, prospective randomized trials was done in which136 individuals were included. Sample size was calculated using WHO EPI sample size calculator. Among them 86 were males and 50 were females. Patients were explained about the objective of the study and an informed written consent was taken. Anthropometric measurments of all the patients were taken, as well as body mass index (BMI) and hip to waste ratio as per WHO standards. 5CC venous blood was drawn from large ante cubital vein, was centrifuged and ran for blood chemistry. Liver function tests which included alanine immunotransferase (ALT), alkaline phosphatase (ALP), aspartate aminotransferase (AST) and serum albumin were measured, additionally fasting serum Insulin like growth factors (IGF) level and glycosylated hemoglobin (HBA1C) were also measured before and an at the end of study. All patients in our study were above age 40 years, and those patients were included who have NAFLD and type II DM. NAFLD was defined radiologically as increase liver echogenicity from surrounding structures like kidney and spleen, evidence of hepatomegaly and blurring of intrahepatic vessels.[10] Hence inclusion criteria and exclusion criteria are as follow:

Inclusion criteria:

1. Age >40 years
2. No hx of alcohol abuse
3. No hx of previous liver disease
4. No hx of use of drugs or toxin intake history
5. Patients not taking any multivitamin supplements

Exclusion criteria:

1. Age less than 40 years
2. Hepatitis B or C positive
3. Hx of chronic liver disease
4. Hx of extensive abdominal wall surgeries
5. Exposure to phosphorus, barium salts or antimony

Patients were randomly allocated in two groups, one group was given capsule Vitamin D 20,000IU orally once weekly for 24 weeks and other group was given placebo for the same duration. Both groups A and B contain equal participants i.e. 68. Pre Vitamin D LFTs and fasting IGF, HBA1c were measured and latter repeated at 24th week after completion of study.

Results:

Two groups were made, each contained 68 individuals. In group A, among 68 participants 46 were males and 22 were females, similarly in group B, 50 were male and 18 were females. Patients in group A and B were also divided further based on having NAFLD alone, DM alone and NAFLD and DM both. In group A, 18 participants had NAFLD alone, 13 had DM alone and rest 37 had both NAFLD and DM. Similarly, in Group B, 14 patients had NAFLD, 19 had DM alone and rest 35 participants had both NAFLD and DM. (table 1.1 and figure 1.1)

Patients in Group A were given oral Vitamin D tablet 20,000IU once weekly for 24 weeks and Group B was given placebo in a similar fashion for the said period. LFTs which included ALT, AST ALP and S. Albumin were measured before and at the end of study as well fasting IGF and HBA1c.

In group A, at the start of study, in patients having NAFLD alone, the ALT was 85±10, in those with DM ALT was 63±7 and in patients with NAFLD and DM, the ALT was 110±9. Similarly, AST showed 60±6, 43±5 and 89±8 respectively. Albumin also followed similar trend with 29±3, 30±3 and 26±4 respectively. IGF levels were also measured and they were 100±10, 80±5 and 85±3 were observed respectively. HBA1C levels were also measured and they were as, 5.8±.5, 8.2±1.3 and 7.9±.7 (figure 1.1)

In group B, at the start of study, all chemical markers were measured as of group A. In patients having NAFLD alone, the ALT was 82±7, in those with DM, ALT was 64±4, and in NAFLD plus DM, ALT was 107±7. Similarly, AST showed 57±4, 47±5 and 95±8 respectively. Albumin also followed similar trend with 27±3, 29±3 and 25±4 respectively. IGF levels were also measured and they were 96±10, 75±4 and 88±3 were observed respectively. HBA1C levels were also measured and they were as, 5.5±.5, 8.8±1.3 and 7.3±.7 (figure 1.2)

After taking oral tablet of Vitamin D and placebo for 24 weeks, LFTs, serum IGF and HBA1C were measured. Patients in group A who were given Vitamin D tablet showed significant improvement in LFTs trend and modest improvement in IGF and HBA1C.

In Group A, among the 18 patients with NAFLD, who had ALT as 85±10, after vitamin D, ALT improved to 73±5, in those with DM, ALT improved to 61±5 and in NAFLD and DM, ALT improved to 86±4. Similarly, AST also showed improvement in trend which was 52±3, 41±2 and 77±4. Albumin levels improved following vitamin D ingestion which showed 32±1, 30±2 and 32±2. IGF levels showed modest improvement which were as 97±5, 85±3 and 94±6. HBA1C trends were 5.5±1, 8.0±1 and 7.5±1 (figure 1.3)

In group B, in patients with NAFLD, ALT showed 80±2, in those with DM, ALT was 63±1, and in NAFLD and DM, ALT was 105±3. Similarly, AST showed 56±1, 47±2, and 93±2 respectively. Albumin showed no significant improvement with pre and post placebo same levels. IGF and HBA1C also did not show any betterment pre and post placebo. (figure 1.4)

Group A n=68	**Group B** n=68
Gender: Male 46 Female 22	Gender: Male 50 Female 18

Table 1.1 (Demographic data)

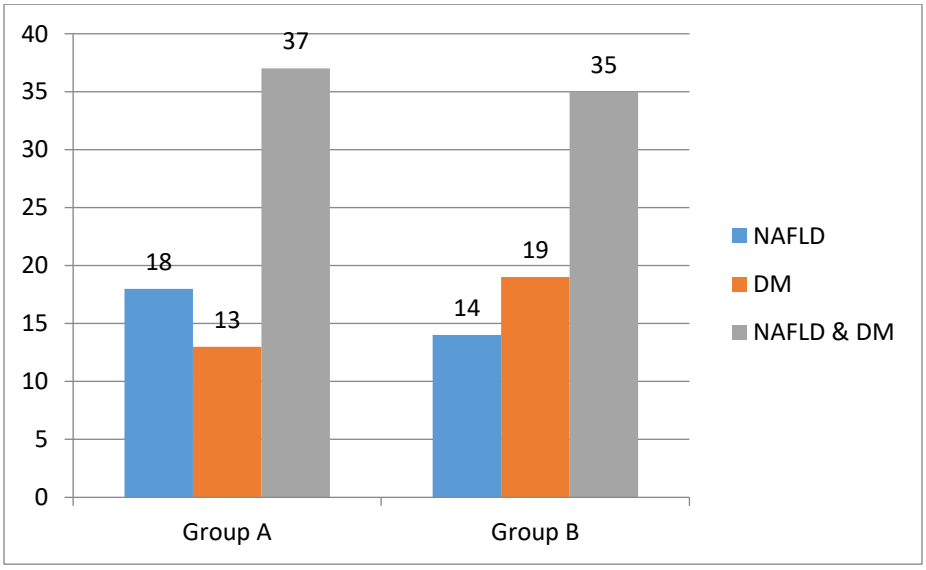

Figure 1.1 (Division of groups)

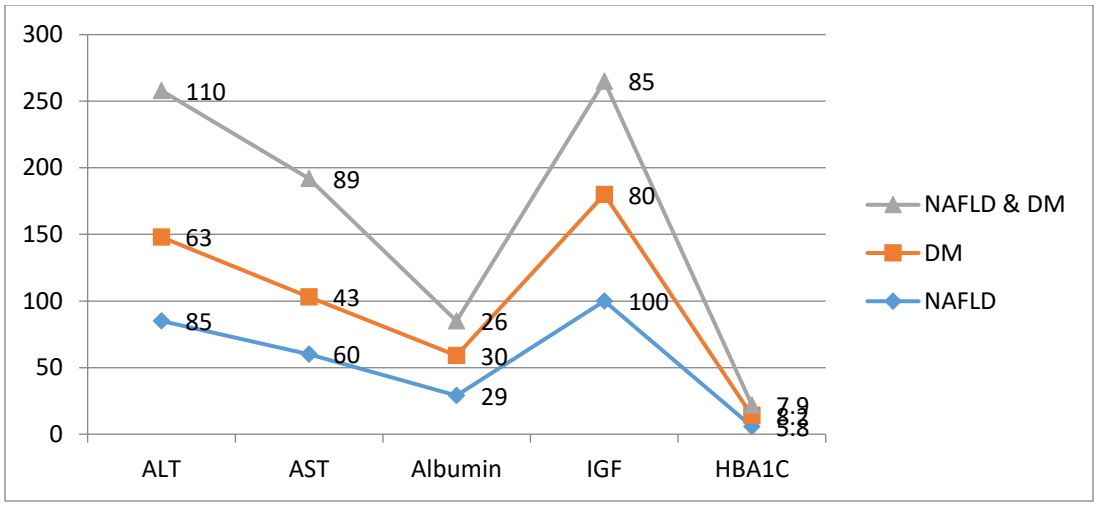

Figure 1.2 (Biochemical Parameters of Group A)

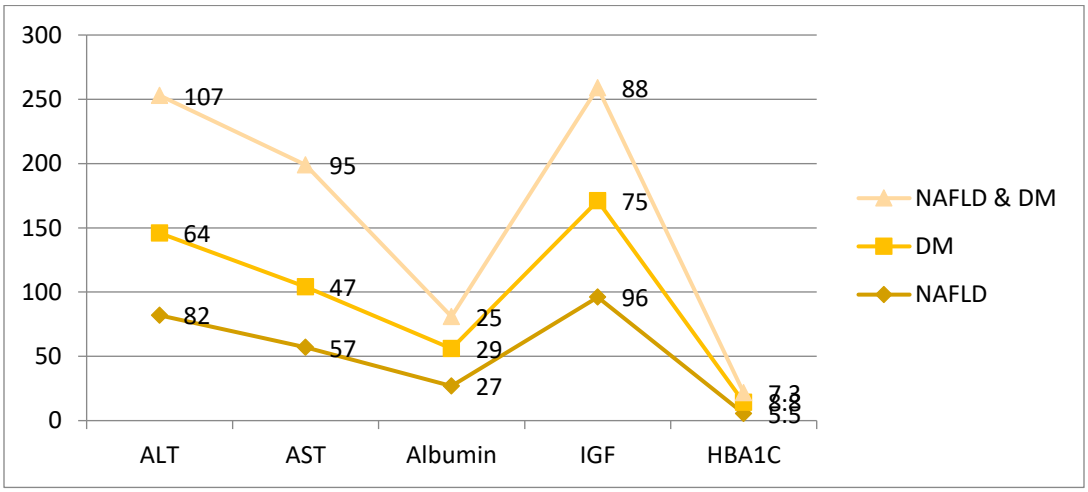

Figure 1.3 (Biochemical Parameters of Group B)

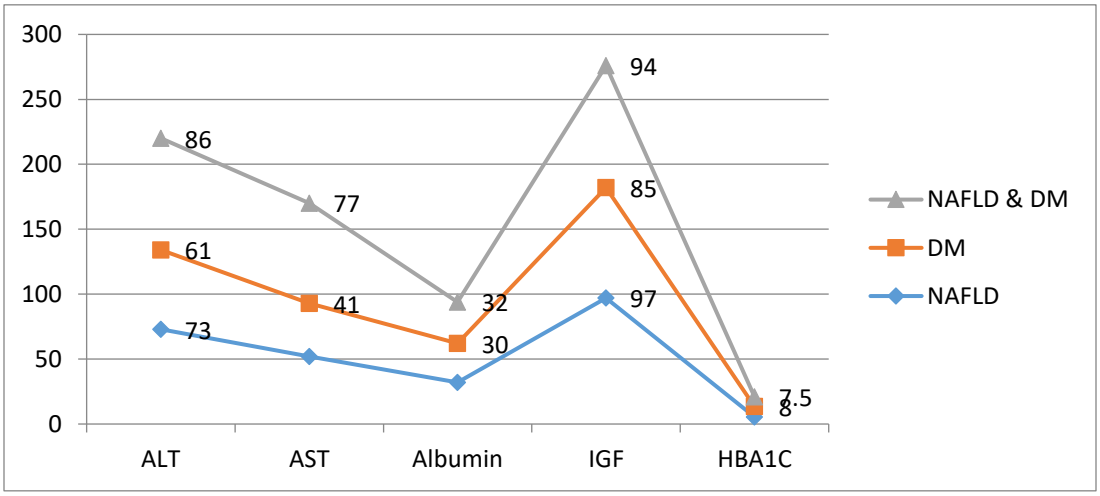

Figure 1.3 (Biochemical parameters post Vitamin D intake)

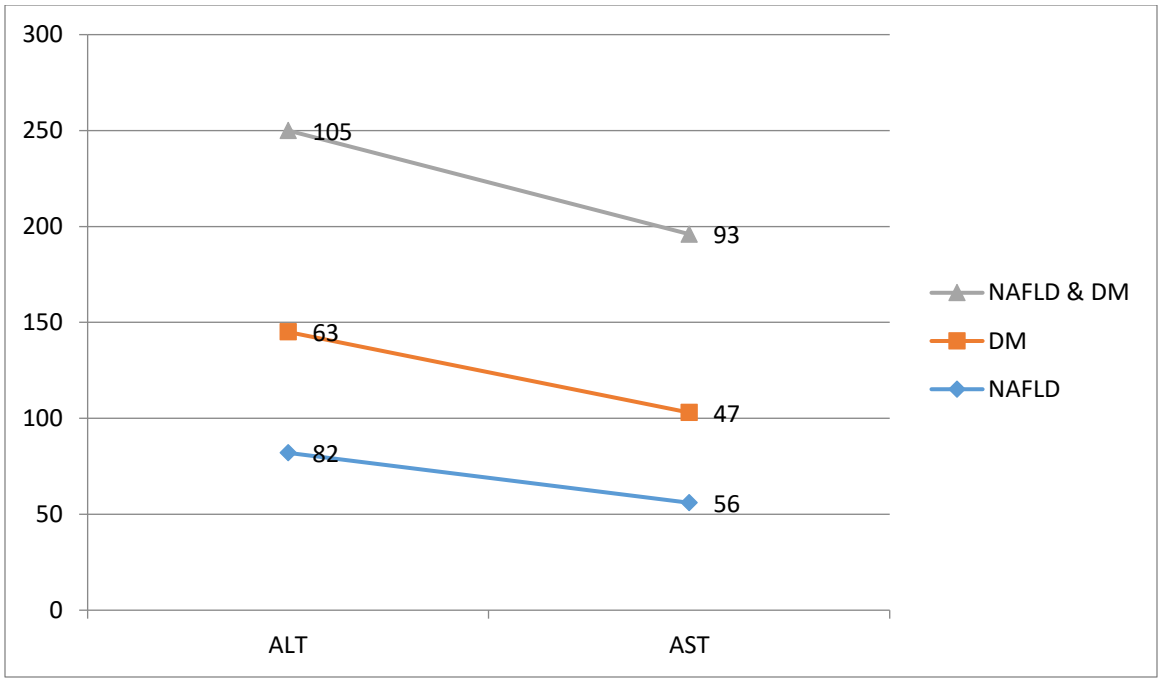

Figure 1.4 (Biochemical parameters in group B, post placebo)

Discussion:

Non-alcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver diseases from simple steatosis to end-stage liver disease with decompensated cirrhosis, liver failure and hepatocellular carcinoma. It has also been recently became clear that NAFLD also increases risk of extrahepatic diseases such as type 2 diabetes mellitus (T2DM), cardiovascular disease, and chronic kidney disease.[11] NAFLD is a rapidly growing disease around the world with the highest prevalence in the Middle Eastern countries. [12] NAFLD is now the most common cause of liver enzyme abnormalities worldwide and is usually considered as the hepatic manifestation of metabolic syndrome.[13]

Multiple studies around the world suggested that low levels of Vitamin D are strongly associated with features of the metabolic syndrome particularly NAFLD and may play an important role in modifying the risk for cardio-metabolic outcomes including Type 2 diabetes, hypertension and cardiovascular disease[14,15]

In a systematic review conducted by J Mitri in 2023, they found that having vitamin D levels above 25ng/ml was associated with 43% less chance of developing cardiovascular disease as compared to levels less than 19ng/ml.[16]

In another Women's Health Study, an intake of > 511 international units (IU)/day of vitamin D was associated with a 27% lower risk of developing type 2 diabetes compared with an intake of < 159 IU/day.[17] In 2014, Park et al. performed a cross-sectional study to investigate the relationship between vitamin D levels and NAFLD and reported a substantial link between vitamin D insufficiency and NAFLD as well.[18]

In a study conducted in 2019 by Mallikarjun et ell showed that after treatment with vitamin D post 6 months, the ALT showed significant improvement in trend as compared to before the study and in contrast with control group.[19]

Nakano *et al.* investigated on animal model the impact of sunlight therapy on the progression of NAFLD. Phototherapy ameliorated IR and hepatic steatosis caused by a choline-deficient and iron-supplemented L-amino acid defined (CDAA) diet. In particular, phototherapy improved histology with regard to hepatocyte apoptosis, inflammation and fibrosis, and increased serum adiponectin levels, and led to a reduced hepatic

expression of the profibrotic transforming growth factor.[20]

A study conducted by Sharifi et ell revealed that by giving 50,000iu vitamin D every 14 days for 4 months and then observing Serum aminotransferases, high-sensitive C-reactive protein (hs-CRP), tumor necrosis factor α, and malondialdehyde (MDA). It was found that MDA and hs-CRP had significant decreasing trend, suggesting that vitamin D may prove to be beneficial future drug in reducing inflammation and hepatic injury and reversing histological feature of NAFLD.[21]

In our study, we also found results comparable to above studies, in our study 68 individuals were given oral vitamin D tablet as an empirical therapy to observe its effect on liver function test in patients with NAFLD and Diabetes type II. Our results showed that liver function tests improved significantly in patients who took vitamin D as compared to placebo. ALT and AST exhibited most improvement in trend following vitamin D intake. Albumin did not show any significant betterment and serum IGF also improved to modest extent. HBA1C also show improvement in group taking vitamin D. The most significant improvement was seen in patients in those who have both NAFLD and diabetes, highlighting the fact that vitamin D treatment offers hepatoprotective effect as well as improve glycemic control and insulin tolerance. It further shed its light that empirical treatment with vitamin D has good effects on synthetic functions of liver.

Limitation of Studies:

It is a single center study with small sample size, hence its results cannot be generalized on whole population. Multiple studies in various centers should be done to form better guidelines of empirical treatment with vitamin D, however this study highlighted the fact that vitamin D can be used as treatment option for NAFLD and diabetes.

Conclusion:

Oral vitamin D has significant effect on improving synthetic function of liver in NAFLD and also improving glycemic profile in diabetes. The most significant improvement was seen in ALT and AST, highlighting the importance of oral vitamin D treatment.

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