

# Vitamin D in NAFLD, Diabetes, and Depression: A Mechanistic Link

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## ABSTRACT

**Background:** Non-Alcoholic Fatty Liver Disease (NAFLD), Type 2 Diabetes Mellitus (T2DM), and depression are interlinked chronic conditions that share common pathophysiological mechanisms such as insulin resistance, chronic inflammation, and oxidative stress. Emerging evidence suggests that Vitamin D deficiency may represent a common underlying factor that contributes to the development and progression of these conditions. **Objectives:** This review aims to examine the multifaceted role of Vitamin D in the pathogenesis and clinical progression of NAFLD and T2DM, particularly in the presence of comorbid depression. **Materials and Methods:** A comprehensive literature review was conducted using peer-reviewed studies, meta-analyses, and clinical trials published in databases such as PubMed, Scopus, and Google Scholar. Evidence was critically analyzed to identify common biological pathways and therapeutic implications. **Results:** Vitamin D influences insulin sensitivity,  $\beta$ -cell function, lipid metabolism, immune modulation, and neuroendocrine regulation. Its deficiency has been associated with worse glycemic control, hepatic steatosis, and depressive symptoms. While interventional studies report modest improvements in insulin resistance and inflammatory markers, findings remain inconclusive regarding long-term hepatic or psychiatric outcomes. Depression, through HPA axis dysfunction and lifestyle factors, further exacerbates metabolic dysregulation and Vitamin D deficiency. **Conclusion:** Vitamin D deficiency is a shared modifiable risk factor in NAFLD, T2DM, and depression. A multifactorial approach that combines Vitamin D supplementation with mental health interventions and lifestyle modifications holds promise in improving outcomes. Personalized treatment strategies and further research are warranted to clarify the long-term benefits of Vitamin D in this triad of chronic diseases.

**Keywords:** Depression, Insulin Resistance, Multifactorial Management, NAFLD, Type 2 Diabetes Mellitus, Vitamin D Deficiency.

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## INTRODUCTION

Nonalcoholic Fatty Liver Disease (NAFLD) include basic steatosis to more serious conditions such as Nonalcoholic Steatohepatitis (NASH), progressive fibrosis, cirrhosis, and hepatocellular cancer.<sup>1</sup> Hepatic fat accumulation exceeds 5% of hepatocytes by histological examination or 5.6% by proton magnetic resonance spectroscopy or quantitative fat/water-selective MRI in the absence of significant alcohol intake and other steatosis causes.<sup>1,2</sup>

NAFLD has become the most common chronic liver disease worldwide, with prevalence rates around 31% by imaging and

12.2% by histology, of which roughly 5% progress to NASH.<sup>2</sup> Although fibrosis in NAFLD progression gradually, advanced stages substantially elevate morbidity and mortality, highlighting the importance of exploring mechanistic factors such as Vitamin D deficiency that may influence disease progression.<sup>3</sup> Cardiovascular disease is the main cause of death in NAFLD, but NASH significantly raise the risk of liver-related mortality, including hepatic decompensation and hepatocellular carcinoma.<sup>2</sup>

NAFLD and T2DM frequently coexist, affecting nearly 59.67%-70% of diabetic patients. This overlap increases cardiovascular risk by 1.87 times and contributes to structural and functional cardiac abnormalities, including diastolic dysfunction and vascular changes.<sup>4</sup> NAFLD exacerbates diabetic microvascular complications - such as chronic kidney disease and retinopathy-by releasing inflammatory and oxidative mediators that heighten systematic insulin resistance and promote dyslipidemia. Hepatokines such as fetuin-A, FGF21, and RBP4 contribute to



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this metabolic imbalance. Notably, fetuin-A impairs insulin signaling by inhibiting insulin receptor tyrosine kinase activity.<sup>4,5</sup>

T2DM and even prediabetes is strongly associated with advanced NAFLD phenotypes. Additionally; presence of metabolic risk factors further increases progress of NAFLD.<sup>4,6</sup> A study proposed a predictive model using BMI, waist circumference metabolic and liver biomarkers, achieving 90% specificity for identifying NASH in T2DM patients with NAFLD.<sup>7</sup>

Vitamin D's active form (1,25-Dihydroxy Vitamin D<sub>3</sub>) is responsible for calcium, bone homeostasis, metabolism and immunity. It promotes monocyte differentiation, reduces lymphocyte proliferation, and suppresses major pro-inflammatory cytokines.<sup>8</sup> These immunomodulatory actions are relevant to chronic low-grade inflammation, a key mechanism-linking T2DM and obesity-related disorders. Vitamin D also exhibits antiproliferative effects in cancer cell lines, suggesting a regulatory role in growth and differentiation pathways affected in metabolic diseases.<sup>8,9</sup>

Aside from skeletal health, Vitamin D deficiency is also implicated in the pathophysiology of depression, cardiovascular disease, and some cancers.<sup>10</sup> Vitamin D, a secosteroid hormone, exerts pleiotropic effects through the Vitamin D Receptor (VDR), which is widely expressed in the liver, pancreas, adipose tissue, and immune cells. Through VDR activation, Vitamin D regulates over 200 genes that control cellular proliferation, immune responses, metabolism, and hepatic lipid homeostasis processes central to NAFLD pathogenesis.<sup>11,12</sup>

## OBJECTIVES

This review aims to:

- To examine the multifaceted role of Vitamin D in the pathophysiology and interplay of Nonalcoholic Fatty Liver Disease (NAFLD), Type 2 Diabetes Mellitus (T2DM), and depression.
- To explore the molecular mechanisms by which Vitamin D influences glucose metabolism, insulin secretion, and insulin sensitivity, focusing on its role in calcium homeostasis and pancreatic  $\beta$ -cell function.<sup>13</sup>
- To study the impact of genetic variations in the Vitamin D Receptor (VDR) on insulin signaling, adipocyte differentiation, and inflammatory regulation, and their contribution to T2DM and metabolic dysfunction.<sup>14,15</sup>
- To understand the link between Vitamin D deficiency and the progression of NAFLD in individuals with T2DM.<sup>16,17</sup>
- To explore the interconnected roles of Vitamin D in endocrine, immune, and neuropsychiatric regulation.

## PATHOPHYSIOLOGY OF NAFLD IN TYPE 2 DIABETES MELLITUS

### Insulin Resistance and Hepatic Steatosis

The central pathogenic mechanism linking Nonalcoholic Fatty Liver Disease (NAFLD) and Type 2 Diabetes Mellitus (T2DM) is Insulin Resistance (IR), which affects key metabolic organs such as the liver, adipose tissue, and skeletal muscle. This systemic IR promotes a pro-inflammatory and pro-atherogenic environment, leading to the release of pro-inflammatory and lipotoxic mediators. In adipose tissue, IR stimulates lipolysis, boosting the Flow of Free Fatty Acids (FFAs) to the liver and muscles. The resulting "lipotoxicity" exacerbates hepatic fat accumulation and promotes hepatocyte apoptosis.<sup>4</sup>

Hepatic triglyceride accumulation arises from three main sources: circulating FFAs (59%), de novo lipogenesis (26%), and dietary fat (14%). Elevated FFAs in the liver may be oxidized, secreted as Very Low-Density Lipoprotein (VLDL), or re-esterified and stored.<sup>4,18</sup> In the insulin-resistant state, hepatic DNL is upregulated, glycogen synthesis is reduced, and gluconeogenesis is increased. Glycolysis-derived intermediates like pyruvate and acetyl-CoA are redirected into lipogenic pathways, worsening hepatic steatosis. Additionally, the activation of Protein Kinase C (PKC) disrupts Insulin Receptor Substrate (IRS) signaling, while ceramide accumulation inhibits Akt, further impairing insulin action.<sup>4</sup>

Progression of simple steatosis to Nonalcoholic Steatohepatitis (NASH) is driven by oxidative stress, mitochondrial dysfunction, and inflammatory cytokines, all contributing to necroinflammation and hepatic fibrosis.<sup>19</sup> A "second hit" in the form of hepatocyte regenerative failure accelerates fibrogenesis. The interaction of metabolic stress, inflammation, and cellular injury is pivotal to the worsening liver pathology in T2DM patients with NAFLD.<sup>4</sup>

### Impact of Vitamin D on NAFLD Pathogenesis

#### *Anti-Inflammatory and Antioxidant Properties*

Vitamin D exhibits strong immunomodulatory effects through regulation of gene transcription involved in inflammation. The active form decreases systemic and hepatic inflammation by inhibiting pro-inflammatory cytokines such IL-1, IL-6, and TNF- $\alpha$  and increasing anti-inflammatory pathways. These actions are critical in preventing the progression of hepatic steatosis to NASH (Figure 1). Moreover, Vitamin D mitigates oxidative stress, thus offering cellular protection to hepatocytes.<sup>16</sup>

#### *Regulation of Glucose and Lipid Metabolism*

Vitamin D plays a very important role in glucose homeostasis by enhancing insulin sensitivity and promoting pancreatic  $\beta$ -cell function. These effects are mediated by the Vitamin D Receptor

(VDR), which regulates genes related to metabolic regulation. Furthermore, Vitamin D Impacts lipid metabolism by regulating the expression of genes involved in lipid intake and storage. These actions are particularly relevant in NAFLD, a condition often characterized by IR and dyslipidemia. Through its metabolic effects, Vitamin D may help attenuate hepatic lipogenesis and fat accumulation, thereby potentially slowing NAFLD progression (Figure 2).<sup>16,20</sup>

## Role of Depression in NAFLD and T2DM Progression

### *Mechanistic Links between Depression and NAFLD*

Depression is becoming recognized as a risk factor for the advancement of both T2DM and NAFLD. One important process is dysregulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis. A meta-analysis of over 18,000 individuals revealed that patients with depression exhibit significantly elevated cortisol and Adrenocorticotrophic Hormone (ACTH) levels, with the most pronounced effects observed in melancholic, psychotic, and endogenous subtypes, as well as in older, hospitalized populations.<sup>21</sup>

This chronic HPA axis activation impairs glucocorticoid feedback control and leads to prolonged hypercortisolemia, which promotes hepatic lipogenesis, impairs lipid oxidation, and contributes to central adiposity and insulin resistance.<sup>22</sup> These metabolic alterations are key contributors to hepatic steatosis. Additionally, depression is linked to higher levels of pro-inflammatory cytokines such IL-6, TNF- $\alpha$ , and CRP which exacerbate hepatic inflammation and fibrogenesis, thereby accelerating NAFLD progression.<sup>23,24</sup>

## Depression's Effect on Glycemic Control and Insulin Resistance

### *Influence on Lifestyle and Vitamin D Status*

Depressive symptoms affect to physical activity, diet and sunlight exposure, which leads to Vitamin D deficiency.<sup>25</sup> Parker *et al.* (2016) tried to establish the relation between the depression and Vitamin D levels (Figure 3).<sup>26</sup>

## Impact on Glycemic Regulation and Treatment Adherence

Depression is consistently associated with suboptimal self-care behaviors in T2DM patients.<sup>27</sup> These behaviors result in glycemic instability, increased HbA1C levels, and worsened insulin resistance. Pariente *et al.* noted that symptoms such as fatigue, anhedonia, and low motivation commonly seen in major depressive disorder interfere with routine diabetes management.<sup>24</sup> L Egede *et al.* highlighted a 2.3-fold increased risk of medication non-adherence among patients with comorbid depression, along with lower engagement in self-monitoring and dietary compliance.<sup>28</sup>

## Neuroendocrine and Inflammatory Mechanisms

Physiologically, depression-induced hyperactivation of the HPA axis leads to sustained elevations in cortisol, a glucocorticoid that promotes hepatic gluconeogenesis and antagonizes insulin signaling. This results in impaired glucose uptake and chronic hyperglycemia-hallmarks of T2DM. Reduced glucocorticoid receptor sensitivity, as seen in dexamethasone suppression test resistance, further perpetuates cortisol overproduction.<sup>23</sup> Concurrently, inflammatory cytokines (e.g., IL-6, TNF- $\alpha$ ) exacerbate glucocorticoid resistance and directly impair insulin signaling.<sup>24</sup> These combined behavioral, neuroendocrine, and immune pathways underscore the role of depression as a bidirectional contributor to poor glycemic control and the progression of NAFLD in T2DM patients.<sup>28,29</sup>

## Vitamin D Deficiency in NAFLD, T2DM, and Depression: A Common Thread

### *Prevalence of Vitamin D Deficiency in NAFLD and T2DM*

Vitamin D deficiency is now widely recognized as a global public health concern, with more than one billion people affected worldwide. It is especially prevalent in people with chronic metabolic diseases like T2DM and NAFLD.<sup>16,30</sup> The co-occurrence of T2DM and NAFLD further intensifies the risk of hypovitaminosis D due to overlapping pathophysiological mechanisms.

Numerous cross-sectional and longitudinal investigations have found that people with T1DM and T2DM had considerably reduced serum levels of 25-Hydroxy Vitamin D [25(OH)D].<sup>31</sup> A comprehensive meta-analysis by Schöttker *et al.* (2014), published in the *BMJ*, confirmed that serum 25(OH)D levels are persistently low across geographic, seasonal, and demographic subgroups, supporting the widespread nature of Vitamin D deficiency in patients with metabolic conditions such as T2DM and NAFLD.<sup>32</sup>

In a five-cohort meta-analysis, individuals with 25(OH)D concentrations >25 ng/mL demonstrated a 43% lower risk of developing T2DM compared to those with concentrations <14 ng/mL.<sup>33</sup> The Ely Study found that serum 25(OH)D levels remained in the deficient (<75 nmol/L) or insufficient (<50 nmol/L) range for most of the year. Notably, frank deficiency (<25 nmol/L) was found in approximately 72% of women, suggesting a gender-based vulnerability.<sup>33,34</sup> Low 25(OH)D levels (<52.5 nmol/L) are linked to a nearly doubled risk of hyperglycemia and a 1.5-fold increased risk of hypertension or hypertriglyceridemia. These metabolic abnormalities highlight the systemic impact of Vitamin D insufficiency in at-risk populations.<sup>35</sup>

## The Direct link Between Vitamin D and Depression

Multiple studies have found a significant inverse connection between serum 25(OH)D concentrations and depressed symptoms. For instance, subjects in the lowest Vitamin D

quartile had Beck Depression Inventory (BDI) scores that were twice as high as those in upper quartiles. Fibromyalgia patients with Vitamin D levels <25 nmol/L reported significantly higher depression scores on Hospital Anxiety and Depression Scale (HADS).<sup>32</sup>

Vitamin D has neuroregulatory effects via its Receptor (VDR), which is broadly distributed across brain areas involved with mood regulation, such as the prefrontal cortex, hippocampus, and hypothalamus.<sup>36</sup> It influences neurogenesis, neurotransmitter synthesis, and inflammatory signaling within the CNS. Its neuroprotective roles are supported by its ability to upregulate tyrosine hydroxylase, inhibit nitric oxide synthase, and stimulate nerve growth factor production.<sup>26,36</sup>

In a Chinese cohort, men with blood 25(OH)D levels  $\geq 92$  nmol/L had significantly lower risks of depression, particularly during periods of low sunlight exposure.<sup>37</sup> Similarly, longitudinal analyses by Milaneschi *et al.* (2014) and meta-analyses by Chan *et al.* (2011) and Spedding (2014) further confirmed that people with low Vitamin D levels were more likely to develop depression over time, indicating a potential dose-response relationship.<sup>38-40</sup>

Milaneschi *et al.* (2014) also shows that the linking Vitamin D to mental wellness and cognitive decline. Hypovitaminosis D has been proposed as a potential cause of depression. Research has demonstrated that the prefrontal cortex, amygdala, and hippocampal regions of the brain contain Vitamin D Receptors (VDR) and 1 $\alpha$ -hydroxylase, which catalyze the creation of 1,25-dihydro-xy Vitamin D (calcitriol, the bioactive form of Vitamin D). Through the overexpression of neurotrophic factors

(nerve growth factor, neurotrophin-3, and neurotrophin-4) found in the neocortex and hippocampal regions, Vitamin D metabolites preserve the integrity of neurons. Additionally, Vitamin D influences inflammatory pathways, which have been connected to depression. It does this by downregulating autoimmune pathways that produce proinflammatory cytokines and increasing anti-inflammatory pathways through VDR-mediated gene transcription.<sup>38</sup>

## Possible Mechanisms of Vitamin D Deficiency and NAFLD Progression in Depressed

### T2DM Patients

The link between lower Vitamin D levels, depression, and metabolic dysfunction can be explained by a variety of biochemical and behavioral factors. Depression often leads to reduced physical activity and increased indoor confinement, both of which reduce cutaneous synthesis of Vitamin D.<sup>32,41</sup> Changes in dietary intake may further contribute to suboptimal Vitamin D levels. While these factors may confound causal inference, studies stratifying for age and BMI have demonstrated that the link between low Vitamin D and depressed symptoms remains strong.<sup>32</sup>

Vitamin D supplementation studies confirm this biological plausibility, with increases in serum 25(OH)D, decreases in Parathyroid Hormone (PTH), and stable calcium levels-factors that influence both neuroendocrine and metabolic pathways. Patients with Vitamin D insufficiency have consistently reported higher HADS scores as well as higher feelings of anxiety and despair.<sup>25,42</sup>

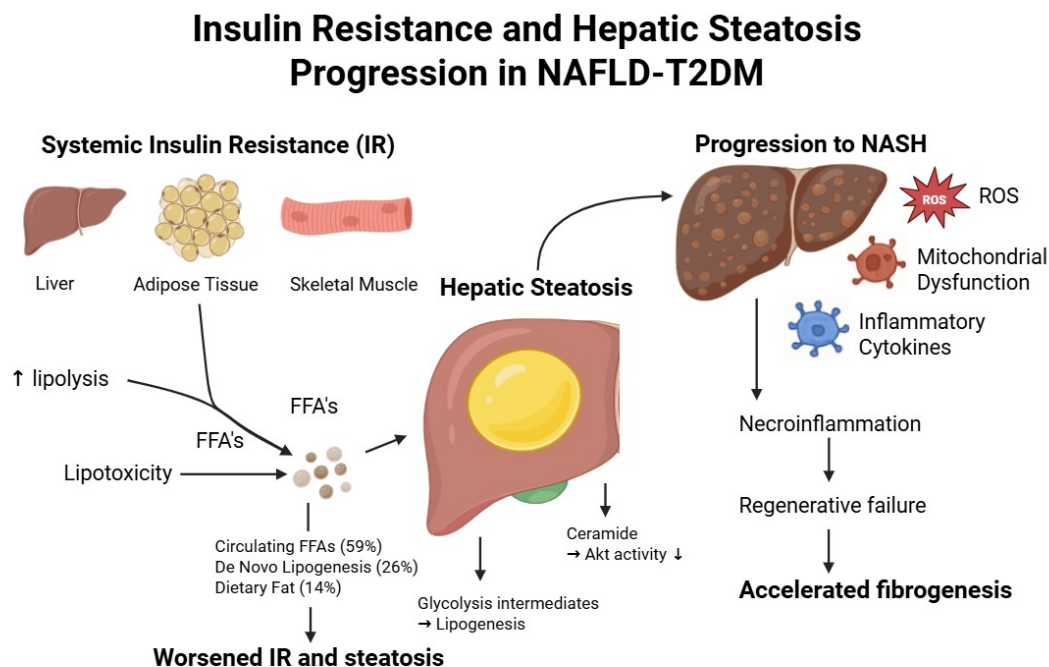


**Figure 1:** Insulin resistance and hepatic steatosis progression in NAFLD-T2D.

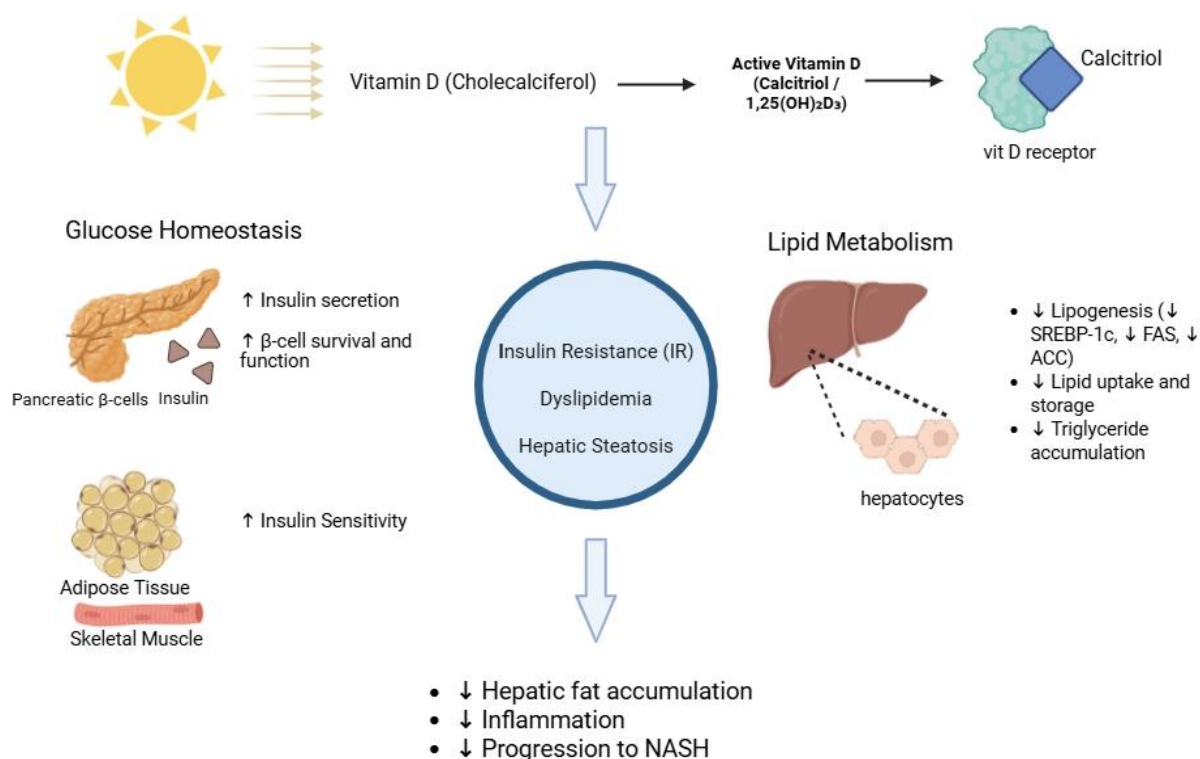


**Figure 2:** Mechanistic role of Vitamin D in glucose homeostasis and lipid metabolism.

At a physiological level, Vitamin D lowers inflammatory pathways (e.g., NF- $\kappa$ B), HPA axis hyperactivation and pro-inflammatory cytokines like IL-6 and TNF- $\alpha$ -all of which are higher in depression and metabolic syndrome.<sup>43</sup> Vitamin D also regulates neuroendocrine function through its action on regions of the brain implicated in HPA axis modulation. It has been shown to enhance the function of glucocorticoid receptors, potentially restoring HPA axis sensitivity.<sup>26</sup>

In the context of glucose metabolism, Vitamin D enhances  $\beta$ -cell function, suppresses chronic inflammation, and reduces secondary hyperparathyroidism all of which contribute to improved insulin sensitivity. In T2DM patients with coexisting depression, these pathways are often dysregulated, compounding the metabolic burden and accelerating NAFLD progression.<sup>31</sup>

Chiu *et al.*, found that Vitamin D status is independently associated with enhanced insulin sensitivity and inversely related to post-challenge glucose levels, indicating its role in glucose regulation.<sup>44</sup> The Ely Study supported this link, demonstrating a long-term association between low 25(OH)D and higher HOMA-IR, fasting glucose, and insulin levels.<sup>34</sup>

Moreover, Vitamin D may interact with key metabolic pathways involving leptin and fibroblast growth Factor 23 (FGF23), via regulatory enzymes such as *Cyp27b1*.<sup>45</sup> Animal models suggest that these pathways affect adiposity and energy expenditure, with potential parallels in human metabolic diseases.<sup>35</sup>

In patients with coexisting T2DM and depression, Vitamin D insufficiency may be a key modifiable risk factor that worsens hepatic steatosis and inflammation. Its deficiency promotes systemic inflammation, worsens insulin resistance, and impairs  $\beta$ -cell function, each a central driver of NAFLD. Additionally, its role in modulating the HPA axis and mood regulation underscores its unique position at the intersection of endocrine, hepatic, and psychiatric pathophysiology.<sup>24,46</sup>

## Clinical and Epidemiologic Evidence

### Studies assessing Vitamin D Status in NAFLD-T2DM Patients

Several studies suggest Vitamin D's larger metabolic significance with both NAFLD and T2DM.<sup>6,47</sup> Chen *et al.* (2023) conducted a meta-analysis of RCTs and found that Vitamin D raised serum 25(OH)D but did not significantly change HOMA-IR, fasting glucose, or insulin levels.<sup>48</sup>

Schöttker *et al.* BMJ meta-analysis ( $n=26,000$ ) showed that individuals with low 25(OH)D had a significantly increased risk of all-cause mortality and cardiovascular mortality, especially those with pre-existing cardiovascular disease-an overlapping comorbidity in T2DM and NAFLD.<sup>32,49</sup>

Hosseini-Nezhad and Holick demonstrated, through many observational studies, that low 25(OH)D levels are inversely related to glycaemic indicators and incidence T2DM.<sup>16</sup> While NAFLD-specific data are scarce, the substantial relationship between Vitamin D and glucose intolerance suggest that

hepatic outcomes may be extrapolated due to shared metabolic pathways.<sup>16,50</sup> Li *et al.* (2023) updated a meta-analysis of 12 RCTs and reported that Vitamin D supplementation significantly increased 25(OH)D and lowered LDL-C, but had no significant effect on the ALT, AST, HOMA-IR, fasting glucose, or other lipids.<sup>51</sup>

Research of healthy people found that serum Vitamin D levels linked inversely with metabolic abnormalities such as increased Body Mass Index (BMI) and dyslipidemia [contributor in NAFLD and T2DM] which supports Vitamin D role metabolic health.<sup>52</sup>

Mitri *et al.* through cohort studies found that higher Vitamin D intake was related with decreased incidence of T2DM. In the Women's Health Study, Vitamin D intake >511 IU/day was associated with a 27% reduction in diabetes risk.<sup>53</sup> In the Finnish cohort, serum 25(OH)D >30 ng/mL were associated with a 72%

decreased incidence of T2DM in men. These outcomes further confirm the role of Vit.D.<sup>54</sup>

The Study found that low baseline Vitamin D concentrations were inversely linked with fasting glucose, 2-hr glucose, fasting insulin, HOMA-IR, and a composite metabolic risk score over a 10-year period.<sup>55</sup> These relationships remained significant even after controlling for BMI, IGF-1, parathyroid hormone, and physical exercise, strengthening the argument for Vitamin D's metabolic influence.<sup>55,56</sup>

Mendelian randomization experiments provide further genetic evidence to support these correlations. In Danish populations genetically determined reductions in 25(OH)D levels were related with a 1.51-fold greater incidence of T2DM.<sup>57</sup> However, similar associations were not observed in East Asian cohorts, suggesting possible ethnic or environmental modifiers influencing the Vitamin D-T2DM-NAFLD axis.<sup>58</sup>

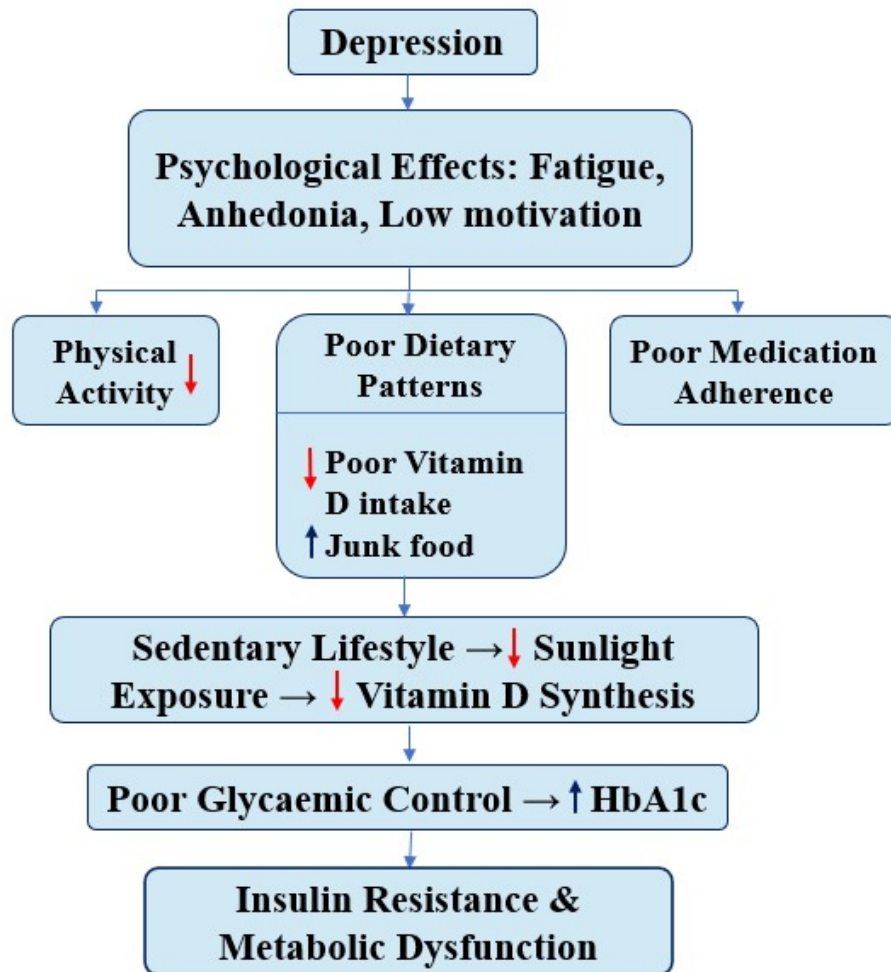


**Figure 3:** Interrelationship between depression, lifestyle factors, and metabolic dysfunction.

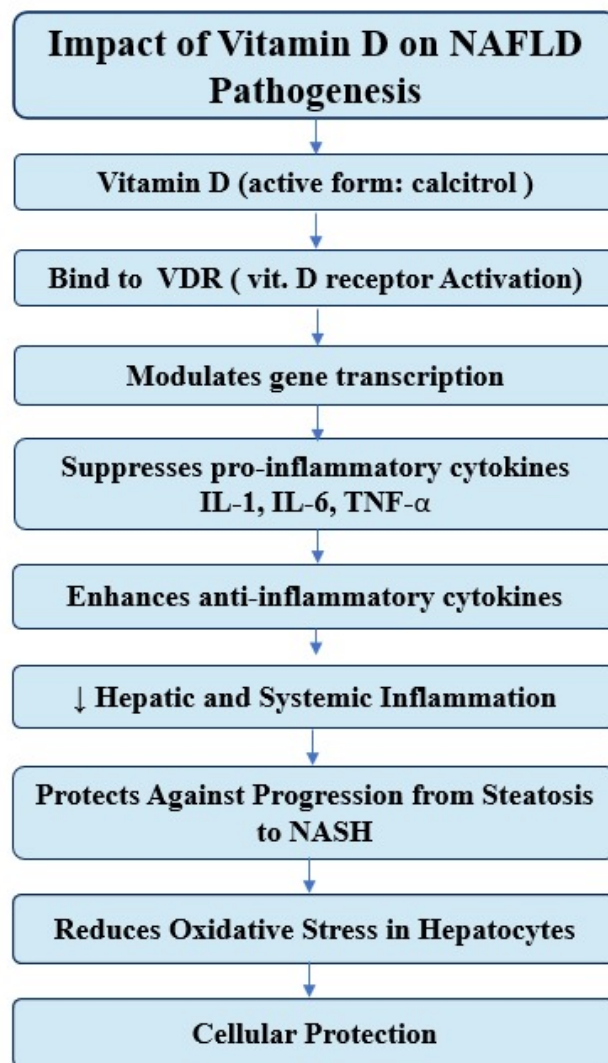


**Figure 4:** Role of Vitamin D in NAFLD pathogenesis.

### Impact of Vitamin D Supplementation on NAFLD Progression in T2DM

Several Randomized Controlled Trials (RCTs) have looked into the metabolic benefits of Vitamin D supplementation for those with T2DM or impaired glucose tolerance which showed better improvement in glycemic management (Figure 4).<sup>59</sup> The observed improvements in metabolic markers suggest potential indirect benefits of vit.D in hepatic health.<sup>59,60</sup>

A meta-analysis of 15 RCTs found that Vitamin D supplementation led to a statistically significant reduction in fasting plasma glucose and a modest improvement in insulin resistance among patients with T2DM or prediabetes.<sup>61</sup> However, these findings imply that Vitamin D may help with early metabolic abnormalities, its significance in long-term glycemic regulation and NAFLD reversal is unknown.<sup>12,46,62</sup>

Supplementation may be more beneficial for persons with Vitamin D insufficiency (<50 nmol/L) or a BMI <30 kg/m<sup>2</sup>, according to Subgroup analyses.<sup>32,63</sup> For example, one meta-analysis found that HbA1C reductions were more pronounced in non-obese people with lower baseline 25(OH)D levels.<sup>64</sup> However, most clinical trials found that Vitamin D administration had no meaningful effect on new onset T2DM incidence or progression to severe NAFLD stages. Thus, while Vitamin D supplementation may offer metabolic improvements relevant to NAFLD pathogenesis, the current body of evidence does not support its use as a stand-alone therapy for liver-specific outcomes in T2DM populations.<sup>65</sup>

### Potential Therapeutic Implications

#### Can Vitamin D Supplementation Improve NAFLD outcomes in T2DM?

According to Current research Vitamin D treatment causes modest benefits in insulin resistance and fasting glucose levels

in patients with T2DM. However, it has not substantial effect on *HbA1C* or the prevalence of diabetes-related comorbidities.<sup>66</sup> Liver-specific data, particularly regarding steatosis or fibrosis regression in NAFLD, remain limited and inconclusive. As such, Vitamin D supplementation alone is unlikely to yield clinically meaningful hepatic benefits in NAFLD-T2DM patients.<sup>67</sup>

Nevertheless, Vitamin D may serve as a supportive adjunct to broader treatment strategies aimed at improving metabolic and hepatic health. Patients who are Vitamin D deficient and exhibit early insulin resistance may particularly benefit from supplementation, especially if they are also engaged in comprehensive lifestyle and pharmacological interventions.<sup>68</sup>

### **The Need for a Multifactorial Approach: Vitamin D + Mental Health Interventions + Lifestyle**

#### **Modifications**

Emerging evidence highlights the need for an integrative approach that combines Vitamin D repletion with mental health care and lifestyle modifications in patients with comorbid T2DM and NAFLD. Martinekova *et al.* (2025) performed a broad meta-analysis of 46 RCTs in chronic liver disease (mixed etiologies, including NAFLD). They found modest but significant reductions in liver enzymes and insulin resistance with Vitamin D.<sup>69</sup>

A meta-analysis by Shaffer *et al.* (2014) showed that Vitamin D supplementation had a moderate effect on depressive symptoms in people with major depressive disorder, particularly in overweight and obese populations groups commonly affected by NAFLD and T2DM.<sup>70</sup> Similarly, Vellekkatt and Menon (2019) emphasized that Vitamin D acts on neuroinflammatory and oxidative stress pathways that contribute to depression, supporting its use as an adjunct in multimodal treatment strategies.<sup>71</sup> Integrating Vitamin D supplementation with structured psychological therapies, pharmacologic treatments for depression, nutritional counselling, and physical activity programs may yield synergistic effects. This multifaceted approach targets the physiological, behavioural, and emotional contributors to metabolic disease, providing a more comprehensive framework for the managing NAFLD in T2DM patients.<sup>72</sup>

To summarize, while Vitamin D has a supportive function in altering insulin sensitivity, mood regulation, and inflammation, its benefits are most pronounced when administered as part of a comprehensive, multidisciplinary strategy. Future interventional trials that particularly target liver outcomes in Vitamin D-deficient T2DM patients with NAFLD and depression are necessary to verify these integrative treatment models.<sup>30,68</sup>

### **FUTURE DIRECTIONS IN RESEARCH AND PERSONALIZED MEDICINE APPROACHES**

Despite increasing evidence linking Vitamin D deficiency to adverse metabolic and hepatic outcomes in patients with Type 2 Diabetes Mellitus (T2DM) and Non-Alcoholic Fatty Liver Disease (NAFLD), current research is limited by small sample sizes, short durations, and heterogeneity in supplementation protocols.<sup>73,74</sup> As a result, there is an urgent need for larger, well-designed Randomized Controlled Trials (RCTs) to determine role of Vitamin D over NAFLD progression in patients with coexisting T2DM.<sup>75</sup>

Future RCTs should be long-term, multi-center studies with strong liver-specific outcomes, such as MRI-Proton Density Fat Fraction (MRI-PDFF), liver stiffness measurements via FibroScan, and histological improvements in steatosis or fibrosis with proper stratification.<sup>76</sup>

Another important area of focus should be the improvement of Vitamin D dose regimens. Future studies must clarify the most effective and safe supplementation strategies by comparing daily versus intermittent dosing, determining appropriate target serum 25(OH)D levels, and evaluating the sustainability and long-term outcomes of high-dose regimens.<sup>77</sup> Furthermore, the advantages of combining Vitamin D therapy with lifestyle and mental health interventions should be investigated. Since depression, sedentary behavior, and poor dietary habits are common in this population, integrated interventions including psychotherapy, dietary counseling, and structured physical activity may yield synergistic effects when paired with Vitamin D repletion.<sup>78</sup>

Inter-individual differences in response to Vitamin D supplementation should also be investigated using genetic and epigenetic methods. Polymorphisms in genes such as *VDR*, *GC*, and *CYP2R1* may affect serum 25(OH)D levels and biological responses, informing precision medicine approaches. In addition, systems biology tools like transcriptomics, metabolomics, and Mendelian randomization can help unravel causal pathways linking Vitamin D to insulin resistance, hepatic inflammation, and depression, thereby guiding biomarker-based patient selection and treatment tailoring.<sup>79</sup>

Furthermore, future trials should incorporate psychological endpoints, including depression severity, cognitive function, and health-related quality of life. Given the bidirectional link of depression and metabolic dysfunction, Vitamin D's neuropsychiatric effects could significantly influence clinical outcomes in NAFLD and T2DM populations. Studies should be conducted to determine whether addressing Vitamin D deficiency alleviates depression symptoms, lowers inflammatory cytokines, and improves patients' mental well-being.<sup>80</sup>

## CONCLUSION

Non-Alcoholic Fatty Liver Disease (NAFLD) and Type 2 Diabetes Mellitus (T2DM) are intricately linked metabolic disorders with overlapping pathophysiological mechanisms, prominently featuring insulin resistance, chronic inflammation, and oxidative stress. Depression, a common comorbidity in T2DM, further complicates disease management by influencing glycemic control, behavior, and systemic inflammatory pathways. Emerging evidence suggests that Vitamin D deficiency may represent a unifying factor across these conditions, exerting significant effects on metabolic, hepatic, and neuropsychiatric outcomes. Although many findings showed the involvement of Vitamin D in the control of T2DM, NAFLD and depression, further largescale exposure and interpretation is essential for the better correlation.

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## ABBREVIATIONS

**NAFLD:** Non-alcoholic Fatty Liver Disease; **T2DM:** Type 2 Diabetes Mellitus; **NASH:** Non-Alcoholic Steatohepatitis; **NAFL:** Non-Alcoholic Fatty Liver; **HCC:** Hepatocellular Carcinoma; **RBP4:** Retinol-Binding Protein 4; **FGF:** Fibroblast Growth Factor; **IFN:** Interferon; **IL:** Interleukin; **AST:** Aspartate Aminotransferase; **ALT:** Alanine Aminotransferase; **VDR:** Vitamin D receptor; **NHANES:** National Health and Nutrition Examination Survey; **FFAs:** Free Fatty Acids; **IR:** Insulin Resistance; **DNL:** De Novo Lipogenesis; **VLDL:** Very-Low-Density Lipoprotein; **IRS:** Insulin Receptor Substrate; **PK:** Protein Kinase; **HPA:** Hypothalamic-Pituitary-Adrenal Axis; **ACTH:** Adrenocorticotrophic Hormone; **HbA1c:** Hemoglobin A1c (glycated hemoglobin); **TNF:** Tumor Necrosis Factor; **25(OH) D:** 25-Hydroxyvitamin D; **BDI:** Beck Depression Inventory; **HADS:** Hospital Anxiety and Depression Scale; **BMI:** Body Mass Index; **PTH:** Parathyroid Hormone; **HOMA-IR:** Homeostatic Model Assessment of Insulin Resistance; **RR:** Relative Risk; **CI:** Confidence Interval; **RCTs:** Randomized Controlled Trials; **MRI-PDFF:** Magnetic Resonance Imaging-Proton Density Fat Fraction; **CYP2R1:** Cytochrome P450 family 2 subfamily R member 1; **GC:** Glucocorticoid; **IU:** International Units; **NF-κB:** Nuclear Factor Kappa-Light-Chain-Enhancer Of Activated B cells; **BMJ:** British Medical Journal; **IGF:** Insulin-Like Growth Factor.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHORS CONTRIBUTION

**Kirti Barkale, Gauri Khaladkar, Gayatri Kotwal:** Data collection, Writing- original draft; **Umesh Laddha:** Supervision, Writing-review and editing; **Gangadhar Magar:** Conceptualization, Data collection, Writing- original draft.

## SUMMARY

NAFLD, Type 2 Diabetes Mellitus (T2DM), and Depression frequently coexist, sharing common metabolic and inflammatory pathways that exacerbate disease progression and clinical outcomes. Clinical studies with limited subjects suggested associations between low Vitamin D levels and increased risk of NAFLD, T2DM, and depression. Future research requires large-scale, randomized controlled trials with stratification based on Vitamin D status, disease stage, and comorbid depression to clarify supplementation benefits.

## REFERENCES

- Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. *Nature medicine*. 2018;24(7):908-22.
- Younossi ZM, Loomba R, Anstee QM, Rinella ME, Bugianesi E, Marchesini G, et al. Diagnostic modalities for nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, and associated fibrosis. *Hepatology*. 2018;68(1):349-60.
- Angulo P, Machado MV, Diehl AM. Fibrosis in nonalcoholic Fatty liver disease: mechanisms and clinical implications. In *Seminars in liver disease* 2015;35(02):132-45. Thieme Medical Publishers.
- Dharmalingam M, Yamasandhi PG. Nonalcoholic fatty liver disease and type 2 diabetes mellitus. *Indian journal of endocrinology and metabolism*. 2018;22(3):421-8.
- Ameka MK. The role of FGF21 in regulating energy homeostasis. *The University of Iowa*; 2017.
- Targher G, Corey KE, Byrne CD, Roden M. The complex link between NAFLD and type 2 diabetes mellitus-mechanisms and treatments. *Nature reviews Gastroenterology and hepatology*. 2021;18(9):599-612.
- Bazick J, Donithan M, Neuschwander-Tetri BA, Kleiner D, Brunt EM, Wilson L, et al. Clinical model for NASH and advanced fibrosis in adult patients with diabetes and NAFLD: guidelines for referral in NAFLD. *Diabetes care*. 2015;38(7):1347-55.
- Uitterlinden AG, Fang Y, Bergink AP, Van Meurs JB, Van Leeuwen HP, Pols HA. The role of Vitamin D receptor gene polymorphisms in bone biology. *Molecular and Cellular Endocrinology*. 2002;197(1-2):15-21.
- Banerjee P, Chatterjee M. Antiproliferative role of Vitamin D and its analogs-a brief overview. *Molecular and cellular biochemistry*. 2003;253(1):247-54.
- Gaurav, Yadav R, Berad A. Systematic review: Causes, symptoms, and treatment of vitamin D3 deficiency. *Int J Life Sci Biotechnol Pharma Res*. 2025;14(2):269-275. doi:10.69605/ijlbpr\_14.2.2025.49.
- Verstuyf A, Carmeliet G, Bouillon R, Mathieu C. Vitamin D: a pleiotropic hormone. *Kidney international*. 2010;78(2):140-5.
- Barchetta I, Cimini FA, Cavallo MG. Vitamin D and Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD): an update. *Nutrients*. 2020;12(11):3302.
- Fu Z, R. Gilbert E, Liu D. Regulation of insulin synthesis and secretion and pancreatic Beta-cell dysfunction in diabetes. *Current diabetes reviews*. 2013;9(1):25-53.
- Tourkochristou E, Mouzaki A, Triantos C. Gene polymorphisms and biological effects of Vitamin D receptor on nonalcoholic fatty liver disease development and progression. *International Journal of Molecular Sciences*. 2023;24(9):8288.
- Vijay GS, Ghonge S, Vajjala SM, Palal D. Prevalence of vitamin D deficiency in type 2 diabetes mellitus patients: a cross-sectional study. *Cureus*. 2023;15(5):e38952. doi:10.7759/cureus.38952.
- Hosseini-nezhad A, Holick MF. Vitamin D for health: a global perspective. In *Mayo clinic proceedings* 2013; 88(7):720-55. Elsevier
- Khan S, Ali A, Khan S, Bakillah A, Damanhoury G, Khan A, et al. Current therapies in alleviating liver disorders and cancers with a special focus on the potential of Vitamin D. *Nutrition and metabolism*. 2018;15(1):13.
- Kawano Y, Cohen DE. Mechanisms of hepatic triglyceride accumulation in non-alcoholic fatty liver disease. *Journal of gastroenterology*. 2013;48(4):434-41.
- Masarone M, Rosato V, Dallio M, Gravina AG, Aglitti A, Loguercio C, et al. Role of oxidative stress in pathophysiology of nonalcoholic fatty liver disease. *Oxidative medicine and cellular longevity*. 2018;2018(1):9547613.

20. Alvarez JKA, Ashraf A. Role of Vitamin D in insulin secretion and insulin sensitivity for glucose homeostasis. *International journal of endocrinology*. 2010;2010(1):351385.
21. Stetler C, Miller GE. Depression and hypothalamic-pituitary-adrenal activation: a quantitative summary of four decades of research. *Biopsychosocial Science and Medicine*. 2011;73(2):114-26.
22. Janssen JA. New insights into the role of insulin and Hypothalamic-Pituitary-Adrenal (HPA) axis in the metabolic syndrome. *International journal of molecular sciences*. 2022;23(15):8178.
23. Shao Q, Wu Y, Ji J, Xu T, Yu Q, Ma C, et al. Interaction mechanisms between major depressive disorder and non-alcoholic fatty liver disease. *Front Psychiatry*. 2021;12:711835. doi:10.3389/fpsyt.2021.711835.
24. Pariante CM, Lightman SL. The HPA axis in major depression: classical theories and new developments. *Trends in neurosciences*. 2008;31(9):464-8.
25. Armstrong DJ, Meenagh GK, Bickle I, Lee AS, Curran ES, Finch MB. Vitamin D deficiency is associated with anxiety and depression in fibromyalgia. *Clinical rheumatology*. 2007;26(4):551-4.
26. Parker GB, Brothchie H, Graham RK. Vitamin D and depression. *J Affect Disord*. 2017;208:56-61. doi:10.1016/j.jad.2016.08.082.
27. Shrestha M, Ng A, Al-Ghareeb A, Alenazi F, Gray R. Association between subthreshold depression and self-care behaviors in people with type 2 diabetes: a systematic review of observational studies. *Systematic Reviews*. 2020;9(1):45.
28. Egede LE, Ellis C. Diabetes and depression: global perspectives. *Diabetes research and clinical practice*. 2010;87(3):302-12.
29. Wilson JB, Epstein M, Lopez B, Brown AK, Lutfy K, Friedman TC. The role of neurochemicals, stress hormones and immune system in the positive feedback loops between diabetes, obesity and depression. *Front Endocrinol (Lausanne)*. 2023;14:1224612. doi:10.3389/fendo.2023.1224612.
30. Argano C, Mirarchi L, Amodeo S, Orlando V, Torres A, Corrao S. The role of Vitamin D and its molecular bases in insulin resistance, diabetes, metabolic syndrome, and cardiovascular disease: state of the art. *International journal of molecular sciences*. 2023;24(20):15485.
31. George PS, Pearson ER, Witham MD. Effect of Vitamin D supplementation on glycaemic control and insulin resistance: a systematic review and meta-analysis. *Diabetic medicine*. 2012;29(8):e142-50.
32. Schöttker B, Jorde R, Peasey A, Thorand B, Jansen EHJM, de Groot L, et al. Vitamin D and mortality: meta-analysis of individual participant data from a large consortium of cohort studies from Europe and the United States. *BMJ*. 2014;348:g3656. doi:10.1136/bmj.g3656.
33. Lowe NM, Bhojani I. Special considerations for Vitamin D in the south Asian population in the UK. *Therapeutic advances in musculoskeletal disease*. 2017;9(6):137-44.
34. Forouhi NG, Luan JA, Cooper A, Boucher BJ, Wareham NJ. Baseline serum 25-hydroxy Vitamin D is predictive of future glycemic status and insulin resistance: the Medical Research Council Ely Prospective Study 1990-2000. *Diabetes*. 2008;57(10):2619-25.
35. Bouillon R, Marocci C, Carmeliet G, Bikle D, White JH, Dawson-Hughes B, et al. Skeletal and extraskeletal actions of Vitamin D: current evidence and outstanding questions. *Endocrine reviews*. 2019;40(4):1109-51.
36. Eyles DW. Vitamin D: brain and behavior. *Journal of Bone and Mineral Research Plus*. 2021;5(1):e10419.
37. Li G, Mbuagbaw L, Samaan Z, Falavigna M, Zhang S, Adachi JD, et al. Efficacy of Vitamin D supplementation in depression in adults: a systematic review. *The Journal of Clinical Endocrinology and Metabolism*. 2014;99(3):757-67.
38. Milaneschi Y, Hoogendijk W, Lips PT, Heijboer AC, Schoevers R, Van Hemert AM, et al. The association between low Vitamin D and depressive disorders. *Molecular psychiatry*. 2014;19(4):444-51.
39. Spedding S. Vitamin D and depression: a systematic review and meta-analysis comparing studies with and without biological flaws. *Nutrients*. 2014;6(4):1501-18.
40. Chan R, Chan D, Woo J, Ohlsson C, Mellström D, Kwok T, et al. Association between serum 25-hydroxyvitamin D and psychological health in older Chinese men in a cohort study. *Journal of affective disorders*. 2011;130(1-2):251-9.
41. Humble MB. Vitamin D, light and mental health. *Journal of Photochemistry and Photobiology B: Biology*. 2010;101(2):142-9.
42. Muscogiuri G, Mitri J, Mathieu C, Badenhop K, Tamer G, Orio F, et al. Mechanisms in endocrinology: Vitamin D as a potential contributor in endocrine health and disease. *European journal of endocrinology*. 2014;171(3):R101-10.
43. Ju SY, Lee YJ, Jeong SN. Serum 25-hydroxyvitamin D levels and the risk of depression: a systematic review and meta-analysis. *The Journal of nutrition, health and aging*. 2013;17(5):447-55.
44. Chiu KC, Chu A, Go VL, Saad MF. Hypovitaminosis D is associated with insulin resistance and  $\beta$  cell dysfunction. *The American journal of clinical nutrition*. 2004;79(5):820-5.
45. Latic N, Erben RG. FGF23 and Vitamin D metabolism. *Journal of Bone and Mineral Research Plus*. 2021;5(12):e10558.
46. Leung PS. The potential protective action of Vitamin D in hepatic insulin resistance and pancreatic islet dysfunction in type 2 diabetes mellitus. *Nutrients*. 2016;8(3):147.
47. Xing Y, Cheng T, Zhou F, Ma H. The association between vitamin D and type 2 diabetes mellitus complicated with non-alcoholic fatty liver disease: an observational cross-sectional study. *Diabetes Metab Syndr Obes*. 2022;15:269-280. doi:10.2147/DMSO.S348870.
48. Chen X, Zhao Y, Zhang R, Zhao Y, Dai L. The effect of Vitamin D supplementation on some metabolic parameters in patients with nonalcoholic fatty liver disease: A systematic review and meta-analysis of 8 RCTs. *Medicine*. 2023;102(42):e35717.
49. Wang L, Song Y, Manson JE, Pilz S, März W, Michaëlsson K, et al. Circulating 25-hydroxy-Vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. *Circulation: Cardiovascular Quality and Outcomes*. 2012;5(6):819-29.
50. Lange NF, Graf V, Caussy C, Dufour JF. PPAR-targeted therapies in the treatment of non-alcoholic fatty liver disease in diabetic patients. *International Journal of Molecular Sciences*. 2022;23(8):4305.
51. Li D, Fu N, Wu H. Effect of Vitamin D supplementation on various parameters in patients with non-alcoholic fatty liver disease: An updated meta-analysis. *Clinical and Experimental Hepatology*. 2023;9(4):396-404.
52. Barchetta I, Angelico F, Ben MD, Baroni MG, Pozzilli P, Morini S, et al. Strong association between non alcoholic fatty liver disease (NAFLD) and low 25 (OH) Vitamin D levels in an adult population with normal serum liver enzymes. *BMC medicine*. 2011;9(1):85.
53. Mitri J, Muraru MD, Pittas AG. Vitamin D and type 2 diabetes: a systematic review. *European journal of clinical nutrition*. 2011;65(9):1005-15.
54. Zur R. The Association Between Serum Level of 25-Hydroxyvitamin D and Non-Alcoholic Fatty Liver Disease. *University of Haifa (Israel)*; 2017.
55. Alvarez JA. Vitamin D and insulin sensitivity among African American and European American adolescents and adults. *The University of Alabama at Birmingham*; 2011.
56. Cheng L. Associations of Sedentary Behavior, Physical Activity, Body Composition, Sleep and Vitamin D With Bone Stiffness Cross-sectional and Longitudinal Findings From the IDEFICS and I. Family Cohort. *Universitaet Bremen (Germany)*; 2021.
57. Tang SS, Zhao XF, An XD, Sun WJ, Kang XM, Sun YT, et al. Classification and identification of risk factors for type 2 diabetes. *World Journal of Diabetes*. 2025;16(2):100371.
58. Zhao Y, Li D, Shi H, Liu W, Qiao J, Wang S, et al. Associations between type 2 diabetes mellitus and chronic liver diseases: evidence from a Mendelian randomization study in Europeans and East Asians. *Front Endocrinol (Lausanne)*. 2024;15:1338465. doi:10.3389/fendo.2024.1338465.
59. Gulseth HL, Wium C, Angel K, Eriksen EF, Birkeland KI. Effects of Vitamin D supplementation on insulin sensitivity and insulin secretion in subjects with type 2 diabetes and Vitamin D deficiency: a randomized controlled trial. *Diabetes care*. 2017;40(7):872-8.
60. Khan RS, Bril F, Cusi K, Newsome PN. Modulation of insulin resistance in nonalcoholic fatty liver disease. *Hepatology*. 2019;70(2):711-24.
61. Mirhosseini N, Vatanparast H, Mazidi M, Kimball SM. Vitamin D supplementation, glycemic control, and insulin resistance in prediabetics: a meta-analysis. *Journal of the Endocrine Society*. 2018;2(7):687-709.
62. Aggelatopoulou I, Tsounis EP, Triantos C. Vitamin D and metabolic dysfunction-associated steatotic liver disease (MASLD): Novel mechanistic insights. *International journal of molecular sciences*. 2024;25(9):4901.
63. Lerchbaum E, Trummer C, Theiler-Schwetz V, Kollmann M, Wölfler M, Pilz S, et al. Effects of Vitamin D supplementation on body composition and metabolic risk factors in men: a randomized controlled trial. *Nutrients*. 2019;11(8):1894.
64. Li X, Liu Y, Zheng Y, Wang P, Zhang Y. The effect of Vitamin D supplementation on glycemic control in type 2 diabetes patients: a systematic review and meta-analysis. *Nutrients*. 2018;10(3):375.
65. Tacke F, Canbay A, Bantel H, Bojunga J, De Laffolie J, Demir M, et al. Updated S2k clinical practice guideline on non-alcoholic fatty liver disease (NAFLD) issued by the German Society of Gastroenterology, digestive and metabolic diseases (DGVS)-April 2022-AWMF registration No.: 021-025. *Zeitschrift für Gastroenterologie*. 2022;60(09):e733-801.
66. He S, Yu S, Zhou Z, Wang C, Wu Y, Li W. Effect of Vitamin D supplementation on fasting plasma glucose, insulin resistance and prevention of type 2 diabetes mellitus in non diabetics: A systematic review and meta-analysis. *Biomedical reports*. 2018;8(5):475-84.
67. Mak AL, Lee J, van Dijk AM, Vali Y, Aithal GP, Schattenberg JM, et al. Systematic review with meta-analysis: diagnostic accuracy of Pro-C3 for hepatic fibrosis in patients with non-alcoholic fatty liver disease. *Biomedicine*. 2021;9(12):1920.
68. Szymczak-Pajor I, Drzewoski J, Śliwińska A. The molecular mechanisms by which Vitamin D prevents insulin resistance and associated disorders. *International journal of molecular sciences*. 2020;21(18):6644.
69. Martinekova P, Obeidat M, Topala M, Váncsa S, Veres DS, Zolcsák Á, et al. Role of Vitamin D supplementation in chronic liver disease: a systematic review and meta-analysis of randomized controlled trials. *Nutrition Reviews*. 2025;83(11):2043-54.
70. Shaffer JA, Edmondson D, Wasson LT, Falzon L, Homma K, Ezeokoli N, et al. Vitamin D supplementation for depressive symptoms: a systematic review and meta-analysis of randomized controlled trials. *Psychosomatic medicine*. 2014;76(3):190-6.
71. Vellekkatt F, Menon V. Efficacy of Vitamin D supplementation in major depression: A meta-analysis of randomized controlled trials. *Journal of postgraduate medicine*. 2019;65(2):74-80.
72. Shea S, Lionis C, Atkinson L, Kite C, Lagojda L, Chaggar SS, et al. Support needs and coping strategies in non-alcoholic fatty liver disease (NAFLD): A multidisciplinary approach to potential unmet challenges beyond pharmacological treatment. *Livers*. 2022;3(1):1-20.
73. Boutari C, Pappas PD, Anastasilakis D, Mantzoros CS. Statins' efficacy in non-alcoholic fatty liver disease: A systematic review and meta-analysis. *Clinical Nutrition*. 2022;41(10):2195-206.

74. Barchetta I, Cimini FA, Cavallo MG. Vitamin D supplementation and non-alcoholic fatty liver disease: present and future. *Nutrients*. 2017;9(9):1015.
75. Mantovani A, Dalbeni A. Treatments for NAFLD: state of art. *International journal of molecular sciences*. 2021;22(5):2350.
76. Brennan PN, Dillon JF, McCrimmon R. Advances and emerging therapies in the treatment of non-alcoholic steatohepatitis. *touchREVIEWS in Endocrinology*. 2022;18(2):148.
77. Grant WB, Al Anouti F, Boucher BJ, Dursun E, Gezen-Ak D, Jude EB, *et al.* A narrative review of the evidence for variations in serum 25-hydroxyVitamin D concentration thresholds for optimal health. *Nutrients*. 2022;14(3):639.
78. Sochacka K, Kotowska A, Lachowicz-Wisniewska S. The Role of Gut Microbiota, Nutrition, and Physical Activity in Depression and Obesity-Interdependent Mechanisms/Co-Occurrence. *Nutrients*. 2024;16(7):1039.
79. Bahrami A, Sadeghnia HR, Tabatabaeizadeh SA, Bahrami-Taghanaki H, Behboodi N, Esmaeili H, *et al.* Genetic and epigenetic factors influencing Vitamin D status. *Journal of cellular physiology*. 2018;233(5):4033-43.
80. Jawad MY, Meshkat S, Tabassum A, Mckenzie A, Di Vincenzo JD, Guo Z, *et al.* The bidirectional association of nonalcoholic fatty liver disease with depression, bipolar disorder, and schizophrenia. *CNS spectrums*. 2023;28(5):541-60.

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