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The Pathogenesis of Obesity-Related Co-Morbidities: The Role of Vitamin-D Deficiency and Cellular Senescence

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ABSTRACT:

The goal of this scoping review is to better understand how obesity interacts with vitamin D insufficiency, cellular ageing, and metabolic implications, including subclinical atherosclerosis and non-alcoholic fatty liver disease (NAFLD). An important global health issue, obesity has biological, environmental, behavioural, and hereditary components. An energy imbalance is the primary cause of obesity at all stages of life, and it has numerous and, first and foremost, widespread effects. Given its link to low serum vitamin D levels, obesity has received extensive study in the literature, with numerous postulated pathways tying the two disorders together.

Furthermore, it has been demonstrated that obese people collect signs of accelerated cellular senescence. Subclinical atherosclerosis begins in an early stage and leads to significant cardiac events. Obesity, poor vitamin D levels, and senescent cells are major factors in the continuous low-grade inflammation that subclinical atherosclerosis is associated with. Furthermore, studies have shown that obesity, vitamin D insufficiency, and cellular senescence play crucial roles in the development of NAFLD, which is the hepatic manifestation of the metabolic syndrome. As a result, we listed the key factors linking these illnesses together.

Keywords: vitamin D deficiency; cellular senescence; obesity; non-alcoholic fatty liver disease;subclinical atherosclerosis.

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INTRODUCTION:

Three factors—obesity, vitamin D deficiency (VDD), and cellular senescence—have been linked to the emergence of subclinical atherosclerosis and non-alcoholic fatty liver disease (NAFLD), according to years of research. Obesity affects people of all ages globally and is a severe chronic health issue [1]. Numerous studies have shown that obesity exacerbates cellular senescence, which causes a cell-cycle arrest and a pro-inflammatory response that both accelerate ageing and age-related illnesses [2]. Obesity has been linked to VDD across all age groups and in both sexes [1,3]. The major indicator of vitamin D status, circulating 25-hydroxyvitamin D (25(OH) D), has been shown in numerous genetic investigations to be reduced by excessive obesity [1,3]. VDD in obese individuals typically has no immediate effects, but it may have subclinical effects on numerous organs and predispose them to an unfavourable metabolic state [4]. On the other hand, there is no evidence to support a protective effect of vitamin D against obesity, and the effects of vitamin D supplementation on obese people do not generally go beyond reducing the negative effects of numerous obesity-induced cardiometabolic illnesses [1,3]. Through vascular remodelling, which causes subclinical atherosclerosis and ultimately results in catastrophic cardiac events, obesity promotes cardiovascular disorders [5]. This scoping review aims to discuss obesity, VDD, and cellular senescence and the possible mechanisms by which they contribute to the occurrence and progression of subclinical atherosclerosis and NAFLD. Additionally, a wide spectrum of liver disorders are associated with obesity, including NAFLD, which is emerging as a serious health problem due to its potential to progress to end-stage liver cirrhosis [6].

MATERIALS AND METHODS:

We looked at studies that had already been written about obesity-related illnesses, including NAFLD and subclinical atherosclerosis, and their connections to VDD and cellular senescence. PubMed, PubMed Central, Cochrane Database of Systematic Reviews, MEDLINE, MedlinePlus, Google Scholar database, and WHO reports published from 2000 to 2021 were the databases used for article extraction. The main search phrases were subclinical atherosclerosis, vitamin D deficiency, non-alcoholic fatty liver disease, obesity, and obesity-related cardiometabolic disorders. We focused on the interaction between obesity, VDD, and cellular senescence as pathophysiological mechanisms that contribute to subclinical atherosclerosis and NAFLD in our scoping review.

Obesity and Its Associated Alteration in Adipose Tissue Microenvironment

The dangerous and excessive buildup of bodily fat is known as obesity [7].Body mass index (BMI) is typically used as a biomarker for obesity [8], and the World Health Organization [7] defines obesity as having a BMI of 30 kg/m2. Most people who are classified as obese based on their BMIs do develop obesity-related cardiometabolic illnesses. However, some people may maintain their health for a longer period of time throughout their lives and are referred to as having metabolically healthy obesity (MHO) [8–10]. The long-term exposure to both

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general and abdominal obesity [8,10,11] puts people with MHO at risk for developing cardiometabolic issues later in life even though they have no other cardiovascular risk factors [9]. Waist circumference has been suggested as an additive tool to reflect the cardiometabolic risk, especially among those with MHO, as BMI does not reflect abdominal adiposity and is therefore insufficient to capture the risk among those with MHO [8,9,11]. Waist circumference has been linked to both all-cause and cardiovascular mortality. Abdominal obesity is defined as having a waist circumference more than 88 cm for women and 102 cm for males [8].Obesity is a significant risk factor for a number of debilitating long-term chronic conditions, including diabetes, NAFLD, some forms of cancer, and atherosclerotic cardiovascular diseases (ASCVD) [7,12,13]. One of the main causes of the burden brought on by these illnesses is the ongoing increase in obesity rates [12]. Understanding obesity-induced remodelling of the adipose tissue (AT) microenvironment and the change of its cellular components is necessary to grasp the principles of the mechanisms driving obesity-related diseases.

In terms of behaviour, AT is similar to an endocrine organ [14]. Adipokines, a class of bioactive cytokines that it can create, include some anti-inflammatory cytokines like adiponectin [14,15]. Obesity increases the expression of pro-inflammatory adipokines produced by AT, including leptin, TNF, and interleukin-6 (IL-6) [14,15]. Due to the imbalance between anti- and pro-inflammatory molecules, metabolic dysfunction and cardiovascular disease are promoted, and this also causes low-grade inflammation to persist over time [14,15].The body stores energy in its adipose tissue, and as extra fat builds up, adipocytes release free fatty acids (FFAs) into the bloodstream, which further reduces insulin sensitivity [16].

Vitamin D Overview

Ergocalciferol and cholecalciferol are the two main forms of the fat-soluble vitamin D [17,18]. Vitamin D3 is created when ultraviolet B radiation (UVB) strikes the skin; vitamin D2 is obtained exogenously, whereas the latter is provided through dermal synthesis [17–19]. Dermal synthesis produces the majority of the vitamin D in the body, which is due to the small number of dietary types that contain vitamin D2 [17,18]. For activation, both forms go through two enzymatic hydroxylation processes [17,18]. The first is the renal hydroxylation of 25(OH)D by 1-hydroxylase, creating the physiologically active calcitriol (1,25-dihydroxyvitamin D/1,25(OH)2D), and the second is the hepatic hydroxylation by 25-hydroxylase, forming 25-hydroxyvitamin D (25(OH)D) [17,18]. Other extra-renal tissues have also been found to express 1-hydroxylase, but to a lesser extent [17]. The main form of vitamin D found in circulation is 25(OH)D, which is the precursor to calcitriol [17,18].

Vitamin D binding protein (DBP), a carrier protein that transports more than 80% of the circulating vitamin D, binds both 25(OH)D and calcitriol in the bloodstream [18–20]. DBP is a highly polymorphic protein that is generated from the liver. In addition to its many roles in

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transporting vitamin D, it also has a significant impact on the regulation of circulation vitamin D levels [19,20]. Although vitamin D does not affect the control of DBP formation, other factors such as oestrogen levels, certain cytokines, parathyroid hormone, and dexamethasone treatment do [19,20].

Vitamin D deficiency

Measurements of 25(OH)D are used to determine whether vitamin D levels are adequate because they show both dietary and dermal synthesis-produced vitamin D [21]. Researchers' definitions of vitamin D deficiency (VDD), or "insufficiency," as it is frequently called, vary, as do various international recommendations. The Institute of Medicine (IOM) considers serum 25(OH)D levels below 12 ng/mL to be deficient and to pose a risk to bone health, levels between 12 and 20 ng/mL to be inadequate for both bone and overall health, levels above 20 ng/mL to be adequate (sufficient), and levels above 50 ng/mL to be of concern as they have been linked to adverse effects [17]. However, the Endocrine Society Clinical Practice Guidelines classify 25(OH)D levels between 21 and 29 ng/mL as insufficient and below 20 ng/mL as deficient [21].It is not advised to measure physiologically active calcitriol (1,25(OH)2D), as its short half-life makes it a subpar indication of vitamin D status [22].

Cellular Senescence

Over the past ten years, cellular senescence has been recognised as a cause of aged and malfunctioning cells. It is described as the permanent halt of cell development brought on by stress [23,24]. Cellular stresses that cause senescence at both the cellular and molecular levels include oncogenic activity, telomere erosion, genomic damage, oxidative stress, and genetic instability. Senescence plays a physiologically fundamental role in normal development, tumour suppression, tissue repair, and maintaining tissue homeostasis. This is in addition to the well-known destructive effects of senescent cells in aggravating several age-associated conditions, such as atherosclerosis, cardiovascular diseases, renal insufficiency, neurodegeneration, glaucoma, and much more. It is difficult to fully comprehend the senescence mechanism in order to benefit from it while minimising its drawbacks.

The Interrelation between Obesity, Vitamin D Deficiency, Cellular Senescence, andObesity-Related Co-Morbidities

The Link between VDD and Obesity: Numerous studies have been done on the reciprocal association between VDD and obesity in the literature [1,3]. It is widely recognised that obesity raises the risk of VDD at any age [1, 3]. However, it does not appear that states of low vitamin D levels cause obesity [1, 3], although this is not a consistent finding across all investigations. On the other hand, a systematic evaluation of cohort studies that examined the causal link between the two disorders found that VDD is a factor in the development of obesity. Despite the controversy surrounding the relationship between VDD and obesity, it is impossible to imagine VDD playing a role in enhancing the negative effects of obesity, and

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calcitriol is well established for its ability to reduce obesity-related harm [1]. Here, we discuss some potential pathways that could shed more light on the connection between VDD and obesity.

Vitamin D Uptake, Storage, and Metabolism in the Adipose Tissue: Given that the majority of vitamin D in humans is stored in AT [1], it is thought that the overwhelming percentage of body fat in obese people sequesters vitamin D, lowering circulating 25(OH)D levels. The total AT content of 25(OH)D is directly correlated with serum 25(OH)D [1]. Following exposure to the sun, it was discovered that circulating 25(OH)D levels were marginally lower in obese people than in lean people. This finding could be attributed to the fast assimilation of vitamin D by AT, which in turn lowers the availability of vitamin D metabolites required for target tissues [1]. Additionally, this causes serum volumetric dilution, which lowers 25(OH)D levels [1].

Alteration of Cutaneous Vitamin D Production in Obesity: Although higher vitamin D synthesis is predicted since fat people have a bigger surface area, other investigations have found the contrary to be true. An negative connection between sun exposure and BMI was shown in a population-based study.Obese people avoided sun exposure when sunbathing behaviours were compared across BMI groups, which in turn decreased their vitamin D synthesis.

Surgically Induced Malabsorption: Various elements, including vitamin D, are malabsorbable postoperatively after bariatric procedures such gastric bypass. However, there is no proof that obesity reduces the amount of vitamin D your body absorbs from food. Since vitamin D is fat-soluble and high-fat diets have been found to promote calcium absorption, it is a fortunate fact that those with malabsorption only suffer minor disruptions of the vitamin D-calcium equilibrium.

The Link between VDD and Cellular Senescence: The results of senescence, ageing, and diminished vitamin D production are demonstrated by the evidence. When compared to younger persons, the cutaneous generation of vitamin D in the elderly is believed to be about 70% reduced [25]. Due to age-related changes in dermal structural characteristics including shrinkage and decreased flexibility, 7-dehydrocholesterol, the precursor for the production of vitamin D in the skin, is significantly decreased with ageing [25]. Additionally, the generation of calcitriol is hampered by the age-related decline in renal function [26].

VDD and Subclinical Atherosclerosis: In numerous research [27-31], the link between serum VDD and cardiovascular comorbidities has been shown. Among those with VDD, peripheral vascular disorders, cardiac ischemia, hypertension, and cardiac-associated mortality in general are all very common [30]. Furthermore, prospective studies have demonstrated that VDD correlates favourably with CAC and endothelial dysfunction [28,30], promotes atherosclerotic plaque growth and expansion, elicits systemic inflammation, and elevates coronary artery calcium scores and vascular stiffness, all of which are observed in

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subclinical atherosclerosis. Additionally, vitamin D supplementation has been shown to have athero-protective benefits [27,31].

The Association between NAFLD and VDD: It is not quite apparent how VDD affects NAFLD or how exactly it does so. However, certain mechanisms could account for a portion of its contribution. The functions of vitamin D are carried out by its hepatic receptor, vitamin D receptor (VDR), and deficiencies in vitamin D-VDR axis signalling may be the cause of the inverse relationship between the expression of hepatic VDR and the severity of NAFLD, which further supports the relationship between VDD and NAFLD [32]. Inflammatory-mediated and immunomodulatory processes, as well as some impairment of its anti-inflammatory activities, are thought to be additional ways that VDD can worsen NAFLD [32]. However, since liver-hydroxylation is a crucial step in vitamin D production, it cannot be ruled out that NAFLD also worsens vitamin D status. Hepatic impairment may possibly explain why vitamin D stores are depleted in the majority of liver illnesses [32].

The Association between NAFLD and Subclinical Atherosclerosis: The literature on the relationship between NAFLD and subclinical atherosclerosis has recently grown significantly. NAFLD has been linked to vulnerable high-risk atherosclerotic plaques, CAC, and carotid artery inflammation, all of which are signs of subclinical atherosclerosis in the absence of any underlying cardiometabolic diseases.

CONCLUSIONS:

In conclusion, NAFLD and subclinical atherosclerosis are prevalent diseases linked to obesity. VDD is a prominent occurrence that is frequently linked to obesity, primarily as a result. Numerous pathogenic processes are implicated by both obesity and VDD in the pathogenesis of subclinical atherosclerosis and NAFLD, and it is established that increased cellular senescence may be one of the key mechanisms underlying both disorders.

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