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The Role of Vitamin D in Cardiovascular Health-Linked Adipose Tissue

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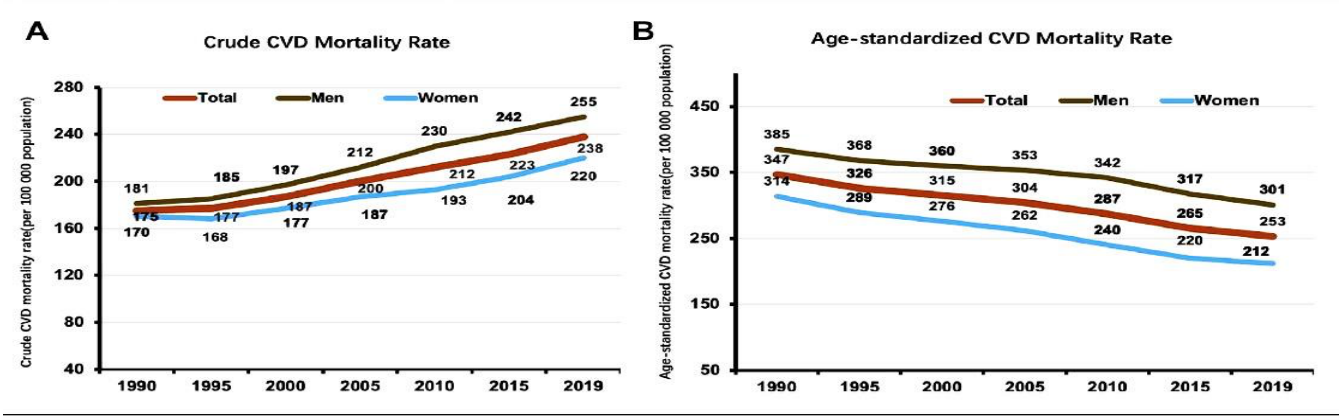
Abstract

The rapid increase in the prevalence of cardiovascular diseases and low vitamin D levels are both considered important public health issues. low level of vitamin D can promote endothelial dysfunction and the development of atherosclerosis. also Vitamin D receptors are also expressed in the cardiomyocytes of the left ventricle. One of the important mechanisms by which vitamin D affects cardiovascular health is its effect on adipose tissue. Vitamin D can modulate the inflammatory response of immune cells and adipocytes inside adipose tissue. Given the importance of vitamin D levels and their relationship to adipose tissue in people with cardiovascular disease, understanding the mechanisms of action of vitamin D in adipocytes may have a significant impact on maintaining cardiovascular health. In the present review, we focus on mechanisms through which vitamin D may influence adipose tissue associated with cardiovascular disease. In addition to checking whether vitamin D supplementation can be a treatment option to improve adipose tissue function and thus prevent cardiovascular disease.

Keywords: cardiovascular, Vitamin D, Adipose tissue, Vitamin D supplementation

introduction: Cardiovascular diseases (CVD) is dangerous chronic diseases, and they are one of the important causes that lead to death [1]. Despite the current and advanced development in methods of preventing (CVD)diseases around the world , this disease is still one of the important health problems that cause death worldwide [2]. The prevalence of cardiovascular diseases is increasing among the world's population. The death rate in Asia has exceeded (50%)out of (18.6) deaths that occurred in 2019 worldwide [1,3,4]. The premature death rate due to cardiovascular diseases worldwide reached 34%,the death rate was higher in the United States at 23%, while in Europe it was 22%[4]. The death rate due to cardiovascular diseases in Asia increased from 5.6 million to 10.8 million deaths, where the percentage increased from 23% to 35% from 1990 to 2019 (Figure 1) [4].



(A) Crude CVD mortality (per 100,000 population) from 1990 to 2019 in men **(green line)**, women **(blue line)**, and the total population **(red line)** in Asia. **(B)** Age-standardized CVD mortality (per 100,000 population) from 1990 to 2019 in men **(green)**, women **(blue)**, and total population **(red)** in Asia. All data were obtained from the open database of the Global Burden of Disease Study in the Global Health Data Exchange (2). CVD = cardiovascular diseases.

Figure. (1) CVD Mortality From 1990 to 2019 in Asia) [4]

CVD are one of the main causes of increased death among young people in Iraq [5]. CVD include: coronary heart disease, rheumatic heart disease, cerebrovascular diseases, stable angina pectoris, unstable angina pectoris, myocardial infarction and others, this definition according to the World Health Organization [6].

There are many risk factors that cause cardiovascular diseases , including non-modifiable risk factors such as (age, gender, and genetic factors), while modifiable risk factors include (diabetes, high blood pressure, physical inactivity, smoking, alcohol intake ,unhealthy diet, overweight obesity, increased adipose tissue[7].

The World Health Organization has paid great attention to reducing the risk of modifiable CVD, such as hypertension, dyslipidemia, obesity ,and unhealthy diet to control the high prevalence of heart diseases that cause death and associated diseases [8,9,10,11]. obesity and Overweight have adverse effects on both morbidity and mortality. The prevalence of obesity increased from 10.8% - 14.9% between men and women from 1975 to 2014, respectively. The prevalence of obesity in Iraq increased in 2015, as the prevalence rate was high in southern Iraq in Basra and reached 55.1%, while in northern Iraq, specifically in Erbil, the prevalence rate reached 40.9 % [12]. In recent years, Vitamin D deficiency is considered one of the modern risk factors causing cardiovascular diseases. Studies have indicated that maintaining normal vitamin D levels ensures the safety of the heart and blood vessels [13].

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Vitamin D

Vitamin D(Vit D) is a fat-soluble hormone which has many roles in organizing physiological processes through its interactions with vitamin D receptors(VDR) [14]. Main metabolic pathways of Vit D in the human body From 7-dehydrocholesterol, previtamin D3 is produced inside the skin by ultraviolet radiation with wavelength (290-315) and is converted to vitamin D3 by a thermal reaction, Vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) can be taken from local foods (dairy products, fish, mushrooms) orally, from dietary supplements or from foods fortified with vitamin D. Both orally ingested and cutaneously synthesized Vit D are metabolized by hepatic 25 hydroxylases into 25 (hydroxy) Vit D [25(OH)D], the main 25 hydroxylase being a microsomal enzyme (gene CYP2R1 By 1,α-hydroxylation inside the kidneys 25-(OH) D is converted into 1,25-hydroxy vitamin D3 [1,25-(OH)2 D3], which is functionally active. [1,25(OH)2D] after release into the circulatory system can be absorbed by many target tissues through processes mediated by vitamin D receptors can exert its effects. The main transport -protein of Vit D and its receptor is the Vit D binding protein(DBP). By 24hydroxylase the effectiveness of vitamin D is inhibited (Figure 2) [15,16].

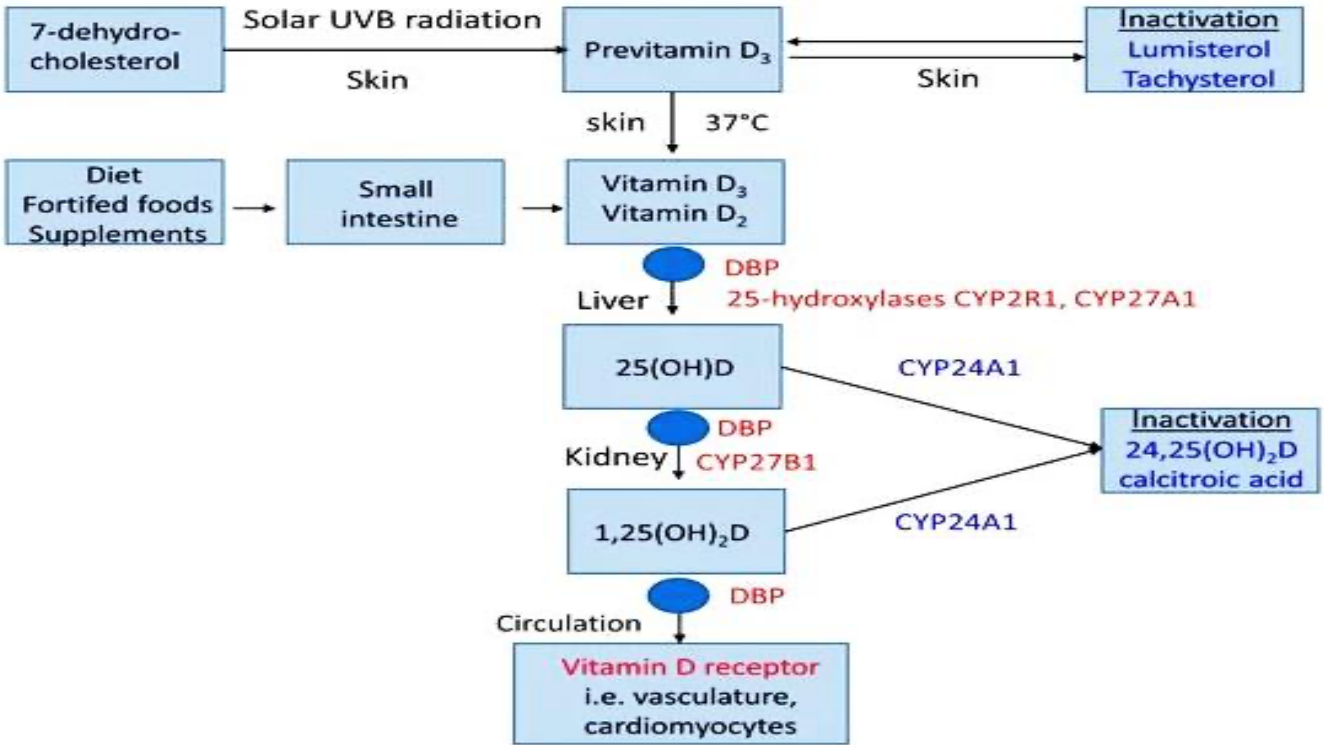

Figure .(2) The main metabolic pathways of vitamin D)[15].

[1,25(OH)2 D] is a steroid hormone (Figure 3), Through membrane-bound receptors exerts non-genomic cellular effects and as the major pathway, genomics cellular impacts through cytosolic receptors. The Binding of 1,25 (OH) 2D leads to a conformational change in the VDR, Which leads to hetero dimerization with the retinoid receptor X and ultimately to the transfer of this compound to the nucleus, where it links to the elements of the VitD response in the stimulated region of the target genes. A group of cells shows extrarenal 1α-hydroxylase activity, Which suggests that in these cells biological influence are determined by the sum of circulating ,locally made [1,25(OH) 2D] [17].

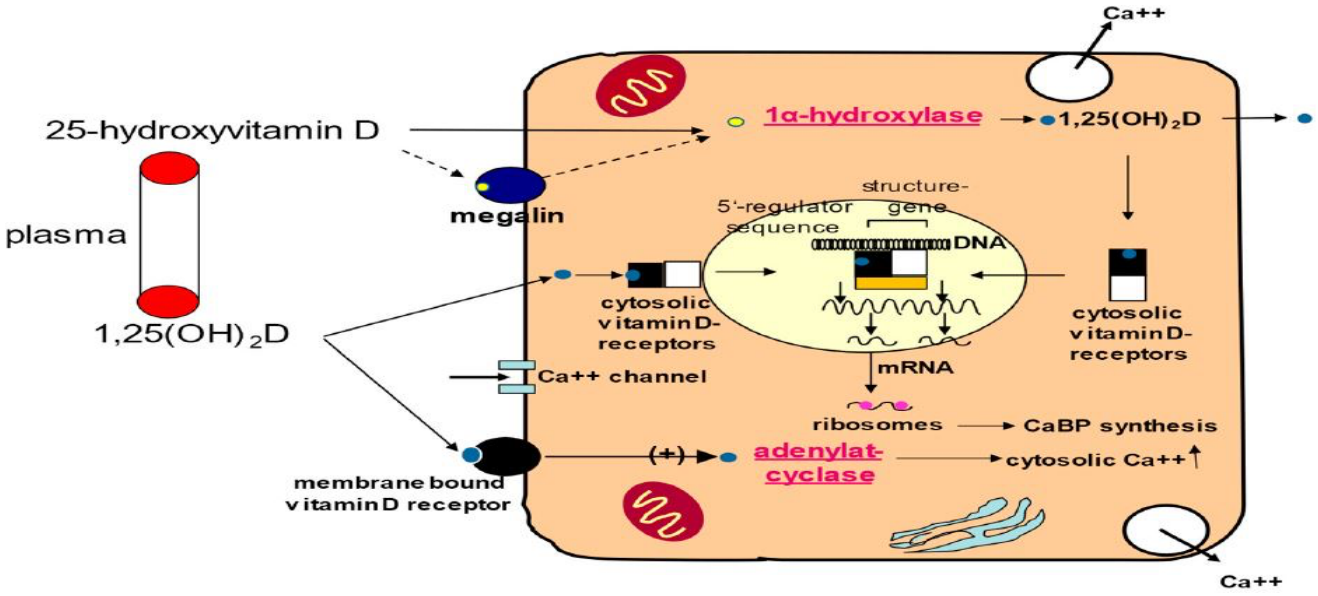

Figure . (3) suggested effects of Vit D signaling in cardiomyocytes)[26].

Vitamin D deficiency

According to the recommendations of the global consensus, vitamin D deficiency is diagnosed if the serum concentration of the vitamin is less than (12ng/mL), while the diagnosis is considered vitamin D deficiency if the concentration is between (12-20ng/mL) [18,19], While the diagnosis is considered normal if the concentrations are not less than 20 ng/mL and not more than (50 ng/mL)[18,20,21,22,23]. Previous studies indicate that the prevalence of vitamin D deficiency (VDD) is widespread worldwide and affects 50% of the population, with almost 1 billion people around the world suffering from VDD [24]. As for in Iraq, the prevalence of VDD has been reported, specifically in the north of it in the city of Duhok, previous studies have indicated the prevalence of vitamin D deficiency among females and younger adults [25,26]. In another study, the prevalence of VDD was reported in central Iraq in the city of Babylon reached 76% among 500 women with VDD (10 ng / mL) found in 19.6 %[27]. The prevalence of VDD in Saudi Arabia has been recorded similar to previous prevalence indicators [28]. In a study conducted in the city of Basra, located in southern Iraq, the rate of VDD increased reached 60%

from 3,692 people [29]. Because vitamin D deficiency is common in the world's population, there has been great interest in the functions of non-classical vitamin D and its association with the risk of developing a range of pathological conditions such as (cancer, obesity, metabolic syndrome, cancer, autoimmune diseases and cardiovascular disease) [30]. In a study conducted by Chowdhury et al., VDD was found to be related with an increased risk of CVD [31]. VDD has also been associated with CVD such as dyslipidemia, blood pressure, diabetes, in addition to CVD such as stroke, myocardial infarction ,and heart failure(HF) [32].

Effects of vitamin D on the cardiovascular system

The effects of Vit D on cardiovascular public health can be predicted in two ways, either by straight effects on the cardiovascular system or by impacts on classic cardiovascular hazard factors [33,34]. Both the 1α-hydroxylase and VDR are found in vascular tissues such as vascular smooth muscle cells, cardiomyocytes and endothelial cells,Also in the cardiomyocytes of the left ventricle, VDR are expressed, and VDD can be linked to heart failure and cardiac hypertrophy [35,36]. 1,25 (OH)2D in cardiomyocytes can induce many non-genomic and genomic impacts, Regulation of calcium metabolism intracellular [37]. There are many evidences that prove, similar to the regulation of hydrolytic 1,25(OH)2D circulation, the synthesis of 1,25(OH)2D in the heart and blood vessels is also regulated by (FGF-23) and (PTH) [38,39].FGF23 leads to hypertrophic growth of cardiomyocytes [40]. The different effects of VitD on the cardiovascular(CV), in addition to the activation of VDR, can also be mediated by (PTH) (Figure 4).

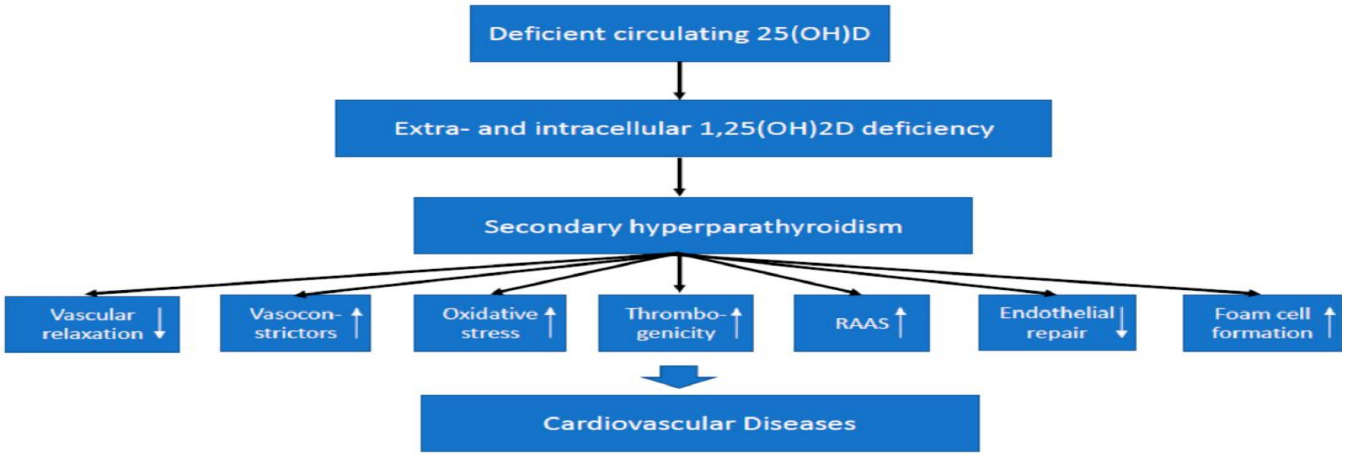

Figure. (4) Effect of VDD on the risk of CVD . Notes: RAAS = renin angiotensin aldosterone system.[40]

Diets that do not contain enough vitamin D and Deletion of VDR stimulates calcification of the aortic and the formation of osteoblast-like cells of vascular smooth muscle cells, similar to excess vitamin D[41,42].

In adipose tissue, Vit D has been shown to have a role in Endocrine and adipocyte growth and metabolic functions [43]. The isolation of Vit D in a big amount of adipose tissue and a decrease in Vit D metabolism may contribute to VDD in obesity. VDR is expressed in adipose tissues and Vit D regulates various aspects of adipose biology including the formation of lipids as well as the metabolic and endocrine function of adipose tissue that can contribute to a high risk of metabolic diseases in vitamin D deficiency. It is believed that elevated levels of fatty acids and changes in lipid-derived factors and pro-inflammatory cytokines combined with a reduced level of adiponectin from a higher mass of dysfunctional adipose tissue, aggravate cardiovascular diseases in obesity[44]. Furthermore, VDD and high adipose tissue level in obesity increase the risk of CVD, which increases the mortality rate and diseases by more than 2-fold.

Vitamin D and Adipose tissue

Gene encoding of enzymes that metabolize Vit D and expression of the VDR gene in adipocytes of adipose tissue have been observed. What we have mentioned indicates that Vit D affects the target genes regulation in adipose tissue by paracrine mechanisms, autocrine and endocrine [45]. Furthermore gene of VDR expression in visceral adipose tissue depends on concentration of 25(OH)D [46]. Therefore, Vit D regulates the metabolism of adipose tissue(AT), which acts as a deposition of Vit D [47]. And a temporary storage system for the slow release of the molecule in order to minimize the uncontrolled synthesis of its, 1,25(OH)2D that active form [48]. Relationship between adipose tissue and Vit D is complex ,and the function of adipose tissue to regulate Vit D in the circulatory system is unclear. Previous studies using radioisotopes have shown the accumulation of vitD in adipose tissue because it is lipophilic[47, 49]. Numerous studies indicate that the Vit D modulation and its effects on adipose tissue depend on the levels of fatty deposits and the degree of obesity [50]. And that losing obesity enhance circulating levels of 25 (OH) D [51]. Moreover, the levels of Vit D in adipose tissue vary according to the degree of obesity, ranging from 4-500 ng/g, depending on the person's weight difference [52]. It has been proven that Vit D in adipose tissue after (5-3 years) of VitD supplementation may have a clinically effect on the serum 25 (OH) D level in the following year [53]. Previous studies have shown an inverse relationship between vitamin D and obesity, where a low level of vitamin D in the blood was found in people with obesity [54,55]. Many different hypothesis have been suggested that explain the relationship between adipose tissue and Vit D, for example (volumetric dilution The increased adipose tissue in obese people stores large amounts of Vit D. Therefore, VDD occurs in obese people due to the increased storage of high amounts of Vit D in the fat mass [56]. The biological availability of Vit D may decrease due to the sequester of Vit D by adipose tissue [57]. It has been suggested in other studies that a decrease in level of 25 (OH) D is related with an increase in levels of 1,25-(OH)2 D in obese individuals [58].

Vit D has immune modulatory effects and anti-lipid activity, as well as reduces inflammation of adipose tissue. New studies have suggested that vitamin D and the vitamin D receptor play a role in adipose tissue. While the VDR and 25 (OH) D (CYP27B1) receptor genes were expressed in the human adipocyte [59]. Evidence suggests that the VDR and 1,25-(OH)D and 25(OH) D are involved in adipose tissue by endocrine and autocrine actions, an endocrine analogue of vitamin D [60]. Some evidence has shown that the expression of the VDR in adipose tissue and levels of exercise and food intake are associated with VDD in obesity[61]. Similar to VDD, obesity is an important risk factor for cardiovascular disease [62]. Obesity and VDD are epidemic diseases and are associated with the risk of developing cardiovascular diseases [63].

Cardiovascular diseases and Vitamin D and adipose tissue

The dilution of Vit D in AT increases with increasing body mass, and therefore the level of 25(OH)D in the serum decreases. Therefore, VDD occurs in people with obesity because increasing body size causes dilution of Vit D in AT, the function of adipose tissue in people with obesity is very important to reduce the risk of developing diseases associated with obesity, such as diabetes and cardiovascular diseases [64]. The results suggest that the metabolism of 25(OH)D may vary depending on the distribution of adipose tissue and include previously unexplored pathways illustrating the variability in the role of vitamin D in cardiovascular diseases [65]. In another study the results showed an association between vitamin D deficiency and several cardiac metabolic factors, adipokines and insulin resistance were associated in the risk of heart disease, however, the modification of the model with visceral adipose tissue mitigated all these relationships [66]. Obviously both the Vit D status and the risk of cardiac metabolism are modified by obesity. The rate of VDD was three times higher in people with an increase in visceral adipose tissue (VAT), and the volume of subcutaneous adipose tissue (SAT) in obesity [67].

Three mechanisms have been proposed to link a low concentration of 25-OH D with obesity [68]. 1- Reduced 1-alpha hydroxylase (CYP24A1 gene) responsible for the conversion of Vit D into the active form. 2- Decreased VDR in adipocytes cause decreased vitamin D production[69,70]. 3- Increased sequestration of Vit D in AT and reduced biological availability [71]

Some mechanisms have been proposed that show the Association of low vitamin D with the risk of cardiovascular disease [72]. as some studies have shown that the weakening of the significant relationship between the features of cardiovascular diseases (high triglycerides in the blood, diastolic blood pressure) and levels of 25(OH)D after adjusting the total fat mass indicates that any relationship between them is completely driven by obesity . In the subgroup of patients with larger FAT and larger WC an increase in adiponectin was detected. This means that difference in abdominal fat mass have an effect on the 25-OH D adiponectin relationship. In light of the current results, we suggest that supplementation of vitamin D may have a helpful impact on obesity by modulating adipose secretions. Because diverse adipose tissue is the cause of the cardiometabolic disturbances in people with obesity,

therefore, it is required to conduct many tests to check whether vitamin D supplements can be an important option to improve the function of adipose tissue, thus prevent diseases that related with obesity ,such as the risk of cardiovascular disease.

Treatment of cardiovascular diseases with vitamin D supplements

We suggest that obese patients raise their vitamin D levels by taking dietary supplements or exposure to sunlight to reduce cardiometabolic. Where evidence has proven that vitamin D supplements can be used to prevent obesity-related diseases and thus prevent cardiovascular risks[73]. However, some experiments have shown that vitamin D supplements do not support the main effect of their use in the Prevention of cardiovascular diseases [74]. When Vit D enters the oral circulation, it is enzymatically activated in the liver to 25(OH)D by cytochrome P450 enzymes. interferential with metabolism due to obesity and associated cardiac metabolic dysfunction may result in a poor response to supplementation of Vit D on the amount of circulating 25(OH)D and its terminal activity. Surgically induced weight loss in humans has been shown to lead to increased (CYP2R1) activity in AT [75]. In fact, the effects of with vitamin D3 supplement, 2000 IU/day, on serum levels of 25-(OH)D, were significantly attenuated across higher BMI categories [76].

Conclusion

In summary, Vitamin D receptor is expressed in adipose tissues and Vitamin D regulates various aspects of adipose biology including the formation of lipids as well as the metabolic and endocrine function of adipose tissue that can contribute to a high risk of metabolic diseases in vitamin D deficiency. Although some studies have proven the use of vitamin D supplements in the Prevention of cardiovascular diseases associated with adipose tissue, but some studies have not been clear results, therefore, it requires several laboratory experiments to determine whether vitamin D supplements can be a therapeutic option to improve the function of adipose tissue

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