



## Trabajo Original

## Obesidad y síndrome metabólico

### Obesity, related diseases and their relationship with vitamin D deficiency in adolescents

#### *Obesidad, enfermedades relacionadas y su relación con la deficiencia de vitamina D en adolescentes*

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### Abstract

**Introduction:** The rise in prevalence of obesity has occurred concomitantly to that of vitamin D deficiency (VDD). The aim of this narrative review was to describe the relationship between obesity and such related diseases as VDD in adolescents, in an effort to warn of the risks of this deficiency during this period of growth and development.

**Methods:** We searched the electronic databases PubMed, Medline, Scielo, Science Direct and Lilacs for articles from between 2000 and 2015 on the topics obesity and obesity-related diseases and VDD in adolescents. We included articles written in English, Spanish and Portuguese of the analytical variety (transverse and longitudinal), systematic reviews, meta-analysis and controlled clinical trials on humans, and excluded studies that were done on animals, inconclusive or with undefined methodology.

**Results:** We produced an overview of VDD in obesity, in cardiovascular diseases, in type 2 diabetes mellitus, in systemic hypertension, and in dyslipidemia. The prevalence of VDD was considered high in obese adolescents and their relationship with the obesity and related diseases was found in adolescents. These findings forewarn of possible clinical repercussions in the health of the adolescents, foremost because of how essential vitamin D is to growth and development, and for its interaction with obesity and obesity-related diseases.

**Conclusion:** The worldwide rise in the obesity rate alongside the progressively increasing of vitamin D deficiency in adolescents is alarming. This relationship of VDD with the obesity and related diseases was found in adolescents. Vitamin D supplementation is considered promising measure to take with obese adolescents.

#### Key words:

Obesity. Vitamin D deficiency. Adolescents. Obesity-related diseases.

### Resumen

**Introducción:** el aumento de la prevalencia de la obesidad se ha producido de forma concomitante a la deficiencia de vitamina D (DVD). El objetivo de esta revisión fue describir la relación entre la obesidad y las patologías asociadas a la obesidad y la DVD en adolescentes, en un esfuerzo por advertir los riesgos de esta deficiencia durante este período de crecimiento y desarrollo.

**Métodos:** se realizaron búsquedas en las bases de datos electrónicas PubMed, Medline, Scielo, Science Direct y Lilacs para los artículos de entre 2000 y 2015 sobre temas como la obesidad y las patologías asociadas a la obesidad y DVD en adolescentes. Se incluyeron artículos escritos en inglés, español y portugués de la variedad analítica (transversal y longitudinal), revisiones sistemáticas, metaanálisis y ensayos clínicos controlados en seres humanos, y excluyendo los estudios que se realizan en animales, no concluyentes o con metodología indefinida.

**Resultados:** se produjo una visión general de DVD en la obesidad, las enfermedades cardiovasculares, la diabetes mellitus, la hipertensión sistémica y en la dislipidemia. La prevalencia de DVD se considera alta en adolescentes obesos y su relación con las patologías asociadas a la obesidad fueron encontradas en adolescentes. Estos datos advierten sobre posibles repercusiones clínicas en la salud de los adolescentes, sobre todo debido a la forma esencial de vitamina D en el crecimiento y el desarrollo, y por su interacción con la obesidad y las patologías asociadas a la obesidad.

**Conclusión:** el aumento mundial de la tasa de obesidad junto con el aumento progresivo de la deficiencia de vitamina D en los adolescentes es alarmante. Se encontró una relación en adolescentes entre VDD y obesidad y enfermedades relacionadas. La suplementación de vitamina D se considera una medida promisoriosa para tratar a los adolescentes obesos.

#### Palabras clave:

Obesidad. Deficiencia de vitamina D. Adolescentes. Patologías asociadas a la obesidad.

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## ABBREVIATIONS

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BMI: Body Mass Index.  
BP: Blood Pressure.  
CCS: Centro de Ciências da Saúde.  
CVD: Cardiovascular Diseases.  
DM: Diabetes Mellitus.  
IR: Insulin Resistance.  
PTH: Parathyroid Hormone.  
SH: Systemic Hypertension.  
25(OH)D: 25-hydroxyvitamin D.  
1,25(OH)2D: 1,25-dihydroxyvitamin D.

## INTRODUCTION

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The prevalence of obesity has taken epidemic proportions worldwide over the last few decades, both in adult and pediatric populations (1). Ng et al. (2) estimated the global, regional and national prevalence of overweight and obesity in adults, adolescents and children ( $n = 19,244$ ) during the period between the 1980s and 2013, obtaining the prevalence by age, sex and country, and demonstrated that the number rose from 857 million in 1980 to 2.1 billion in 2013, with a 47.1% prevalence in children and adolescents. In relation to developed nations, 23.8% of boys and 22.6% of girls were overweight or obese. Whereas in developing nations, Brazil included, the prevalence of 8.1% in 1980 rose to 12.9% in 2013 in boys, and from 8.4% to 13.4% in girls (2).

A recent study (1) on examining the prevalence of obesity reported by National Health and Nutrition Examination Survey from 1999 to 2012 in a representative sample of children and adolescents between the ages of 2 and 19 in the United States ( $n = 26,690$ ), revealed that 17.3% were class 1 obese (BMI 30.0-34.9 kg/m<sup>2</sup>), 5.9% were class 2 (BMI 35.0-39.9 kg/m<sup>2</sup>), and 2.1% were class 3 obese (BMI  $> \text{or} = 40.0$  kg/m<sup>2</sup>). According to the authors, the more serious forms of obesity are on an upward trend, and complementary research on the causes and solutions for this problem is in order.

In Latin America, a systematic review (3) showed that 16.6% to 35.8% of adolescents between the ages of 12 and 19 are obese. In adolescents, the heavy consumption of food high in saturated fats and sugars coupled with a decrease in the amount of cereals, fruits, vegetables (4) and dairy ingested create the nutritional paradox that is the coexistence of obesity with deficiencies in vitamins and minerals (5), among them vitamin D (6) and calcium (7), nutrients that are essential especially during this period of intense growth and development.

At present, the rise in the obesity rate has occurred concomitantly with that of vitamin D deficiency (VDD) and it is estimated that one billion people worldwide suffer some degree of this insufficiency (8). VDD is currently seen as a pandemic and a public health problem afflicting the classic risk groups of children, pregnant women and the elderly, as well as adolescents and young adults (8,9,10). Looker et al. (10) suggest that the VDD found in children, teenagers and young adults in the United States may be related to the drop in consumption of milk and rise in the incidence of obesity and protection

from the sun. The association between these factors has been found both in adults (11) and in adolescents (12,13).

Though vitamin D has traditionally been studied for its role in calcium homeostasis and bone metabolism, recent revelations about the presence of vitamin D receptors (VDR) in a variety of different tissues, including those of the brain and colon, as well as in immune, vascular and myocardial cells, suggest there is vitamin D involvement and mediation in numerous other systems, not to mention musculoskeletal tissues (14). Vitamin D appears to interact directly or indirectly with the genes responsible for regulating cellular differentiation and proliferation, apoptosis and angiogenesis (15), offering a clue as to why a deficit of it may relate to the pathogenesis of a number of such diseases as cardiovascular diseases (16), type 2 diabetes mellitus (17), systemic hypertension (18) and obesity (19).

Our aim with this study was to identify and describe the association obesity and obesity-related diseases have with vitamin D deficiency in adolescents. The findings we present here serve as a warning of the risks of VDD during this period of great biological importance, and contribute in the prevention and/or reduction of the possible harm done by this deficiency.

## MATERIAL AND METHODS

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This study consists in a narrative review of the knowledge currently available in scientific literature regarding obesity, its obesity-related diseases and association with VDD in adolescents. The selection of articles we include in this study came from extensive research in the electronic databases PubMed, Medline, Scielo, Science Direct and Lilacs, and included studies of the analytical variety (transverse and longitudinal), systematic reviews, meta-analysis and controlled clinical trials conducted on humans, while we excluded studies that were on animals, inconclusive or where the methodology was not properly defined.

For this narrative review we looked at studies from between the years 2000 and 2015, and limited our bibliographic search to studies published in Portuguese, Spanish or English. For the bibliographic search we used the following keywords: adolescent, vitamin D, vitamin D deficiency, obesity, cardiovascular diseases, type 2 diabetes mellitus, systemic hypertension, dyslipidaemia, micronutrients deficiencies. Our searches consisted in phrases combining these keywords or the keywords on their own.

The initial data collection process involved reading the titles and abstracts of the available studies. The articles selected in this first stage were sorted for analysis and integral reading to identify publications relevant to our inclusion/exclusion criteria. Furthermore, we consulted the bibliographies of each of the articles in this review to identify further articles of significance to our study that may have previously escaped our awareness.

## VITAMIN D DEFICIENCY AND OBESITY

The association between VDD and obesity has been identified both in adults (20) and in adolescents (12,13,19,21). A study con-

ducted by Vimalaswaran et al. (20) sought to explore the causality and direct relationship between BMI and 25(OH)D, using genetic markers as instrumental variables. They used data gathered from 21 adult cohorts, with a total of 42,024 participants, and found that for every 1 kg/m<sup>2</sup> increase in BMI there was an associated 1.15% decrease in serum 25(OH)D concentrations.

Evidence suggests that there are several factors contributing to VDD in the obese, among them the presence of receptors in adipose tissues, which would result in the vitamin D being trapped in the adipocytes and thus decreasing its bioavailability for the target tissues (22) the increased antioxidant demand due to the inflammatory component caused by the obesity itself (20), the little exposure obese individuals have to the sun, due to their limitations in mobility and lack of outdoor activities (23) and skin pigmentation/ethnicity (21).

Although lesser in the volume of data in the literature, studies show that obese children and adolescents too have significantly lower serum vitamin D concentrations, like their adult counterparts (12,13,19,21).

A study carried out by Turer et al. (21) with a representative sample of American 6-8-year-old children and adolescents from the NHANES (n = 12,292) found a 49.0% prevalence of VDD among the severely obese (n = 581) and 34.0% among the obese (n = 1897). The prevalence of VDD in the different ethnic groups was respectively 27%, 52% and 87% among severely obese White, Latino and African-American children. The authors stress the importance of vitamin D, for a deficiency in it can cause rickets and stunted growth in children and may trigger and/or exacerbate osteopenia or osteoporosis and increase the risk of fractures during adulthood.

A study with 68 obese American adolescents found that the prevalence of low vitamin D levels was 100% in obese girls and 91% in obese boys (24), and these findings were corroborated by a clinical trial conducted by Lenders et al. (25) on 58 obese adolescents with an average BMI of 36 ± 5 kg/m<sup>2</sup>, where they found an association between body fat and vitamin D deficiency and insufficiency.

Body composition appears to interfere with 25(OH) D synthesis and metabolism hence obese individuals tend to have lower serum concentrations than the non-obese population (26). Campos et al. (26) assessed the influence of visceral and subcutaneous fat on bone mineral density (BMD) in post-pubescent adolescents, and found that visceral fat has a negative effect on bone mass, while the subcutaneous kind has a positive impact only on boys, and suggest that these opposing forms of interaction of adipose tissue on bone mass occur because of the differences in the expression and secretion of the adipokines. It is known that obesity causes a complete change in hormonal and adipokine profile, resulting in altered bone mass. Secretions from visceral adipose tissue are directly related with the development of insulin resistance and type 2 diabetes mellitus (T2DM). The hyperinsulinemia is associated with impaired function of the IGF-1 axis, which is involved in determining bone thickness and length, density and architecture of the mature skeleton. IGF-1 axis impairment would result in low bone mineral density. Additionally, both osteoblasts (bone-forming

cells) and adipocytes (energy-storing cells) are derived from a common mesenchymal stem cell, and agents that inhibit adipogenesis stimulate osteoblast differentiation and vice-versa, those inhibiting osteo-blastogenesis increase adipogenesis. This mechanisms may contribute to the influence of obesity in bone metabolism (16).

Griz et al. (27) suggest that leptin appears to have multiple central and peripheral effects on bone metabolism. Although peripheral leptin has an anabolic effect on bones (with possible inhibition of the osteoclasts) particularly in the appendicular skeleton, the central leptin is deleterious to the axial skeleton, as it seems to activate pathway that inhibits the ability of the kidney to actively synthesize 25(OH) D. Therefore, it seems that the effects of leptin signaling in the bone differ significantly between the axial and appendicular regions.

Study by Carrillo et al. (28) shows a stronger inverse relationship between 25(OH)D and abdominal circumference in obese individuals than when correlating it to total body fat. Oliveira et al. (2013), in a transverse study, found vitamin D insufficiency in 70.6% of the 160 adolescents between 15 and 17 years of age they studied, and serum 25(OH) concentrations were statistically lower in adolescents with abdominal overweight and obesity.

Obesity is a progressive disease and, once present in adolescence is a risk factor for obesity in adulthood, and this risk increases particularly when considering the duration of exposure to the disease, which can cause and / or exacerbate changes metabolic and bone adolescents, by increased demand and thus compromising bone mineral density in adulthood.

### Vitamin D supplementation in obese adolescents

The Institute of Medicine recommends ingesting 600 IU/day of vitamin D for adolescents, with the ceiling for safe consumption of vitamin D set at 4,000 IU/day (29). However, this IOM-proposed recommendation seems not to be enough to bring vitamin D levels to an adequate state in those with greater nutritional demands for and/or factors influencing the availability of 25(OH)D: obese adolescents, black adolescents without sufficient sun exposure.

One randomized, double-blind clinical trial conducted by Putman et al. (30) on 56 healthy American adolescents found that supplementing with between 200 and 1,000 IU of vitamin D3 for 11 weeks did not increase serum 25(OH)D levels; that is, there was no significant difference between the groups. According to Braegger et al. (31), oral vitamin D supplementation should be considered for obese, black adolescents with inadequate sun exposure.

Guidelines established by the Endocrine Society Clinical Practice in 2011 recommend that one- to 18-year-old children and adolescents be given 600-1,000 IU/day (no more than 4,000 IU/day) of vitamin D supplementation, with special attention to those who are at risk of either inadequate serum vitamin D levels or low bone mineral density or both. And for adolescents over 18 years of age, the recommendation is between 1,500 and 2,000 IU/day (maximum 10,000 IU/day) (32).

The Society for Adolescent Health and Medicine (33) recommendation of 2013 is to administer 600 IU/day (400 and 800 IU/day) of vitamin D to healthy adolescents, and at least 1,000 IU/day to adolescents at risk of vitamin D deficiency or insufficiency, including obese adolescents (> 95<sup>th</sup> BMI), in conjunction with the vitamin D from the diet and exposure to the sun. And as far as type of supplementation to be used, SAHM suggests that teenagers should be given vitamin D3 supplementation and/or treatment, if this form of the vitamin is readily available to the patient and their family.

Studies report vitamin D3 to be more efficient than vitamin D2 (34,35), which may have a much shorter half-life than vitamin D3 does in the body (35). However, other findings suggest that vitamin D2 and vitamin D3 are equipotent in increasing serum 25(OH)D concentrations (36,37).

Castaneda et al. (38) suggest that obese adolescents respond poorly to vitamin D supplementation, and for that reason they recommend that obese teenagers be given twice the dose non-obese adolescents are given. The authors compared 40 obese and non-obese Caucasian 12- to 18-year-olds. The prevalence of VDD was 78% in the obese and 61% in the non-obese, and daily supplementation of 2000 IU of vitamin D3 (cholecalciferol) was given over a 12-week period. After the 12 weeks, the increase in serum 25(OH)D levels was found to be significantly greater in the non-obese adolescents, with 89% of their cases having normalized compared to 50% of those of the obese adolescents.

The efficacy of vitamin D supplementation in boosting serum 25(OH)D concentrations seems to be dependent on the initial status of the vitamin and whether obesity is present or not. Non-obese adults are estimated to require consumption of 100 IU to increase serum 25(OH)D by 1.0 ng/mL (39), whereas obese adults require twice the dose to experience an equivalent response (22). According to Belenchia et al. (40) the results obtained with obese adolescents were similar to those with the adults, whereby 4,000 IU/day produced an average increase of 19.5 ng/mL, or 1 ng/mL for every 205 IU ingested, and this daily 4000 IU vitamin D3 dose, the maximum allowable according to the IOM, was considered safe and effective in improving vitamin D nutritional status in obese adolescents.

## Factors that may aggravate VDD in obese adolescents

### *Exposure to the sun*

Although food is a reasonable source of vitamin D, availability, food sources and dietary intake may vary from one country or region to the next, meaning that the adequate amount of this hormone, for it so fulfill its functions satisfactorily, depends almost exclusively on cutaneous synthesis and/or supplementation (41).

Cutaneous vitamin D synthesis is a self-regulated process and, subjected to prolonged exposure to the sun, both pro-vitamin D (7-dehydrocholesterol) and vitamin D3 (cholecalciferol) are transformed into inactive photoproducts, making it so they do not

become toxic as their concentrations increase. Thus, overexposure to the sun does not result in vitamin D intoxication, though it may cause DNA damage and sunburns and thereby increase the risk of skin cancer (42).

Adolescent lifestyle factors, like many hours spent studying indoors and less time spent outdoors, mainly where the obese are concerned, may have an impact on them getting the sun exposure they need to for ideal synthesis of cutaneous vitamin D. And this synthesis may vary according to time of day; season of the year; latitude; altitude; weather conditions; atmospheric pollution, which decreases UVB-photon absorption; skin pigmentation; region of the body exposed; or measures taken as sun protection (14).

Dong et al. (43) assessed 559 adolescents of 14- to 18-year-old residents of southeastern USA, where the climate is sunny, and found that of the total sample, 56.4% and 28.8% had vitamin D insufficiency and deficiency, respectively. And despite Brazil being a tropical country and supposedly having greater exposure to the sun, inadequate serum 25(OH)D concentrations were also found in different regions. Santos et al. (44), having assessed 234 adolescents from South Brazil, found VDD in 36.3% and vitamin D insufficiency in 54.3% of this sample. This findings also corroborate those of Peters et al. (6), who found 60% of 136 adolescent boys and girls from southeastern Brazil's São Paulo State to have vitamin D insufficiency, and only 27.9% of the adolescents reported practicing regular physical activity outdoors.

The literature shows that current sun-exposure habits do not provide the vitamin D status most people need. The results of a study carried out in Manchester, England, suggest that daily exposure of 0.5 SED (standard erythema dose) between 11 am and 1 pm while wearing typical summer clothing was not enough to attain an adequate vitamin D status in late summer (42).

Currently, public health guidelines about the relationship between sun exposure and skin cancer, as well as aesthetic concerns regarding premature aging of the skin, have caused a spike in the use of products with solar protection, which decrease cutaneous vitamin D synthesis. A balance has to be reached in these guidelines so as to reduce the risk of VDD in adults and adolescents, especially for those who are obese.

## ***Non-alcoholic fatty liver disease (NAFLD)***

According to Mann et al. (45), non-alcoholic fatty liver disease (NAFLD) affects around 10% of the pediatric population (45,46). The minority of children undergo biopsy but currently there is no other method to accurately assess the stage of disease. Management is focused at weight loss through a combination of diet and exercise. Here, we present a current review of paediatric NAFLD aimed at non-specialists, with practice points for implementation (45).

This disease is strongly associated with obesity, in particular to visceral fat and insulin resistance, and with the rising prevalence of obesity, it is quickly becoming one of the most common liver diseases among obese children and adolescents (47). In a transverse study involving 41 adolescents with an average

BMI of 59 kg/m<sup>2</sup>, 83% were found to have NAFLD, 24% had steatosis, 7% had liver fibrosis with steatosis, 32% had non-specific inflammation and steatosis, and 20% had nonalcoholic steatohepatitis (48).

Obesity, T2DM and old age were identified as predictors of NAFLD in adults (2) whereas race and ethnicity, male gender, obesity and insulin resistance may be predictors of NAFLD in children and adolescents (49,50). The spectrum of NAFLD varies from hepatic steatosis (HS), which is believed to be benign and non-progressive, to non-alcoholic steatohepatitis (NASH), which is severer and potentially progressive and involves liver inflammation, hepatocellular injury and fibrosis. There is a strong association between HS and obesity, metabolic syndrome, insulin resistance and diabetes mellitus 2, which are all related to vitamin D deficiency or insufficiency (51).

Vitamin D may induce CYP3A4, an enzyme essential to bile acid catabolism, indicating potential involvement in lipid absorption. It can hence be speculated that VDD may exacerbate NASH in part through the insufficient down-regulation of bile acid bioavailability (52).

VDD is often found in patients suffering from chronic liver disease, and active vitamin D can suppress the activation of hepatic stellate cells in vitro and toxin-induced cirrhosis in animals. However, it is not yet clear what values of vitamin D insufficiency or deficiency may go beyond their traditional functions (53).

According to Fraser et al. (54) American adolescents with obesity and related diseases are at a higher risk of developing HS and a higher BMI is an independent predictor of VDD. A study done of children found lower levels of 25(OH)D in those with biopsy-proven NAFLD; it is likely the initial hydroxylation of vitamin D, which occurs in the liver, may decrease when there is pre-existing liver damage, instead of the low vitamin D concentrations causing the liver disease (55).

Attention required age of adolescents and the progressive nature of steatosis liver, in which changes are related much later appearance, and also highlight the multifactorial nature of the pathogenesis of hepatic steatosis.

## VITAMIN D DEFICIENCY AND CARDIOVASCULAR DISEASE

Obesity during adolescence is related to major changes in glucose and lipid metabolism, which may contribute to the development of early atherosclerosis lesions and a higher rate of morbidity and mortality during adulthood due to VDD (56). VDD has been linked to the pathogenesis of IR (57), T2DM (58), SH (59), dyslipidemia (60) and CVD (61). VDRs are found throughout the length of the body and in a number of different types of cells within the cardiovascular system. The vitamin D receptors are found in vascular smooth muscle, endothelium, and cardiomyocytes (14).

It is estimated that 200 genes that are directly or indirectly regulated by 1,25 dihydroxyvitamin D (1,25(OH)<sub>2</sub>D) possess a wide range of biological actions, including inhibition of cell proliferation and induction of terminal differentiation; inhibition of angiogenesis; stimulation of insulin production; induction of apop-

toxis; inhibition of renin production; and stimulation of cathelicidin production (62). According to the experimental studies, some of the protection vitamin D provides blood vessels may be mediated through increased nitric oxide (NO), inhibiting the formation of macrophage foam cells or decrease in the expression of in endothelial-cell adhesion molecules (4). This evidence is supported by observational studies showing that low serum vitamin D concentrations are associated with endothelial dysfunction and increased arterial stiffening (16,63,64).

A randomized clinical trial conducted by Dong et al. (64) found that after 16 weeks adolescents given 400 IU/day of vitamin D<sub>3</sub> saw a serum 25(OH)D increase from 13.6 ± 4.2 ng/ml to 23.9 ± 7.2 ng/ml (mean ± SD) and no decrease in arterial stiffness. In contrast, adolescents taking 2000 IU/day of vitamin D<sub>3</sub> saw a serum 25(OH)D increase from 13.2 ± 3.4 ng/ml to 34.2 ± 12.1 ng/ml (mean ± SD) and a significant reduction in the arterial wall.

A study by Atabek et al. (65) found a prevalence of VDD of 46.6% in obese children and adolescents, and low vitamin D levels were associated to the increase in intima-media thickness ( $p = 0,03$ ) and the metabolic syndrome ( $p = 0,04$ ). Oliveira et al. (19) in cross-sectional study found vitamin D insufficiency in 70.6% of 160 15- to 17-year-olds. The serum 25(OH)D levels were significantly lower in the teenagers with such CVD risk factors as overweight, abdominal obesity, hypercholesterolemia, insulin resistance, hyperinsulinemia, hypertension, and elevated serum PTH concentrations ( $p < 0.05$ ). The high PTH levels, resulting from low levels of serum vitamin D, have been implicated in the impaired insulin release from pancreatic  $\beta$ -cells, and alterations in lipid profile have been associated with increases in PTH in obese teenagers, implying increased risk of cardiovascular morbidity (66).

Despite of cross-sectional studies and of clinical trials that evaluated 25(OH)D concentrations as a potential determinant of cardiovascular disease and T2DM, it remains uncertain whether improving vitamin D status would reduce risk of these conditions.

## VITAMIN D DEFICIENCY AND TYPE 2 DIABETES MELLITUS

The identification of 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D) receptors and the expression of 1- $\alpha$ -hydroxylase in pancreatic  $\beta$ -cells supports the possibility that vitamin D plays a role in the pathogenesis of T2DM (67), since a deficiency in it hinders insulin secretion and induces glucose intolerance (68). It has been found in the obese that during the early stages of the disease, due to insulin resistance, pancreatic  $\beta$ -cells increase insulin production and secretion as a means of compensating, while glucose tolerance remains normal. This state continues for some time, until a decline in insulin secretion and, as a consequence, a decrease in glucose tolerance can be observed. Thus, the increase in endogenous glucose production takes place in the later stages of the development of T2DM (69).

The 1,25(OH)<sub>2</sub>D plays an important role in glucose homeostasis by way of a number of mechanisms. It not only enhances insulin

sensitivity in target cells (liver, skeletal muscle and adipose tissue), but also enhances and improves the function of the  $\beta$ -cells. Furthermore, 1,25(OH)<sub>2</sub>D protects  $\beta$ -cells from harmful immune attacks, directly through its effect on  $\beta$ -cells, but also indirectly by acting on a number of immune and inflammatory cells, including macrophages, dendritic cells and a variety of T cells (70).

Vitamin D may have anti-inflammatory and immunomodulatory effects and exert influence on, for example, the autoimmune condition type 1 diabetes mellitus (T1DM) and alleviate the chronic inflammation so often seen in insulin resistance in T2DM patients (71). Vitamin D may also have a beneficial effect on the action of insulin, either directly, by stimulating the expression of insulin receptors and thereby improving insulin responsiveness to glucose transport, or indirectly, through its role in the regulation of extracellular calcium and ensuring the influx of calcium through the cell membrane and a suitable pool of cytosolic intracellular calcium, as calcium is essential for the intracellular processes mediated by insulin in such insulin-responsive tissues as skeletal muscles and in adipose tissue (72).

In recent years there has been an increase in the prevalence of T1DM in children and adolescents. It hence must be pointed out that T2DM has contributed more than 30% of new cases of diabetes, showing a possible relationship between the rising rate of childhood obesity and the development of this disease (13).

Serum 25(OH)D concentrations of 15 ng/mL have been suggested as the threshold for the adverse effects of VDD on insulin sensitivity in obese African-Americans adolescents. This underscores the role vitamin D plays in promoting the proper pancreatic  $\beta$ -cell function and appropriate peripheral insulin sensitivity and therefore a possible role in the prevention of T2DM (17). Kumar et al. (13) in a representative sample of 1- to 21-year-old children and adolescents with NAFLD ( $n = 6275$ ), found that those with vitamin D deficiency or insufficiency showed a 2.5 times higher risk of high blood glucose, which may precede T2DM, and four times greater risk of developing metabolic syndrome (13).

In a randomized, double-blind, placebo-controlled study involving 35 obese adolescents VDD sufferers (25(OH)D  $19.6 \pm 7.1$  ng/mL) receiving vitamin D<sub>3</sub> supplementation (4000 IU/day) or placebo, what was found after six months was that patients given supplementation showed an increase in serum 25(OH)D levels (19.5 ng/mL as opposed to 2.5 ng/mL in the placebo group;  $p = 0.001$ ), fasting insulin (26.5 compared to 1.2  $\mu$ m/ml in the placebo group;  $p = 0.026$ ), HOMA-IR (21.36 compared to 0.27 in the placebo group;  $p = 0.033$ ), and the leptin-adiponectin ratio (21.41 compared to 0.10 in the placebo group;  $p = 0.045$ ). The authors concluded that the correction of vitamin D inadequacy through supplementation may be an effective adjunct in standard treatments for obesity combined with insulin resistance (40).

However, despite these associations found between serum vitamin D and glucose concentrations, a meta-analysis conducted by George et al. (71) suggests that there is not enough evidence to recommend vitamin D supplementation as a means of improving glycemia or insulin resistance in diabetic patients with impaired glucose tolerance or normal blood sugar. And according to Javed et al. (73) study double-blind, randomized

determined the effect of 2 doses of cholecalciferol (vitamin D<sub>3</sub>) supplementation on insulin action (Si) and pancreatic  $\beta$ -cell function in obese adolescents (body mass index > 95 (th) percentile). The subjects were randomly assigned to receive either 400 IU/d ( $n = 25$ ) or 2000 IU/d ( $n = 26$ ) of vitamin D<sub>3</sub>. There was no correlation between 25(OH)D concentrations and Si or DI. There was a modest but significant increase in 25(OH)D concentration in the 2000 IU/d group ( $3.1 \pm 6.5$   $\mu$ g/L,  $p = 0.04$ ) but not in the 400 IU/d group ( $p = 0.39$ ). There was no change in Si or DI following vitamin D<sub>3</sub> supplementation in either of the treatment groups (all  $p > 0.10$ ). The current study shows no effect from vitamin D<sub>3</sub> supplementation, irrespective of its dose, on  $\beta$ -cell function or insulin action in obese nondiabetic adolescents with relatively good vitamin D status. Whether obese adolescents with vitamin D deficiency and impaired glucose metabolism would respond differently to vitamin D<sub>3</sub> supplementation remains unclear and warrants further studies.

## VITAMIN D DEFICIENCY AND SYSTEMIC HYPERTENSION

The VDD has been associated with higher blood pressure in some studies involving adults and adolescents (13,18,74-77), but not all, according to Snijder et al. (79) serum 25(OH)D was not significantly associated with diastolic (beta 0.00,  $p = 0.98$ ) or systolic (beta 0.06,  $p = 0.11$ ) blood pressure. Although the effects of vitamin D on blood pressure have been known for several decades, some physiological aspects on the modulation of vascular cells still need further clarification. Possible mechanisms linking vitamin D with high blood pressure include the effect improving endothelial function; the inverse association of vitamin D concentrations with the activity of the renin-angiotensin-aldosterone system; and the prevention of secondary hyperparathyroidism by suppressing PTH (13,79). It is known that PTH is an indicator of VDD and has been linked to high blood pressure (79). Snijder et al. (79) conducted a cross-sectional study with 1205 adults at LASA (Longitudinal Aging Study Amsterdam) and found a correlation between PTH and systolic and diastolic blood pressure and the incidence of hypertension.

Pittas et al. (74) included results from four longitudinal observational cohorts with 32,181 patients and a follow-up of 7-10 years. The overall analysis showed that those with vitamin D deficiency were at greater risk of developing hypertension (RR = 1.76; IC 95%: 1.27- 2.44,  $p < 0.05$ ).

Kunutsor et al. (75) conducted a meta-analysis of 11 prospective studies published between 2005 and 2012, with a total of 283,537 participants and 55,816 cases of hypertension and a mean follow-up of nine years, and assessed the association of baseline vitamin D with the risk of developing hypertension. The authors reported a significant inverse association between baseline serum vitamin D and risk of hypertension. In evaluating dose response in five studies reporting the relative risk for vitamin D exposure, the authors found that the risk of hypertension lowered by 12% with every 10 ng/ml increase in 25(OH)D.

Despite the lesser number of studies in the pediatric population, some research has turned up findings similar to those of adults. Kumar et al. (13) found, in a representative sample of one- to 21-years-olds from NHANES (n = 6275), an association between 25(OH)D deficiency (chosen cutoff < 15 ng/mL) and high systolic blood pressure, and those with VDD were found to have at 2.4 times greater risk of developing hypertension.

Ganji et al. (76) studied 5,867 adolescents aged 12-19 years through three cycles at NHANES (2001-2002; 2003-2004, and 2005-2006) and found an inverse association between serum 25(OH)D and systolic blood pressure. These data are in line with those found by William et al. (2011), who in a cross-sectional study involving 5,617 adolescents at NHANES (2003-2006) found an inverse linear association between 25(OH)D and systolic BP in their multivariate analysis ( $p < 0.01$ ).

Parikh et al. (77), leading a clinical trial involving 701 American adolescents of both sexes aged 14 to 18, found that the concentrations of 25(OH)D correlated significantly with systolic ( $r = -0.10$ ,  $p = 0.02$ ) and diastolic ( $r = -0.21$ ,  $p < 0.01$ ) blood pressure. Multivariate linear regression analyses were conducted to examine the contributions of plasma 25(OH)D concentrations to BP. After multivariable adjustment, 25(OH)D concentrations significantly explained the variances in systolic BP ( $R^2 = 0.012$ ,  $p = 0.04$ ), and diastolic BP ( $R^2 = 0.055$ ,  $p < 0.01$ ). The authors conclude that 25(OH)D concentrations are linked with a number of adverse cardiometabolic risk factors in adolescents, regardless of adiposity.

Kao et al. (78) conducted a retrospective cross-sectional study with 229 children and adolescents (age 3-18 years) attending at the two major paediatric hospitals in Melbourne, Australia. Lower serum 25(OH)D levels were associated with systolic ( $p$ -trend = 0.03) and diastolic blood pressures ( $p$ -trend = 0.009). In multivariable-adjusted regression analysis, 25(OH)D was significantly lower in those with elevated blood pressure after adjustment for BMI ( $p$ -trend = 0.004) or total fat mass ( $p$ -trend = 0.01).

## VITAMIN D DEFICIENCY AND DYSLIPIDEMIA

Vitamin D can directly affect the serum lipid concentrations, since vitamin D is considered essential for maintaining adequate levels of apolipoprotein AI, a major component in the lipoprotein of HDL-C (80). A study involving 217 obese children and adolescents ( $12.9 \pm 5.5$  years) in the United States showed a significant association between vitamin D insufficiency and decreased HDL-C ( $p = 0.008$ ). The authors found a significant positive and independent correlation between serum 25(OH)D and apolipoprotein AI (12).

Another study showed an association between 25(OH)D concentrations and hypertriglyceridemia, as well as an association between serum 25(OH)D and dyslipidemia, after adjusting for such potential confounders as BMI. This suggests that 25(OH)D may play an important role in the lipid profile and that this association may be mediated by inflammation, since inflammation was not found when PCR was introduced as a covariate in the analysis (11).

Valle et al. (82,83) found that of the 61 obese children and adolescents they studied, 27.9% (n = 17) were hyperinsulinemic and had significantly higher plasma triglyceride concentrations and lower apolipoprotein AI concentrations than those with normal insulin levels. Vitamin D can directly affect the serum lipid concentrations, since vitamin D is considered essential for maintaining adequate levels of apolipoprotein AI, a major component in the lipoprotein of HDL-C. In said study, insulin was an independent predictor for triglycerides ( $p = 0.004$ ) and apolipoprotein AI ( $p = 0.005$ ), even after adjusting for age, BMI and waist/hip circumference ratio, showing that high insulin values have a direct influence on the lipid profile already in this age group. However, it should be recognized that the results on Vitamin D and blood lipids may be confused with the relationship between this vitamin and obesity (20).

Changes in lipid profile have been linked with elevated PTH in obese adolescents and secondary hyperparathyroidism, *i.e.*, the resulting low serum vitamin D concentrations have been implicated in the release of impaired insulin from pancreatic  $\beta$ -cells (66). Oliveira et al. (19) in a cross-sectional study found vitamin D insufficiency in 70.6% of the 160 15- to 17-years-olds he looked at, and serum 25(OH)D concentrations were statistically lower in adolescents with CVD risk factors like overweight, abdominal obesity, hypercholesterolemia, higher PTH and RI higher levels, hyperinsulinemia and hypertension ( $p < 0.05$ ).

The clinical significance of a low concentration of 25 (OH) D with or without secondary hyperparathyroidism is still largely unknown in adolescents. The DVD adolescents can be found in a more acute longstanding DVD opposition in adults with chronic PTH elevation, and it would be interesting to reflect on the fact that the normal range of laboratory for PTH probably overestimates the normal values for adolescents since it was calculated from populations included adults and elderly subjects.

## DISCUSSION

The worldwide rise in the obesity rate alongside the progressively increasing incidence of vitamin D deficiency in adolescents is alarming. This relationship of VDD with the obesity and related diseases was found in adolescents. And these data warn of possible clinical repercussions in the health of the adolescents, for essential role of vitamin D in growth and development and through the interaction of this vitamin with risk factors for the onset and worsening of some chronic diseases. This review may be significant in helping to identify adolescents at greater risk of having an inadequate vitamin D nutritional status and in supporting interventions aimed to minimize the metabolic consequences of this deficiency in this important period of nutritional demand. Vitamin D supplementation can be considered a promising measure to take with obese adolescents.

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