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PEDIATRIC OBESITY AND VITAMIN D DEFICIENCY: A CONCEPT AND UNDERSTANDING

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ABSTRACT

Pediatrics obesity is a major community health issues globally now days. The commonness of Pediatrics obesity and vitamin D deficiency has increased over in several decades. It is caused by imbalance between calories intake and calories utilized in body. One or more factors cause obesity in children that is Physical, psychological, and social health problems are caused due to childhood obesity. Effective active strategies can be used to prevent and control obesity in children which is more effective. The purpose of this paper is to address various factors influencing childhood obesity and vitamin D deficiency. It is also addressing the sources of Vitamin D, classification, Risk factors, the role of vitamin D on adipose tissue, the genetic role in vitamin D and obesity, the role of inflammation on obesity and Vitamin D status in Middle East, etc.

KEYWORDS: Child Obesity, Pediatric Obesity, Vitamin D Deficiency

INTRODUCTION SYNTHESIS OF VITAMIN D

Vitamin D or sunshine vitamin, its main and major source is obtained from the sun exposure and minor source is obtained from diet (dairy products, oil fish, meat and eggs) [1-16].

It consumed few steps to be synthesized. In the skin, UV-B wavelengths in sunlight convert 7-dehydrocholesterol to cholecalciferol (vitamin D_3), which has the ability to enter the circulation. In the liver, vitamin D_3 by the 1^{st}hydroxylation step it become 25(OH)D. In the kidney, by the 2^{nd} hydroxylation step it converted to $1,25(OH)_2D_3$ which is the bioactive form. Later on, this final active form has the ability to bind to VDRs and act through it [1-16]. VDRs are distributed throughout the body in the endocrine glands, endothelial cells, vascular smooth muscle cells, cardiomyocytes and hemolymphopoietic cells[1,17,18].

CLASSIFICATION

We can define vitamin D deficiency based on the following stratifications of 25(OH)D serum concentration[1,16,19,20,21]:

- Deficiency <50.0 nmol/L or <20.0 ng/mL
- Insufficiency = 50.0–74.9 nmol/L or 20.0–29.9 ng/mL
- Sufficiency ≥75.0 nmol/L or ≥30.0 ng/mL

We can define obesity based on the following stratificationsof BMI:

- Underweight < 18.5
- Healthy = 18.5 to 24.9
- Overweight = 25 to 29.9
- Obese ≥ 30

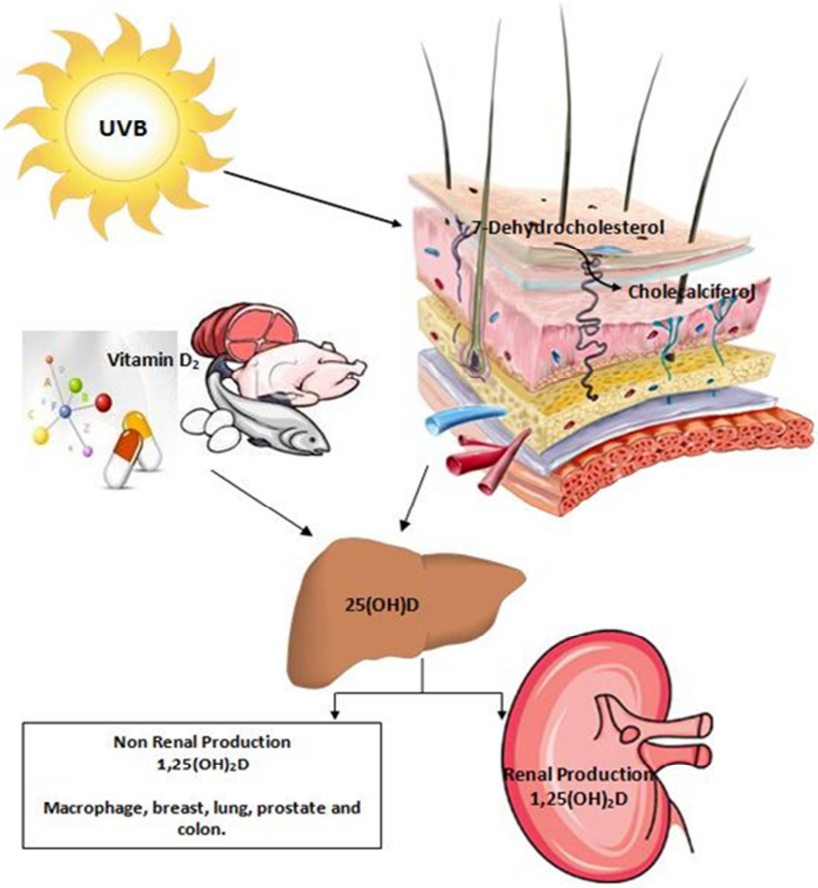


Figure: 1: Synthesis of Vitamin D

RISK FACTORS

Vitamin D deficiency is an independent risk factor for obesity in women [3-30]. In children it is associated with growth retardation and skeletal deformities. Moreover, new evidence providedan association between the levels of 25(OH)D and increasing age, obesity, reducing insulin sensitivity, hypertension, visceral obesity, hypertriglyceridemia, metabolic syndrome, immune function, respiratory diseases, infection, allergy, cancers, and cardiovascular diseases[3-32].

There is an indication signs of deviation in the endocrine system of vitamin D in obese subjects[3]:

- Increase in serum PTH.
- Increase in cAMP.
- Increase in renal tubular reabsorption of Ca.
- Increase circulating $1,25(OH)_2D_3$.

- Decrease in serum level of 25(OH)D.
- Decrease in HDL.
- Increase in triglycerides and LDL.

The risk factors that link the deficiency of vitamin D with child obese subjects: decreased sunlight exposure, season (winter), limited outdoor activity, clothes that limit cutaneous vitamin D synthesis[4-57]. Moreover, low vitamin D levels in the mother during pregnancy play a role on her child's levels and lower birth weight but higher fat mass at 4 to 6 years old child, race (non-white), age of puberty, low milk consumption, female gander[12] and some mutations in VDR [13-74].

A study done by Thomas *et al*. provided an increase in PTH levels and a decrease in 25(OH)D levels in obese subjects. Since these changes normalized after weight loss so, these changes considered as a consequences rather than a risk factors[7-80].

Low Concentration of Vitamin D in Obese Subjects Could be a Result of Deferent Mechanisms

- FTO genotype variation could affect vitamin D levels and weight gain by decreasing the insulin effect in brain tissues, affecting appetite, food choice, and dietary intake from an early age[8-67].
- Direct relationship between circulating adiponectin and vitamin D levels. Inverse relationship between the circulating adiponectin and BMI[2-25]. Furthermore, patients with insulin resistance, type 2 diabetes and cardiovascular disease have lower concentration of adiponectin[2-25].
- The relationship between BMI and serum level of 25(OH)D is inverse, each unit increase in BMIbeing associated with 1.15%lower concentration of 25(OH)D[4-54].
- Body fats acts as a reservoir for vitamin D (lipid soluble vitamin), so increasing the content of body fats will increase its sequestration, leading to decrease its bioavailability[4-55].
- Some studies has been shown that 25(OH)D was stored 33% in fat and 20% in muscle. Based on these studieswe can look at the muscles as another reservoir for vitamin D[4-56].
- In obese subjects and due to hepatic steatosis, the liver may lower the rate of 25(OH)Dsynthesis[4-58].
- High levels of leptin and IL6 (secreted by adipose tissue) may inhabit $1,25(OH)_2D_3$ synthesis[4-59].

The Role of Vitamin D on Adipose Tissue

Recently, new studies classified the adipose tissues as one of the major endocrine organs[4-60]. Divided into two types white and brown, each type has a different cell origin, structure and function[10]. The brown one are present in children only, it has an average life span of 10 years, so most of them disappears in adulthood[10]. At that time, they replaced by the white one[10]. Brown adipose tissues work as thermogenesis[4], while the white adipose tissues serve mainly as energy reserves, secrete hormones, mechanical protection and insulation to the body[10].

In response to high body weight there will be an increase in both fat mass and lean body mass (subtracting body fat weight from total body weight)[11]. That is how we explain the increase in fat mass; the adipose tissues are structurally plastic, so they have the ability to expand and become larger in size and number[4-61].

Some studies have shown that vitamin D has no direct effect on body weight, but it may have an effect on the fat mass and its distribution. This effect was seen only in subjects with 25(OH)D levels less than 50.0 nmol/L[4,62,63] .

The Genetic Role in Vitamin D and Obesity

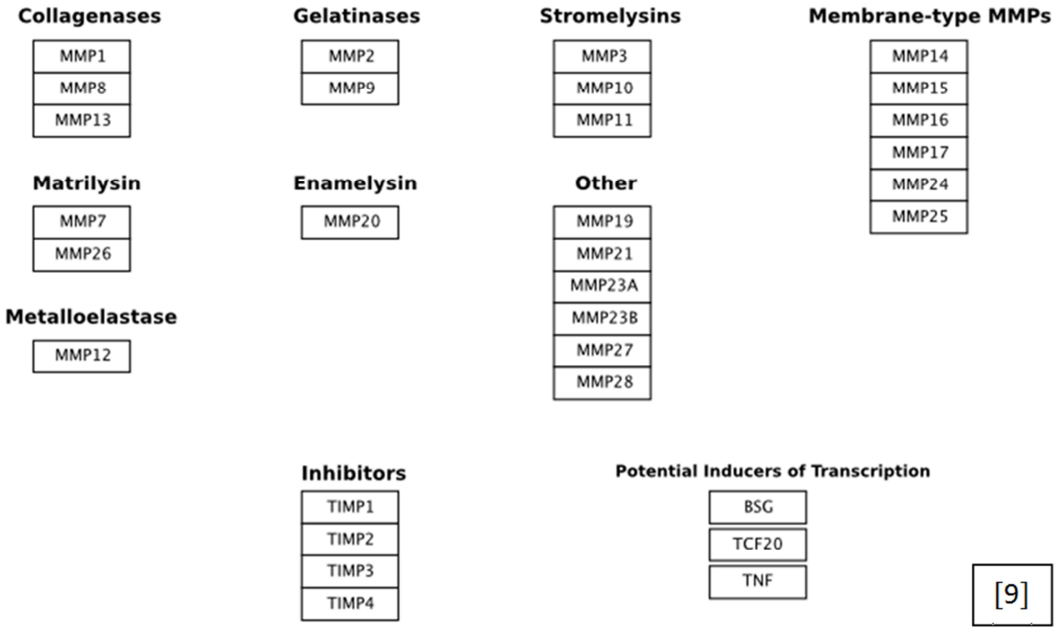
A study in Brazilian Amazon area, was found a significant relationship between an A allele of FTO rs9939609 and being obese during childhood. However, the study provided a pivotal role of vitamin D levels on altering the genotype effects on BMI. Deficient children presented larger increases in BMI for each A allele compared with normal children[8]. The variation at the FTO locus affects BMI in childhood by accelerating adiposity rebound and fat mass deposits[8-68], which may play a role in metabolic disease risk[8-69]. Taken together, we detect an important interaction between FTO and vitamin D levels in relation to childhood obesity, but the mechanisms of this interaction still remain unclear[8]. Furthermore, FTO gene is expressed in the human brain, and there is evidence of a relation between its risk allele and decreased cerebrocortical insulin sensitivity[8-70]. Some studies have mentioned a functional role for insulin in the regulation of energy homeostasis and body weight in the CNS[8-71]. Subsequently, a possible mechanism for the association between FTO genotype and vitamin D levels may involve insulin action at a central level[8,72,73].

The Role of Adiponectin on Vitamin D and Obesity

Adiponectin is a protein produced by adipose tissues and secreted to adipocytes[2-29]. It is located within one of the susceptibility gene loci for obesity[2-24]. Clinical trials has been confirmed a difference in the plasma concentration of adiponectin in obese pediatric subjects between subjects with vitamin D deficiency and subjects with vitamin D sufficiency[2]. Adiponectin circulates in plasma in different forms: trimmers-(LMW), hexamers-(MMW) and hexamers-(HMW)[2-24]. HMW is identified as the most bioactive form[2-24]. The concentration of adiponectin in pediatric obese subjects with vitamin D deficiency was significantly lower than in pediatric obese subjects with vitamin D sufficiency[2]. Moreover, the greatest difference was observed in hexamers-HMW. It has been proved to have insulin sensitizing effects[2-25], regulates centrally food intake and body weight[2-26], cardioprotective[2-27], anti inflammatory and antioxidant properties[2-28], demonstrating that it has a clear clinical important role with respect to obesity and its comorbid conditions[2].

Matrix Metalloproteinases (MMPs) Enzymes

MMPs enzymes play a role in tissue remodeling, migration of leucocytes, inflammation, infection and obesity. These enzymes are produced by different cell types, including lymphocytes, granulocytes, astrocytes, activated macrophages and adipose tissue[3].



Evidence and reports provided a remarkable increase in the levels of some enzymes (MMP-2, MMP-8 and MMP-9) in obese children[3,33,34,35]. Also, it has been shown a correlation between MMP-9 and BMI[3-36]. The study that provided an increase in MMP-8 levels, it also proved a decrease in TIMP-1 levels at the same time in obese subjects more than non-obese[3-37].

MMP-2 promoter haplotype play a role in the percentage of body fat in obese children[3-38]. Functional MMP-9 gene polymorphism is strongly associated with obesity[3-39], and MMP-9 genotypes and haplotypes affect MMP-9 levels in obese subjects[3-40].

VDR-KO mice play a role in some of these enzymes (MMP-2, MMP-9 and MMP-12) by up regulating their expression, reduce body weight, lower serum lept in concentrations and it also enhance the influx of inflammatory cells andphospho-acetylation of NF-κB in lungs[3-41]. Moreover, VDR TaqI polymorphism play a role in decreasing the production of TIMP-1[3-42].1,25$(OH)_2D_3$down regulated MMP-9 levels in keratinocytes, and may reduce the harmful effects of excessive TNF-α-induced proteolytic activity, which play a role in cutaneous inflammation[3-43]. It also inhibits both the basal levels and the staphylococcus-stimulated production of MMP-9 in human blood monocytes and alveolar macrophages[3-44]. In addition, some reports provided a beneficial role of vitamin D analog in reducing the expression of MMP-2, MMP-9, VEGF and PTH-related peptide in Lewis lung carcinoma cells[3-45]. Taken together,1,25$(OH)_2D_3$ may play an important role in obesity by down regulating MMPs levels and regulating TIMPs levels[3].

The Role of Inflammation on Obesity

Inflammatory processes play apivotalrole in obesity. PGs play a role in inflammation. COXs play a role in converting the arachidonic acid into PGs. Some of PGs: PGE_2, $PGF_{2\alpha}$ PGD_2 and PGJ_2 has been reported to induce obesity by different ways,either by inducing adipogenesis or inhabiting lipolysis[3,46,47]. PGE_2 work as enhancer to lipid accumulation in hepatocytes and participated in the development of hepatic steatosis[3-50]. $PGF_{2\alpha}$ is a potent inhibitor of adipocyte differentiation[3,48,49]. COX-2 play a role in activation of PGE_2[3-51], so increase the COX-2 levels will increase the activation rate of PGE_2 which will lead to obesityand vise versa. Interestingly, there is an inverse relationship

between PGs levels and fat mass. Moreover, vitamin D may play a role in modulating the inflammatory process in obese subjects, $1,25(OH)_2D_3$and its analogs has been reported that it has a role in down regulating PGs synthesis by inhibiting selectively the activity of COX-2[3,52,53].

Vitamin D Status in Middle East

Vitamin D deficiency and its comorbid conditions are a pandemic health problem, especially in the Middle East,in particular in Saudi Arabia because of limited outdoor activities and the prevalence of wearing dark skin covering clothes for cultural and religious reasons[13-14]. As a matter of fact, 30-50% of children and adults in UAE, Australia, Turkey, India and Lebanon have been found to have vitamin D deficiency[13,75,76]. Although, Saudi Arabia is one of the sunniest countries, vitamin D deficiency has long been reported as prevalent in Saudi population[15,77,78]. A study done by Ardawi*et al*. reported an approximately 80% prevalence of vitamin D deficiency in 1172 Saudi women from the western region of Saudi Arabia[15-79].

Dosing Considerations of Vitamin D

Nowadays, new studies proved that the optimum dose of vitamin D_3 supplements is depend on body weight [4,65,66], so we suggest that obese subjects have to receive two to three times vitamin D more than non-obese to satisfy their body's vitamin D requirements[4-64].

However, if the target of vitamin D supplementation in obese was to affect one of comorbidities associated with obesity, the dose will be various for each comorbid condition [4].

CONCLUSIONS

The function of adipose tissues is not only as nutritive storage[5]. Recently, it classified as a major endocrine organ. Vitamin D is a fat soluble prohormone. It is easily stored and sequestered in adipose tissue. Also, it can be stored in muscles. The deficiency of vitamin D is common in obese subjects. Many efforts have been made in the understanding of vitamin D metabolism and functions. Interestingly, several studies provided the interrelationship between vitamin D and adipose tissue, it may both regulate and be regulated by vitaminD[6]. It is able to act via numerous genomic and non-genomic mechanisms: including protein expression, inflammation, and cellular metabolism. There is a clear relationship between FTO rs9939609 and being obese in childhood in Brazilian Amazon. Moreover, some evidence proved an association between genetic effects of FTO and vitamin D levels. Likewise, it has been proved a relationship between pediatric obesity, adiponectin and vitamin D levels. The decrease in vitamin D levels will lead to decrease in circulating adiponectin and as a result there will be an increase in the total body weight. In fact, vitamin D deficiency and its comorbid conditions are a pandemic health problem,particularly in Saudi Arabia in the western region due to their food lifestyle, limited outdoor activities and the prevalence of wearing dark skin covering clothes for cultural and religious reasons.

ABBREVIATIONS

PTH,Parathyroid hormone;cAMP,Urinary cyclic adenosine 3,5-monophosphate; $1,25(OH)_2D_3$, 1α, 25-hydroxyvitamin D_3; 25(OH)D, 25-hydroxyvitamin D_3; IL, Interleukin; VDR, Vitamin D receptor;UV-B, Ultraviolet B; BMI, Body mass index;MMPs, Matrix metalloproteinases; TIMP-1, Tissue inhibitor of metalloproteinase-1; VDR-KO, Vitamin D receptor-knock-out; PGs, Prostaglandins; COX, Cyclooxygenase;LMW, Low molecular weight; MMW, Medium molecular weight; HMW, High molecular weight; CNS, Central nervous system.

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