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Artículo de Revisión / Review Article

# The relationship between chronic inflammation associated with obesity and vitamin D deficiency

# Relación entre inflamación crónica asociada a obesidad y déficit de vitamina D

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**SUMMARY**

*Obesity is characterized by an abnormal production of adipocytokines, generating chronic inflammation associated in turn with endothelial dysfunction, atherosclerosis and insulin resistance. On the other hand, it is a risk factor for vitamin D deficiency, thus establishing an inverse relationship between the plasma levels of this nutrient and acute phase proteins with low vitamin D levels, being able to boost the inflammatory response in obesity. In this context, the correction of poor vitamin D status could be an effective addition to the treatment of obesity; however, evidence of future trials that can support the regulatory effects of supplementation is required. The objective of this review is to analyze the existing evidence and establish the relationship between plasma levels of vitamin D and chronic inflammation associated with obesity. The methodology consists of a sensitive search in the PubMed and Trip Database, limiting the search to articles in English and Spanish published through January 2019. Priority was given to clinical trials, original articles and systematic reviews, from which other relevant research was identified.*

*Keywords: Adipocytokines; Adipose tissue; Calcitriol; Chronic inflammation; Obesity; Vitamin D.*

**RESUMEN**

*La obesidad se caracteriza por la producción anormal de adipocitocinas, generando inflamación crónica asociada a su vez a disfunción endotelial, aterosclerosis y resistencia a insulina. Por otra parte, es un factor de riesgo de déficit de vitamina D, estableciéndose una relación inversa entre los niveles plasmáticos de dicho nutriente y proteínas de fase aguda, pudiendo potenciar la respuesta inflamatoria en obesidad. En este contexto la corrección del mal estado de vitamina D podría ser una adición efectiva al tratamiento de la obesidad, sin embargo se requiere evidencia de futuros ensayos que se puedan respaldar los efectos reguladores de la suplementación. El objetivo de esta revisión es analizar la evidencia existente y establecer la relación entre los niveles plasmáticos de vitamina D y la inflamación crónica asociada con la obesidad. La metodología consiste en una búsqueda sensible en las bases de datos PubMed y Trip Database, limitándose la búsqueda a artículos en inglés y español hasta enero 2019. Se priorizó por ensayos clínicos, artículos originales y revisiones sistemáticas, a partir de los cuales se identificaron otras investigaciones relevantes.*

*Palabras clave: Adipocitocinas; Calcitriol; Inflamación crónica; Obesidad; Tejido adiposo; Vitamina D.*

## INTRODUCTION

Obesity has become a serious global health problem due to its close relationship with chronic diseases such as type II diabetes mellitus, hypertension and dyslipidemia, which originates from the imbalance between food intake and energy expenditure[1]. The accelerated increase in the prevalence of excess weight is essentially due to

environmental factors associated with high energy intake, the consumption of food with higher content of saturated fats and simple sugars, together with the decrease in physical activity in all age groups. This generates a process of chronic inflammation that is associated with both insulin resistance (IR) and endothelial dysfunction, which is interrelated with metabolic changes involved in obesity[2]. These processes alter vascular function, especially considering that endothelial dysfunction is a critical component in the development of atherosclerosis[3]. In addition, obesity is a risk factor for vitamin D deficiency. An inverse association between concentrations of this nutrient and levels of body fat has been shown, which could be explained by the large storage capacity of adipose tissue.

This fat-soluble vitamin may reduce its bioavailability. Serum vitamin D levels correlate inversely with excess weight and are associated with metabolic syndrome, glucose intolerance[4] and body mass index (BMI). Thus, vitamin D, may be a possible modulator of inflammatory response. The objective of this review is to analyze the existing evidence and establish the relationship between plasma levels of vitamin D and chronic inflammation associated with obesity.

## REVIEW METHODOLOGY

The present work corresponds to a narrative review, based on a detailed PubMed and Trip Medical Databases search. The search was limited to articles in English and Spanish published through January 2019. Clinical trials, original articles and systematic reviews were prioritized. It should be noted that the selected articles were also used to identify other relevant publications.

### Obesity and chronic inflammation

Obesity is considered a serious health problem worldwide[5], reaching epidemic proportions and becoming a pathology of high morbidity and mortality[6]. According to data provided by the World Health Organization (WHO, 2013), there are more than 1,400 million overweight adults in the world, of which 500 million are obese. These rates of excess weight are essentially due to environmental factors associated with food industrialization and high rates of sedentary lifestyle, generating a serious deregulation at the organic level, characterized by the abnormal production of adipocytokines, the presence of oxidative stress and chronic inflammatory response, contributing to the development of morbid events, such as diabetes mellitus type II, hypertension and dyslipidemia. Adipose tissue is composed mainly of adipocytes, which not only store energy in the form of triglycerides, but also act as an active endocrine organ, secretor of several anti-inflammatory and proinflammatory molecules.

Adipose tissue is one of the most abundant tissues of the human body and represents approximately 10% to 60% of total body weight according to the nutritional status of the individual[7]. This tissue expands through hypertrophy mechanisms, increasing the size of the adipocytes, which enhances the expression and secretion of proinflammatory cytokines that lead to the phosphorylation of the serine 1 substrate of the insulin receptor (IRS-1) through the nuclear factor kappa β (NFkβ), causing IR[8]. Also, hyperplasia occurs with an increase in the number of adipocytes[9], which is triggered by genetic and environmental mechanisms, interfering in the immune regulation of tissues[10]. Obesity is the main component of the chronic inflammatory state.

This process generates a biological defense response, causing a 2 to 3 times elevation of adipocytokines at a systemic level compared to subjects with normal nutritional status[2]. As the body weight increases and as a consequence the adipose tissue increases, the blood supply is exceeded, generating an interaction of necrotic adipocytes with macrophages attracted from the bone marrow, due to the monocyte chemoattractant protein I (MCP1), whose inhibition reduces infiltration and slightly improves IR[11]. Chronic inflammation is associated with both IR and endothelial dysfunction and is interrelated with all metabolic processes involved in obesity that are highly detrimental to vascular function and the health of people1, since endothelial dysfunction is a critical component in the development of atherosclerosis[3].

### Vitamin D metabolism

Vitamin D is a fat-soluble micronutrient, also called calciferol or antirachitic, which corresponds to an unsaponifiable heterolipide of the group of steroids. There are two forms of vitamin D, the first corresponding to $D_2$ or ergocalciferol that is obtained by irradiation of plants[12] and the second is $D_3$ or colecalciferol that is obtained exogenously from the dietary intake of fatty fish or endogenously from its synthesis by exposure to ultraviolet rays at a wavelength of 290 to 315 nm[13]. Provitamin $D_3$, called 7 dehydrocholesterol, undergoes different conjugations and isomerizations transforming itself into vitamin $D_3$, which will later tie to vitamin D Binding Protein or transcalciferin, which will allow its transport to the liver to undergo the first hydroxylation, catalyzed reaction by hepatic 25 hydroxylase, becoming 25 hydroxyvitamin $D_3$ or calcidiol [25OH$D_3$], which in turn will undergo a second hydroxylation, this time at the renal level by 25(OH)$D_3$ 1α hydroxylase, to become 1.25($OH_2$) $D_3$ or calcitriol[14], which will ultimately exert the biological effects, thanks to its action on vitamin D receptor (VDR), which is expressed in most tissues and types of human cells[15], giving pleiotropic characteristics to 1.25($OH_2$)$D_3$[16].

Vitamin D regulates approximately 3% of human genes through its endocrine effects[17]. Its binding to the receptor forms a heterodimer with retinoid receptors, joining DNA sequences, for subsequent transcription and translation processes, giving rise to the expression of different genes, such as forming calcium binding proteins, which will increase the absorption of this from intestine to systemic circulation[18]. For this reason, the production of vitamin D[3] will be conditioned to the concentrations of parathyroid hormone and calcium, stimulating and decreasing respectively their serum levels.

**Relationship between vitamin D and chronic inflammation associated with obesity**

Vitamin D has a recognized role in calcium homeostasis and bone maintenance. According to the the Institute of Medicine, the optimal concentration is 20 ng/ml[19]. Deficiency causes a decrease in the intestinal absorption efficiency of calcium ingested from food, resulting in secondary hyperparathyroidism and accelerated bone turnover, which can lead to osteoporosis or osteomalacia[12], as well as a decrease in the absorption of intestinal phosphorus, since $1,25(OH_2)D_3$ together with parathormone, stimulate the production of fibroblast growth factor 23 (FGF23), a phosphaturic hormone that allows homeostasis of phosphorus[20]. In addition, it has been shown that there is an inverse association between levels of vitamin D and body fat [21]. Recent studies show that hypovitaminosis D is observed in adolescents and obese adults in 90% and 79.4% of cases respectively, associated with high levels of C reactive protein (CRP), total cholesterol and LDL cholesterol[22], which has been confirmed by subsequent research in which vitamin D tends to be inversely related to body fat percentage and waist/height ratio[23]. This can be explained by lower dietary intake, due to the selection of food sources in patients with obesity; reduced cutaneous synthetic capacity[24]; passive processes associated with the sequestration of this nutrient given excessive hyperplasia of adipocytes. Since vitamin D is fat-soluble; which generates a lower bioavailability[25]; altered metabolism since recent research indicates that obesity is characterized by a decrease in the expression of 25-hydroxylase CYP2J2 and 1α-hydroxylase CYP27B1 in subcutaneous adipose tissue, while weight loss is associated with an increase in CYP24A1 expression. Adipose tissue has the ability to metabolize vitamin D locally, however, this can be altered with obesity[26]. Decreased hydroxylation, given by the low concentrations observed in obese subjects of enzymes that catalyze the conversion to active vitamin, decrease the formation of active metabolites in obese individuals[27], which is correlated with comorbidities such as hypertension and diabetes mellitus, markers of subclinical atherosclerosis, and, cardiovascular events such as acute myocardial infarction and cerebrovascular accident. Thus, vitamin D may be able to act as a possible immune modulator, interfering with the chronic inflammatory response[4] since it has been observed to exert protective effects on the vasculature[28], with calcitriol levels <60 pmol/L reported as a cardiovascular risk factor[29].

In this context, serum levels of vitamin D have been found to be inversely proportional to concentrations of proinflammatory cytokines such as tumor necrosis factor α (TNFα) and interleukin 6 ($IL_6$) in obese subjects[4] Vitamin D may even prevent the destruction of pancreatic β cells and reduce the incidence of autoimmune diabetes, possibly secondary to the inhibition of the aforementioned cytokines[30]. On the other hand, vitamin D negatively controls the activation of NFKβ, an important gene regulator that codes for the generation of inflammatory cytokines and influences IR mechanisms[31] Specifically, an inverse relationship between 25(OH)D levels and acute phase proteins is established[32] and increases in IR[4].

Supplementation for 12 months with 83.3 ug/day (3332 IU) of vitamin D induces a decrease in circulating levels of TNFα[29]. However, treatment with 100,000 IU of this vitamin during a period of 3 months had no effect on the endothelial function of obese adolescents with plasma levels lower than 75 nmol/L, despite having increased the levels of 25(OH)D[33]. This result is likely associated with the duration of the study, since other long-duration research has shown the positive impact of vitamin D treatment, guaranteeing endothelial stabilization in an obese population[34]. On the other hand, supplementation with 50 ug of vitamin D for 9 months increased the plasma concentrations of anti-inflammatory cytokine interleukin 10 ($IL_{10}$) and prevented the increase of TNFα in subjects with coronary disease, associated with systemic inflammation[35]. In data provided by Carrillo et al, supplementation with 4000 IU/day of vitamin D in active subjects did not influence the levels of inflammatory biomarkers[36]. On the other hand, polymorphisms in VDR genes are associated with insulin resistance and high glucose concentrations[37], highlighting that vitamin D has a possible stimulatory role in the expression of insulin receptors and its low plasma level could potentiate the inflammatory response in obese subjects. Some studies have shown inverse associations between circulating concentrations of 25(OH)D and elevated fasting glucose and insulin, while others have established a similar inverse relationship to pancreatic β cell function and a positive association with insulin sensitivity[38]. In conclusion it is suggested that the state of hypovitaminosis D is inversely related to the parameters of obesity[17], which is why correcting the poor state of vitamin D through dietary supplementation may be an effective addition to the standard treatment of obesity and its insulin-associated resistance[23-39], however, evidence of future clinical trials is required to support the potential regulatory effects of vitamin D supplementation in order to reduce obesity levels.

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