Serum Vitamin D Level in Lean and Obese Patients
with Metabolic Associated Fatty Liver Disease: a comparative study

**Abstract
Background and aim:** Metabolic dysfunction associated fatty liver disease (MAFLD) affects around one third of the world population. Within the MAFLD population, 19.2% are lean. Low serum vitamin D concentrations were reported to increase the risk of MAFLD. This study aimed to explore the association between serum vitamin D concentration and MAFLD. **Methods:** This cross-sectional study was conducted on 50 Egyptian patients with lean MAFLD (BMI>25 kg/m2) (Gl) and another group (G ll) including 50 consecutive overweight/obese patients with MAFLD (BMI <25 kg/m2). MAFLD patients were evaluated by thorough history taking, full clinical examination, laboratory investigations including serum level of 25 hydroxycholecalciferol by ELISA, abdominal ultrasonography and FibroScan**®** with controlled attenuation parameter (CAP). **Results:** Males were significantly predominant in the lean group (G I) (60%) while females were significantly predominant in G II (62%). Mean serum vit D level was not significantly higher in G I compared to GII (16.38 and 15.44 ng/ml, respectively). Vitamin D deficiency (level> 20 ng/ml) was predominant in G II (70% vs 58.0% in GI) while insufficiency (level: 20-30 ng/ml) was more common in GI (34% vs 26%). Sufficient vitamin D (level <30 ng/ml) was only found in 8% of GI compared to 4% of GII. Serum vitamin D level showed a highly significant negative correlation with steatosis grades in both groups (r=0.87& 0.88 in GI &GII respectively, P-value <0.001 in both groups)**.Conclusion:** MAFLD patients, weather lean or obese, show low serum vitamin D levels, which negatively correlate with steatosis grades.

**Keywords**: Metabolic Associated Fatty Liver Disease (MAFLD); Lean MAFLD; Obese MAFLD; Vit; Controlled Attenuation Parameter (CAP) and FibroScan.

**1. Introduction**

Metabolic associated fatty liver disease (MAFLD) has emerged as the most common cause of liver diseases globally **(1)** and it is predicted to become the leading cause of liver transplantation by 2030 **(2).**

The diagnosis of MAFLD is based on the detection of liver steatosis (liver histology, non-invasive biomarkers or imaging together with the presence of at least one of three criteria that includes overweight or obesity, type 2 diabetes mellitus (T2DM) or clinical evidence of metabolic dysfunction which was defined by the presence of at least two of the following metabolic risk abnormalities: 1) waist circumference ≥ 90/80 cm in Asian men and women; 2) blood pressure ≥ 130/85 mmHg or specific drug treatment; 3) plasma triglycerides ≥ 1.70 mmol/L or specific drug treatment; 4) plasma HDL-cholesterol < 1.0 mmol/L for men and < 1.3 mmol/L for women or specific drug treatment; 5) prediabetes (i.e., fasting glucose levels 5.6 to 6.9 mmol/L, or 2-h post-load glucose levels 7.8 to 11.0 mmol or HbA1c 5.7% to 6.4%; 6) plasma high-sensitivity C-reactive protein (hs-CRP) level > 2 mg/L; and 7) homeostasis model assessment (HOMA)-insulin resistance score ≥ 2.5 **(3).** MAFLD is no longer a diagnosis of exclusion and is based on the presence of metabolic dysfunction, it is now possible to diagnose its coexistence with other liver diseases unlike Nonalcoholic fatty liver disease (NAFLD) which was defined as the presence of > 5% of hepatic steatosis (HS), in the absence of competing liver disease etiologies, such as chronic viral hepatitis, use of medications that induce steatosis such as amiodarone or tamoxifen, and other chronic liver diseases(CLD), such as autoimmune hepatitis, hemochromatosis, Wilson‘s disease (WD), or significant alcohol consumption **(4).**

Recently the 3 acronyms, metabolic dysfunction-associated steatotic liver disease (MASLD), MetSLD, or metabolic steatotic liver disease (MSLD) can be used as the replacement term for NAFLD and metabolic dysfunction-associated steatohepatitis (MASH) as the replacement term for NASH
**(5).**

Although overweight/obesity is closely associated with the development and progression of MAFLD, subtle weight gain that has not led to overweight is an important determinant of incident metabolic disease and MAFLD. Within the MAFLD population, 19.2% of people are lean and 40.8% are non-obese, without difference in the histological severity of disease between lean and obese patients **[6,7].**Up to one-third of patients with MAFLD and a normal BMI meet the criteria for metabolic syndrome .Therefore, the identification, diagnosis, and treatment of non-obese MAFLD is very important **[7].**
The risk factors for non-obese MAFLD remain unclear. Some previous cross-sectional studies showed that vitamin D deficiency was associated with an increased risk of NAFLD, and vitamin D levels were negatively associated with the severity of NAFLD**( 8,9).**

Vitamin D has been associated with many disease pathogenesis including autoimmune disease, cardiovascular disease, cancers, inflammatory processes, and liver diseases **(10,11).**

The pathogenesis of the association between MAFLD and low vitamin D levels is undetermined; however, protective anti-fibrotic and anti-inflammatory function of vitamin D on the hepatic stellate cells has been suggested **(12).** Vitamin D reduces free fatty acid-induced insulin resistance in peripheral tissues and in hepatocytes ***(13)***. Therefore, low vitamin D level may lead to intrahepatic lipid accumulation which is responsible for NAFLD pathogenesis **(14).**

The aim of the present study was to explore the association between serum vitamin D concentration and MAFLD comparing lean and obese patients.

**2. Patients and methods**

This cross-sectional study was carried out on 100 patients with MAFLD attending the outpatient's clinic of the Hepatology, Gastroenterology, and Infectious Diseases Department of Benha University Hospitals ,Egypt, within the period **from** **February 2022 to February 2023.** They were subdivided into 2 groups; lean group (G I) comprised 50 consecutive lean - (BMI>25 **k**g/m2) and obese group (G II) comprised 50 consecutive obese - (BMI <30kg/m2) MAFLD patients. An informed written consent was obtained from each participant before the study. The whole protocol was approved by the Ethical Committee of Benha Faculty of Medicine, Benha university **{M.S24.4.2022}.**

**Inclusion Criteria:**

* **Adult patients of both genders with MAFLD.**

**Exclusion criteria:**

* **Age less than 18 years.**
* **Pregnant females.**
* **Advanced comorbid illnesses and malignancies.**
* **Decompensated liver cirrhosis.**
* **History of intake of steatogenic drugs (amiodaroness, tamoxifen, corticosteroids, estrogens,….ect).**
* **History of intake of vitamin D supplementation (within at least 6 months before the study)**
* **Diseases affecting vitamin D metabolism such as (malabsorption, chronic kidney disease, pancreatic and hepatobiliary disease, …ect).
All the studied patients were subjected to the following:**

**1-Thorough history taking.**

**2-Complete general examination with stress on:** **●Blood pressure:** Average resting blood pressure (BP) was obtained from 3 measurements made with a standard mercury sphygmomanometer at 3-minute intervals.

* **BMI.**
* **Waist circumference.**
* **Abdominal examination with stress on: hepatomegaly and splenomegaly.**

 **4-Anthropometric measurements**

Each subject underwent a physical examination. Measurements of weight (to the nearest 0.1 kg) and height (to the nearest 0.1 cm) were used to calculate the BMI [=(kg/m2)]. Waist circumference (W) was measured on the midaxillary line between the lower border of the rib cage and the upper margin of the iliac crest (15).

###  **5-Biochemical assessments**

After overnight fasting, serum was collected. Biochemical markers, including Total cholesterol (TC), Triglyceride (TG), High density lipoprotein (HDL), Low density lipoprotein (LDL), Fasting blood glucose (FBG), HbA1c, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST)and Serum level of active form of Vitamin D was done using ELISA technique (NOVA, Beijing, China)

**MAFLD Diagnosis**

The diagnosis of MAFLD was based on the detection of liver steatosis by imaging (abdominal ultrasound and FibroScan with CAP (FibroScan expert, Echonsens ,Paris, France) together with the presence of at least one of three criteria that includes overweight or obesity, type 2 diabetes mellitus (T2DM) or clinical evidence of metabolic dysfunction.

Metabolic dysregulation was defined by the presence of at least two of the following metabolic risk abnormalities: 1) waist circumference ≥ 90/80 cm in Asian men and women; 2) blood pressure ≥ 130/85 mmHg or specific drug treatment; 3) plasma triglycerides ≥ 1.70 mmol/L or specific drug treatment; 4) plasma HDL-cholesterol < 1.0 mmol/L for men and < 1.3 mmol/L for women or specific drug treatment; 5) prediabetes (i.e., fasting glucose levels 5.6 to 6.9 mmol/L, or 2-h post-load glucose levels 7.8 to 11.0 mmol or HbA1c 5.7% to 6.4%;.

 **6- Serum vitamin level assessment by ELISA**

**(**NOVA, Beijing, China) where \*Sufficient (<30 ng/ml) \*Insufficient(20-30ng/ml) \*Deficient (>20ng/ml).

**7- Abdominal ultrasonography** (LOGIQ, Korea)

 **8-FibroScan with CAP**

 (FibroScan expert, Echonsens, Paris,france).
F0 (0\_5.4 kPa) F1 (5.5\_6.9 kPa) F2 (7\_ 8.9 kPa) F3 (9\_ 11.4 kPa) F4 (11.5\_ 75 kPa)

S0 (0\_222 dB/m) S1 (223\_ 259 dB/m) S2 (260\_310 dB/m) S3 (311 \_400 dB/m)

**Statistical analysis:**

 These data were tabulated, coded then analyzed using the computer program SPSS (Statistical package for social science) version 26. Descriptive statistics were calculated for the data in the form of mean, standard deviation (±SD) and number and percent. In the statistical comparison between the different groups, the significance of difference was tested using student's t-test to compare between mean of two groups of numerical (parametric) data. For continuous non- parametric data, Mann-Whitney U- test was used for inter-group analysis, data. Inter-group comparison of categorical data was performed by using chi square test (X2-value), Pearson correlation coefficient (r) test was used correlating different parameters. P value <0.05 was considered statistically significant.

 **3.Results**

**Table (1) Comparison between the studied groups regarding demographic data and routine laboratory findings**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  **Lean Group (GI) N0=50** | **Obese group (GII) N0=50** | **Test of sig.** |  **p-value** |
| **Age (Ys) (mean ± SD)** | 41.16  |  10.79 |  45.60 |  11.99 |  t=1.9 |  0.06 |
| **Gender****(No. & %)** | **Male** |  30  |  60.0% |  19 |  38.0% |  X2=4.8 |  0.03\* |
| **Female** |  20 |  40.0% |  31 |  62.0% |
| **Smoking (No. & %)** |  17  |  34.0% |  12 |  24.0% | X2=1.2 |  0.3 |
| **Hypertension (No. & %)** |  13 |  26.0% |  19 |  38.0% | X2=1.6 |  0.2 |
| **Haemoglobin** **(g/dl)** |  12  |  ± 1.1 |  12  |  ±11.2 |  1.8 |  0.07 |
| **WBCs x** **(10ᵌ)/ mmᵌ** |  5.8  |  ±1.2 |  6.1  |  ±1.08 |  1.5 |  0.1 |
| **Platelet count** x**(10ᵌ)/ mmᵌ** |  274  |  ± 36 |  264  |  ±35.9 |  1.3 |  0.2 |
| **ALT** **(U/L** |  28  |  ± 13 |  29  |  ±14.5 |  0.4 |  0.7 |
| **AST** **(U/L)** |  28  |  ±13.7 |  31  |  ±13.2 |  1.1 |  0.3 |
| **HbA1C** **(%)** |  5.7  |  ± 0.68 |  5.8  |  ± 1.2 |  1.2 |  0.2 |
| **FBG (mg/dl)** |  96  |  ±17.6 |  104  |  ± 27 |  1.6 |  0.1 |
| **2HPP** (**mg/dl)** |  170  |  ± 182 |  145  |  ± 40 |  0.9 |  0.4 |
| **S. creatinine** (**mg/dl)** |  0.98  |  ± 0.15 |  0.98  |  ± 0.14 |  0.2 |  0.8 |
| **Cholesterol** **(mg/dl)** |  229  |  ± 51.3 |  226  |  ± 47.8 |  0.3 |  0.8 |
| **TG** **(mg/dl)** |  201  |  ± 57.1 |  197  |  ± 79.9 |  0.3 |  0.8 |
| **LDL (mg/dl)** |  127  |  ± 28.8 |  131  |  ± 29.3 |  0.7 |  0.5 |
| **HDL** **(mg/dl)** |  33 |  ± 7.4 |  34  |  ±16.5 |  0.4 |  0.7 |
|  **Vit D level (ng/ml)** |  16.38  |  ±8.42 |  15.44 |  ±7.21 |  1.8 |  0.07 |

**Table (2): Comparison between mean 25 hydroxy vitamin D level in different fibrosis stages and steatosis grades in the studied groups.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  **Group I** **N0=50** |  **Group II** **N0=50** |  **T** | **p-value** |
|  **Mean ± SD** |  **Mean ± SD** |  |  |
|  **Fibrosis stages**  |  **0** |  17.04 ± 7.28 |  15.53 ± 6.85 |  0.9 |  0.4 |
|  **1** |  16.89 ± 11.89 |  14.87 ± 7.64 |  0.5 |  0.6 |
|  **2** |  9.23 ± 3.30 |  15.72 ± 8.37  |  1.5 |  0.1 |
|  **p-value** |  0.2 |  0.9 |  |  |
| **Steatosisgrades** |  **1** |  24.92 ± 6.05 |  25.02 ± 5.45 |  0.1 |  0.9 |
|  **2** |  17.51 ± 4.86 |  18.12 ± 2.73 |  0.4 |  0.7 |
|  **3** |  9.26 ± 2.78 |  10.05 ± 3.47 |  0.9 |  0.4 |
|  **p-value** |  <0.001\* |  <0.001\* |  |  |

**NB: None of the studied patients had F3 or F4.**

 **Figure (1): Comparison between the studied groups regarding serum levels of 25 hydroxy vitamin**

**Figure (2): Correlation between Steatosis and 25 hydroxy Vit. D level in GI and GII**

Males were predominant in G I (60%) while females were predominant in G II (62%)with statistically significant difference **(Table 1).** There was no statistically significant difference between the studied groups regarding routine laboratory findings **(Table 1).**The mean serum vitamin D level in GI was (16.38 ng/ml) while it was (15.44 ng/ml) in GII with no statistically significant difference (P-value =.6) **(Table 1).** Vitamin D deficiency was more common in G II (70% vs 58.0% in GI) while insufficiency was more common in GI (34% vs 26% in GII). Sufficient vitamin D level was only found in 8% of GI compared to 4% of GII **(Figure 1).** There was no statiscally significant difference between mean vitamin D level in different fibrosis stages in the studied groups and there was a statically signifcant difference in both groups regarding the mean vitamin D level in different steatosis stages**(Table 2).** Serum vitamin D level showed highly significant negative correlations with steatosis grades in both groups (P-value <0.001) **(figure 2).**

**4.Discussion** In this study no statistically significant differences were detected between both groups regarding age with mean age of the lean group 41.16± 10.79 compared to 45.6± 11.99 of the obese group (P-value = 0.06) ,this was in agreement with who conducted their study on  2538 patients where there was no significant differences between lean and obese NAFLD groups regarding age **(15).**

 In the study males were predominant in GI (60.0%) with a statistically significant difference between the two groups while females were predominant in G II (62.0%) (P-value =.03) it may be due to increase the risk of obesity in females in Egypt, this came in agreement with whoreported that the prevelance of MAFLD was significantly higher in men (49.42%) than in women (27.97%) (16).

In the current study, there was no statistically significant difference between lean and obese MAFLD patient groups regarding 25 hydroxy vitamin D level (P-value=0.6). Serum vitamin D was low in both groups (16.38 ± 8.42 in GI vs 15.44 ±7.21 in GII).

This comes in agreement with who demonstrated that serum 25(OH)D3 levels were inversely associated with NAFLD, even in subjects with normal body weight.(17).

In thisinvestigated the role of 25(OH)D in NAFLD patients and matched the NAFLD group with a presumably healthy population that did not undergo liver ultrasonography (US). They found a strong inverse relationship between NAFLD and 25(OH)D levels (18).

Also, reported strong association between hypovitaminosis D and NAFLD which was independent on age, sex, BMI, lipid profile or glucose level (19).

The found a minor but significant difference in 25(OH)D levels between patients with and without NAFLD (20).

That was showed vitamin D deficiency was significantly related to NAFLD in men but not in women (21).

That stated adolescents with suspected NAFLD had significantly lower 25(OH)D levels than adolescents without suspected NAFLD (22).

Our results were in contrary withwho found no significant differences between patients with NAFLD and those without NAFLD in serum vitamin D levels (23,24).

In another study by there is a significant correlation between serum vitamin D concentration and NAFLD in obese but not lean participant (15).

That stated the mechanisms by which 25(OH) vitamin D may induce NAFLD is not clear. The liver converts vitamin D to its active form , 25 (OH) vitamin D so in liver diseases the 25 (OH) vitamin D level is low (25).

This wasfound vitamin D deficiency may induce NAFLD by impairing hepatic lipid metabolism (26).

That was demonstrated Patients with vitamin D deficiency found to have high rates of insulin resistance, metabolic syndrome and inflammatory mediators including IL-4, IL-6 and TNF-α (27).

*Also,* reported that vitamin D receptors widely exist in liver tissue with negative association between vitamin D receptors expression and necro-inflammatory grades of NASH (28).

 However, stated that Vitamin D may be sequestrated in the adipose tissue in obese patients (29).

These contradictory results among studies may be related to differences in the studied population, nutritional, genetic and environmental factors.

 In the current study Vitamin D deficiency was more common in the obese group (70% vs 58.0% in GI) and vitamin D insufficiencies were more common in the Lean group (8% compared to 4% of GII).

This disagrees with who reported that Vitamin D deficiency and insufficiency were more common in the obese group than the lean group and In the obese group, they found that participants with vitamin D deficiency had the highest prevalence of NAFLD (57.60%), followed by those with vitamin D insufficiency (55.73%), and then those with vitamin D sufficiency (43.23%) (*P* < 0.001). In the lean group, the prevalence of NAFLD was comparable among participants with vitamin D deficiency and those with vitamin D sufficiency (11.14% versus 10.89%) (30).

This difference may be due to small sample size used in our study.
Our study revealed that vitamin D deficiency was more common in females than males in both groups with a statistically significant difference in the lean group (P Value=0.0001).This matched with who reported that women with NAFLD, compared to men with NAFLD, had significantly lower levels of 25(OH) D (9.4 ± 6.8 μg/l vs13.6 ± 7 μg/l, p < 0.0001***) (31).***

Also***, reported*** that vitamin D deficiency was greater in females (46.9%) than in males (41.7%) (32).

But this disagrees with  [who reported that Participants with higher 25(OH)D levels were more commonly females (33).](https://onlinelibrary.wiley.com/authored-by/ContribAuthorRaw/Ciardullo/Stefano)

Our study revealed that vitamin D deficiency was more common with higher grades of fibrosis in G I. This came in agreement with who reported that vitamin D status was inversely correlated to Liver fibrosis by fibroscan. In the biopsy-proven NAFLD patients,(34).

Also, demonstrated an inversely association of advanced LF with vitamin D level (35).

 However,revealed that advanced fibrosis identified by non-invasive scores are not connected to the low 25(OH)D in serum (36).

The inconsistent conclusions may result from the different measurements of LF and various vitamin D concentrations.

 In this study, we found that the higher the grade of steatosis the lower the Vitamin D level.

 This matched with who reported that the prevalence of vitamin D sufficiency was significantly lower in the group with higher grade of steatosis (37).

But, this disagrees withwho reported that serum vitamin D is not connected to the CAP-defined NAFLD (34).

Also,found thatno significant association of the reduced vitamin D with the hepatic steatosis was found in general Portuguese population (38).

These different results may be due to different methods used to measure hepatic steatosis and various vitamin D concentrations (38).

Quantified hepatic steatosis according to Hamaguchi's ultrasonographic score (steatosis defined by a score ≥ 2) and in (35)study Participants were categorized as having either vitamin D deficiency (<50 nmol/L) or vitamin D sufficiency (≥50 nmol/L), unlike our study.

 This study still has some limitations. First, the small sample size which might limit generalization of results. Second, We did not perform liver biopsy (the gold standard) or either magnetic resonance proton density fat fraction ( MRI-PDFF) or magnetic resonance spectroscopy (MRS) because of invasiveness with subsequent complications and financial limitations respectively .Third, our study is a cross-sectional study, and further prospective studies are needed to analyze the causal relationship between vitamin D deficiency and progression of MAFLD, as well as prognostic effect of vit D supplementations on MAFLD patients.

**5. Conclusions**

 MAFLD patients, weather lean or obese, show low serum vitamin D levels, which negatively correlate with steatosis grades.

**References**

1. ***Younossi, Z. M., Koenig, A. B., Abdelatif, D., Fazel, Y., Henry, L., and Wymer, M.*** Global epidemiology of nonalcoholic fatty liver diseaseMeta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016; 64 (1): 73-84.
2. ***Cholankeril, G., Wong, R. J., Hu, M., Perumpail, R. B., Yoo, E. R., Puri, P., et al.*** Liver transplantation for nonalcoholic steatohepatitis in the US: temporal trends and outcomes. Dig Dis Sci 2017; 62 (10): 2915-2922
3. **Eslam, M., Newsome, P. N., Sarin, S. K., Anstee, Q. M., Targher, G., Romero-Gomez, M., et al.**  A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol.2020 ;73(1):202–209.
4. ***Younossi, Z. M., Koenig, A. B., Abdelatif, D., Fazel, Y., Henry, L., & Wymer, M.*** Global epidemiology of nonalcoholic fatty liver diseaseMeta-analytic assessment of prevalence, incidence, and outcomes. Hepatology 2016; 64(1): 73-84.
5. **Eslam, M., Newsome, P. N., Sarin, S. K., Anstee, Q. M., Targher, G., Romero-Gomez, M.,** **et al.**  [A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement.](https://pubmed.ncbi.nlm.nih.gov/32278004/)J Hepatol 2023;73(1):202-209.
6. **Eslam, Mohammed, Jian-Gao Fan, and Nahum Mendez-Sanchez.** "Non-alcoholic fatty liver disease in non-obese individuals: the impact of metabolic health." The lancet Gastroenterology & hepatology 5, no. 8 (2020): 713-715.
7. ***Ye, Q., Zou, B., Yeo, Y. H., Li, J., Huang, D. Q., Wu, Y., et al.***  Global prevalence, incidence, and outcomes of non-obese or lean non-alcoholic fatty liver disease: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol. 2020;5(8):739-752.
8. **Liu, S., Liu, Y., Wan, B. O., Zhang, H., Wu, S., Zhu, Z., .et al.** Association between vitamin D status and non-alcoholic fatty liver disease: a population-based study. J Nutr Sci Vitaminol 2019;65(4):303–308.
9. **Zhai, H. L., Wang, N. J., Han, B., Li, Q., Chen, Y., Zhu, C. F., et al.** Low vitamin D levels and non-alcoholic fatty liver disease, evidence for their independent association in men in East China: a cross-sectional study (Survey on Prevalence in East China for Metabolic Diseases and Risk Factors (SPECT-China)): British Journal of Nutrition 2016, 115(8): 1352-1359.
10. **Entezari, Vahid, and Mark Lazarus.** Vitamin D and inflammation. Jt Bone Spine 2010. 77 (6):552–557
11. **Kitson, Matthew T., and Stuart K. Roberts.** "D-livering the message: the importance of vitamin D status in chronic liver disease." *Journal of hepatology* 57, no. 4 (2012): 897-909.
12. ***Abramovitch, S., Dahan-Bachar, L., Sharvit, E., Weisman, Y., Tov, A. B., Brazowski, E., et al.***  Vitamin D inhibits proliferation and profibrotic marker expression in hepatic stellate cells and decreases thioacetamide-induced liver fibrosis in rats 2011. Gut 60 (12):1728–1737.
13. ***Zhou, Q. G., Hou, F. F., Guo, Z. J., Liang, M., Wang, G. B., and Zhang, X.*** 1,25-Dihydroxyvitamin D improved the free fatty-acid-induced insulin resistance in cultured C2C12 cells. Diabetes Metab Res Rev 2008. 24 (6):459–464.
14. **Konstantakis C , Tselekouni P , Kalafateli M and Triantos C.** Vitamin D deficiency in patients with liver cirrhosis. Ann Gastroenterol 2016;29(3):297-306.
15. ***Ashwell M and Gibson S.*** Waist-to-height ratio as an indicator of ‘early health risk’: simpler and more predictive than using a ‘matrix’ based on BMI and waist circumference. BMJ Open 2016 ;6 (3):e010159.
16. **Wang, Q., Shi, X., Wang, J., Zhang, J., and Xu, C.** Low serum vitamin D concentrations are associated with obese but not lean NAFLD: a cross-sectional study. [Nutrition Journal](https://nutritionj.biomedcentral.com/) 2021; 20:30-38.
17. **Hao, Y. P., Ma, X. J., Luo, Y. Q., Ni, J., Dou, J. X., Hu, Y. Q., et *al.***  Serum vitamin D is associated with non-alcoholic fatty liver disease in Chinese males with normal weight and liver enzymes. *Acta Pharmacol* Sin 2014, 35(9): 1150–1156
18. ***Fogelstrand, P. and Boren, J. (2012):*** Retention of atherogenic lipoproteins in the artery wall and its role in atherogenesis. Nutrition, Metabolism and Cardiovascular Diseases2012, 22(1): 1-7.
19. ***Barchetta, I., Carotti, S., Labbadia, G., Gentilucci, U. V., Muda, A. O., Angelico, F., et al.***  Liver vitamin D receptor, CYP2R1, and CYP27A1 expression: relationship with liver histology and vitamin D3 levels in patients with nonalcoholic steatohepatitis or hepatitis C virus. Hepatology 2012, 56(6): 2180-2187.
20. **Rhee, E. J., Kim, M. K., Park, S. E., Park, C. Y., Baek, K. H., Lee, W. Y., et al.** High serum vitamin D levels reduce the risk for nonalcoholic fatty liver disease in healthy men independent of metabolic syndrome. Endocrine Journal 2013, 60(6):743-52.
21. **Park, D., Kwon, H., Oh, S. W., Joh, H. K., Hwang, S. S., Park, J. H.et al.** Is vitamin D an independent risk factor of nonalcoholic fatty liver disease?: a cross-sectional study of the healthy population. Journal of Korean Medical Science 2017, 32(1): 95-101.
22. **Cho, Y. H., Kim, J. W., Shim, J. O., Yang, H. R., Chang, J. Y., Moon, J. S., et al.**  Association between vitamin D deficiency and suspected nonalcoholic fatty liver disease in an adolescent population. Pediatric Gastroenterology, Hepatology & Nutrition 2019, 22(3): 233-241.
23. **Patel, Y. A., Henao, R., Moylan, C. A., Guy, C. D., Piercy, D. L., Diehl, A. M., et al.** Vitamin D is not associated with severity in NAFLD: results of a paired clinical and gene expression profile analysis. The American Journal of Gastroenterology 2016, 111(11): 1591-1612.
24. **De Paula, F. V. L., Ramalho, L. N. Z., De Paula, F. J. A., and Martinelli, A. D. L. C.** Low vitamin D level is not associated with severity of non-alcoholic fatty liver disease in morbidly obese patients. Journal of Hepatology 2017, 66(1): 157-161.
25. **Nair, S.** Vitamin d deficiency and liver disease. Gastroenterology & Hepatology 2010; 6(8):491-503.
26. **Eliades, M. and Spyrou, E.** Vitamin D: a new player in non-alcoholic fatty liver disease?. World Journal of Gastroenterology 2015: 21(6):1718-1729.
27. **Alvarez, J. A. and Ashraf, A.**  Role of vitamin D in insulin secretion and insulin sensitivity for glucose homeostasis. International journal of endocrinology 2010, 2: 351-385.
28. **Barchetta, I., Carotti, S., Labbadia, G., Gentilucci, U. V., Muda, A. O., Angelico, F., et al.** Liver vitamin D receptor, CYP2R1, and CYP27A1 expression: relationship with liver histology and vitamin D3 levels in patients with nonalcoholic steatohepatitis or hepatitis C virus. Hepatology 2012, 56(6): 2180-2187.
29. **Earthman, C. P., L. M. Beckman, K. Masodkar, and S. D. Sibley.** "The link between obesity and low circulating 25-hydroxyvitamin D concentrations: considerations and implications." *International journal of obesity* 36, no. 3 (2012): 387-396.
30. **Huang, Y. P., Zhang, S., Zhang, M., Wang, Y., Wang, W. H., Li, J., et al.** Gender-specific prevalence of metabolic-associated fatty liver disease among government employees in Tianjin, China: a cross-sectional study. BMJ Open 2021;11(12):e056260.
31. **Bennouar, S., Cherif, A. B., Kessira, A., Bennouar, D. E., and Abdi, S.**  Association and interaction between vitamin D level and metabolic syndrome for non-alcoholic fatty liver disease. J Diabetes Metab Disord 2021 ;20(2):1309-1317
32. **Kumar, M., Parchani, A., Kant, R., Das, A., and KUMAR, M.** Relationship Between Vitamin D Deficiency and Non-alcoholic Fatty Liver Disease: A Cross-Sectional Study From a Tertiary Care Center in Northern India. Cureus2023, 15(2):e34921.
33. **Ciardullo, S., Muraca, E., Cannistraci, R., Perra, S., Lattuada, G., & Perseghin, G.** Low 25 (OH) vitamin D levels are associated with increased prevalence of nonalcoholic fatty liver disease and significant liver fibrosis. Diabetes Metab Res Rev 2023;39(5):3628-3639.
34. **Ji, Y., Wei, C. B., Gu, W., and Hou, L. L.** Relevance of vitamin D on NAFLD and liver fibrosis detected by vibration controlled transient elastography in US adults: a cross-sectional analysis of NHANES 2017-2018. Ann Med 2023.;55(1):2209335.
35. **Arai, T., Atsukawa, M., Tsubota, A., Koeda, M., Yoshida, Y., Okubo, T., et al.** Association of vitamin D levels and vitamin D-related gene polymorphisms with liver fibrosis in patients with biopsy-proven nonalcoholic fatty liver disease. Dig Liver Dis 2019;51(7):1036–1042
36. **Wan, B., Gao, Y., Zheng, Y., and Chen, R.** Association between serum 25-hydroxy vitamin D level and metabolic associated fatty liver disease (MAFLD)-a population-based study. Endocr J 2021;68(6):631–637.
37. **Heo, N. J., Park, H. E., Yoon, J. W., Kwak, M. S., Yang, J. I., Chung, S. J., et al. t**he Association between Vitamin D and Nonalcoholic Fatty Liver Disease Assessed by Controlled Attenuation Parameter. Journal of Clinical Medicine 2021;10(12):2611.
38. **Leitão, J., Carvalhana, S., Silva, A. P., Velasco, F., Medeiros, I., Alves, A. C., et al.** No evidence for lower levels of serum vitamin D in the presence of hepatic steatosis. A study on the portuguese general population. Int J Med Sci 2018;15(14):1778–1786.