Biomedicine & Pharmacotherapy 153 (2022) 113285

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

A comprehensive look into the association of vitamin D levels and vitamin D receptor gene polymorphism with obesity in children

Raushanara Akter [a,1], Afrina Afrose [a,1], Shahana Sharmin [a], Rifat Rezwan [a], Md. Rashidur Rahman [b], Sharmind Neelotpol [a,*]

[a] School of Pharmacy, Brac University, 66 Mohakhali, Dhaka, Bangladesh
[b] Department of Pharmacy, Jashore University of Science and Technology, Jashore 7408, Bangladesh

ARTICLE INFO

Keywords:
Vit-D
Obesity
Children
VDR gene polymorphisms
Single nuclear polymorphisms (SNPs)

ABSTRACT

Childhood obesity accounts for several psychosocial and clinical consequences. Psychosocial consequences include lower self-esteem, social isolation, poor academic achievement, peer problems, and depression, whereas clinical consequences are cardiovascular diseases, type 2 diabetes, dyslipidemia, cancer, autoimmune diseases, girls early polycystic ovarian syndrome (PCOS), asthma, bone deformities, etc. A growing number of studies have uncovered the association of childhood obesity and its consequences with vitamin-D (vit-D) deficiency and vitamin-D receptor (VDR) gene polymorphisms such as single nucleotide polymorphisms (SNPs), e.g., *Taq*I, *Bsm*I, *Apa*I, *Fok*I, and Cdx2. Considering the impact of vit-D deficiency and VDR gene polymorphisms, identifying associated factors and risk groups linked to lower serum vit-D levels and prevention of obesity-related syndromes in children is of utmost importance. Previously published review articles mainly focused on the association of vit-D deficiency with obesity or other non-communicable diseases in children. The nature of the correlation between vit-D deficiency and VDR gene polymorphisms with obesity in children is yet to be clarified. Therefore, this review attempts to delineate the association of obesity with these two factors by identifying the molecular mechanism of the relationship.

1. Introduction

Childhood obesity is an emerging public health concern globally. In developing countries where the prevalence of childhood obesity is upsurging alarmingly [1], this disease is also approaching epidemics in many developed countries, such as several European countries, Australia, the USA, and Canada. Contributing factors of increased childhood obesity in the developing region include changes in lifestyle represented by physical inactivity, decreased outdoor activity, less exposure to sunlight, unhealthy diet, living pattern, socio-economic development, and demographic and epidemiological transition [1,2].

According to the WHO, childhood obesity is a major public health challenge for the 21st century, and it is linked to many psychosocial consequences such as lower self-esteem, social isolation, poor academic achievement, peer problems, and depression [1,3]. Obesity in children is also correlated with non-communicable diseases (NCD) such as cardiovascular diseases, Type 2 diabetes, dyslipidemia, fatty liver disease, cancer, multiple sclerosis, autoimmune diseases, girl's early polycystic ovarian syndrome (PCOS), asthma, and bone deformities [1,3–6].

Vit-D is a fat-soluble seco-steroid hormone found in the diet or synthesized in the skin when 7-dehydrocholesterol reacts with the sunlight. The biologically inactive vit-D3 is hydroxylated into active calcitriol [1,25$(OH)_2$D]. Vit-D is required for bone metabolism, maintaining calcium and phosphorus homeostasis in the body, and cell differentiation, proliferation, and hormone secretion [7]. The vit-D analogs and their structures are listed in the Fig. 1 below.

The concentration of vit-D (25-OHD) below 20, 21–29, and 30–100 ng/mL indicates a vit-D deficiency, insufficiency, and

Abbreviations: Vit-D, (Vitamin D); VDBP, (Vitamin D Binding Protein); VDR, (Vitamin D Receptor); CYP, (Cytochrome P Iso enzyme); WHO, (World Health Organization); PCOS, (Polycystic Ovarian Syndrome); NCD, (Non-Communicable Disease); UVB, (Ultraviolet B); PTH, (Parathyroid Hormone); T1D, (Type 1 Diabetes); T2D, (Type 2 Diabetes); PAR-2, (Proteinase Activated Receptor); NFAT, (Nuclear Factor of Activated T cells); VDD, (Vitamin D Deficiency); BMI, (Body Mass Index).

* Corresponding authors at: School of Pharmacy, Brac University, 66 Mohakhali, Dhaka, Bangladesh.
E-mail address: sharmind@bracu.ac.bd (S. Neelotpol).

[1] Equal Contribution

https://doi.org/10.1016/j.biopha.2022.113285
Received 26 April 2022; Received in revised form 27 May 2022; Accepted 9 June 2022
Available online 18 June 2022

sufficiency, respectively [8]. Several research have revealed that there is a strong association of vit-D deficiency with obesity. In obese children, vit-D deficiency occurs due to sequestration of vit-D by the fat tissues since vit-D is soluble in fat [6,9,10]. In addition to that, the higher vit-D storage capability of adipose tissues precludes vit-D release in sufficient quantity, which results in a vit-D deficiency in children [6]. Diseases that interfere with fat absorption and prevent vit-D metabolite activation also cause a vit-D deficiency in children [11]. Apart from this, some medications such as glucocorticoids, antiseizure drugs, antifungal drugs, fat malabsorption, and genetic factors (Vit-D receptor gene polymorphism) are linked to vit-D deficiency [6].

Studies have shown that there is a negative correlation between serum 25-OHD and body fat. Vit-D is active in the fat tissues and coupling of vit-D with the VDR exerts multiple biological functions and plays a crucial role in regulating gene expression. It has been reported that over-expression of the human VDR gene in adipocytes is linked to reduced energy expenditure and induction of obesity [7]. Previous reports have also shown that VDR variants are associated with adipocyte phenotypes, and these variations in the DNA sequence are known as polymorphisms. Several polymorphisms of the VDR gene have been identified by the restriction recognition sites such as single nucleotide polymorphisms (SNPs), e.g., *Taq*I, *Bsm*I, *Apa*I, and *Fok*I. Furthermore, VDR mRNA stability can be influenced by a poly (A) microsatellite linked to SNPs if they become functional [12]. VDR gene polymorphism has been identified as a crucial factor contributing to children's obesity in many studies previously conducted [13–16].

Childhood obesity significantly impacts psychosocial behavior and is associated with many non-communicable diseases of children. Identification of associated factors and risk groups linked to lower serum vit-D level and prevention of obesity-related syndromes of children is of utmost importance. Previously published review articles mainly emphasized the association of vit-D deficiency with obesity or other non-communicable diseases in children. The nature of the correlation of vit-D deficiency as well as VDR gene polymorphism with obesity is yet to clarify. Therefore, this review attempts to delineate the association between obesity and vit-D deficiency and VDR polymorphism identifying the fundamental molecular mechanism of the relationship.

2. Prevalence of obesity in children

Obesity in children is currently a global public health crisis, and it has been alarmingly increasing day by day. The number of children and adolescents (aged 5–19 years) who are obese is predicted to rise to 254 million by 2030, according to projections by the World Obesity Federation using data from the NCD Risk Factor Collaboration [17]. According to de Onis et al., about 35 million of 43 million obese children are from developing countries, and around 17.5 million obese children are reported to be living in Asia [18]. Childhood obesity is constantly rising in Asian countries, and this list is led by China, where childhood obesity has increased by 0.45% and 0.16% in girls and boys, respectively [19]. A recent study reported that 15% and 5% of school-aged children are obese in North America and European countries, respectively [20]. Four countries, such as Greece, the USA, Italy, and Mexico, are in the leading position in childhood obesity, topped by the USA [21]. Turer et al. in 2013 reported that obesity among children has surprisingly increased from 6.5% to 18% in North America [22]. Currently, 30% of North American children are obese [21]. The prevalence of vit-D insufficiency among children and adolescents with obesity is exceptionally high: 96.0% in Germany, 78.4% in the United States, and up to 92.0% in the Russian Federation [21]. In 2010 irrespective of sex, 17.8% of urban children were reported to be obese in Dhaka city of Bangladesh [23].

3. Vit-D synthesis, metabolism, and its biological functions

Vit-D (Calciferol) is now recognized as a prohormone and was first identified as a vitamin in the early part of the 20th century. Two main biologically inter precursors of vit-D are D2 (Ergocalciferol) and D3 (Cholecalciferol). Vit-D2 is plant-derived whereas vit-D3 is synthesized

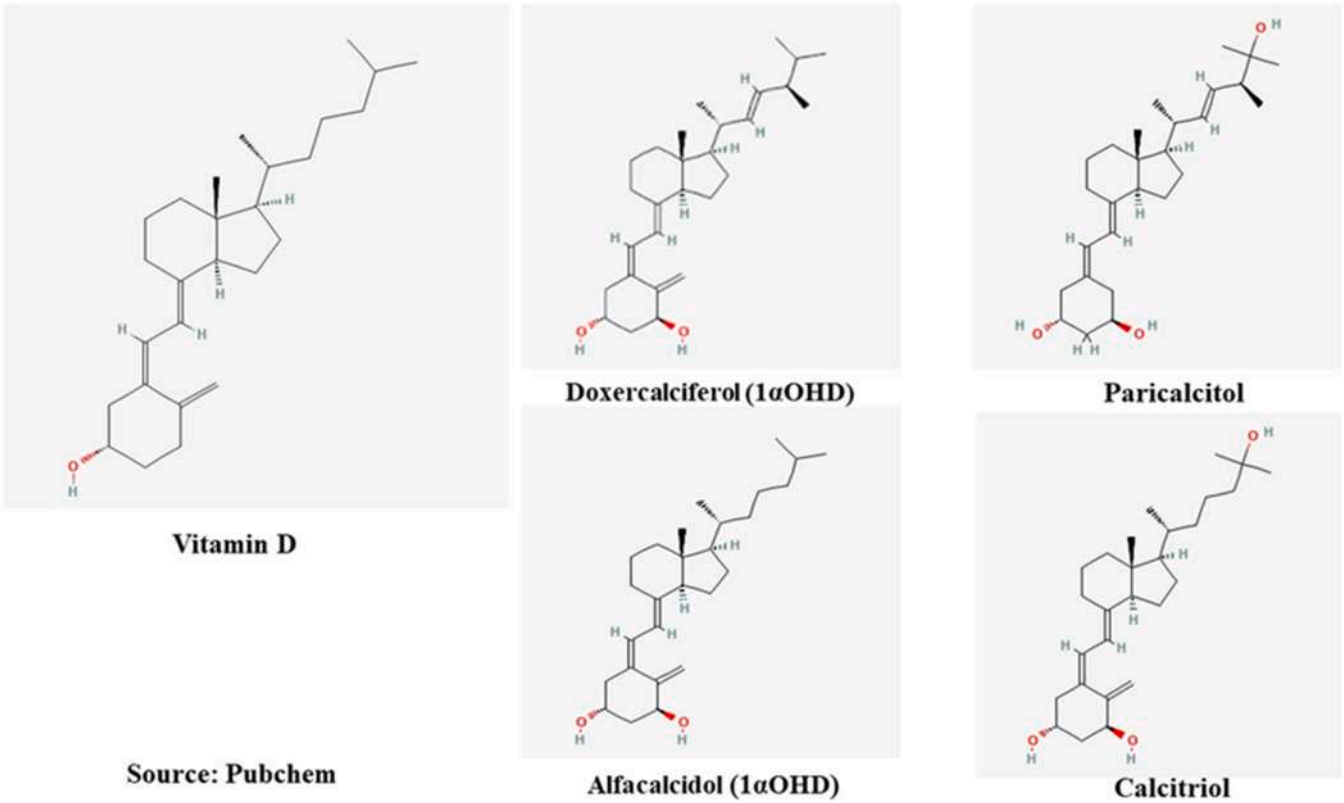

Fig. 1. Structures of vit-D and analogs.

in the skin in presence of ultraviolet B (UVB) radiation [24,25]. Vit-D3 is an essential micronutrient and a fat-soluble prohormone. It is evident that 80% of systemic vit-D3 comes from the epidermis, and the remaining 20% is obtained through diet as D2 [26]. It is photochemically synthesized in the skin from 7-hydroxycholesterol by UVB radiation on exposure to sunlight [8]. In the presence of UVB wavelengths, between 290 and 315 nm, biochemical reaction isomerizes pre-D3 to D3. However, UVB presents for a limited hour which also varies with latitude and season. Therefore, personal and environmental factors like skin pigmentation, clothes, and the use of sunscreen need to be taken into consideration to maximize the formation of pre-D3 in the body [27] (Fig. 2). After entering the systemic circulation, vit-D binds with vit-D binding protein (VDBP), and subsequently, it is converted into 25-hydroxy vitamin D3 [25(OH)D3] in the liver through the first hydroxylation. Mainly, a patient's vit-D status is determined by measuring the concentration of 25(OH)D3 in the serum [28]. However, 25(OH)D3 is biologically inactive, and it is transported via blood's VDBP to the kidney, where the second hydroxylation occurs to convert this inactive form to biologically active form 1,25-dihydroxy vitamin D3 [1, 25-$(OH)_2$D3] by the enzyme 1-α hydroxylase and is directly stimulated by parathyroid hormone (PTH) (Figure2) [28–30].

The half-life of 25(OH)D, the major circulating metabolite of vit-D, is 21–30 days [31]. Whereas the half-life of 1,25$(OH)_2$D3 is 4–15 h [32,33] and this is responsible for serum calcium and phosphate homeostasis via kidney, small intestine, and bone [34].

Vit-D plays a vital role in the human body, and it has both genomic and non-genomic functions. Vit-D binds with nuclear VDRs to influence gene transcription in more than 30 different cells, including bone, muscle, intestine, kidney, skin, lungs, etc. On the other hand, vit-D exerts non-genomic functions in the liver, parathyroid cells, pancreatic β-cells, bone, and intestine, where it works like a steroid hormone by binding with VDRs on the cell membrane through activation of signal transduction pathways [30].

Vit-D, a vital micronutrient, performs several crucial biological functions, including the growth and development of the human body [3]. It regulates bone, calcium, and phosphorus homeostasis in the body by enhancing bone resorption, increasing intestinal absorption of calcium and phosphorus, and reducing renal excretion of these two minerals, thus preventing rickets and osteomalacia [6,8]. Apart from this phosphocalcic function vit-D also plays a major role in the regulation of various physiological processes such as immune modulation, cell proliferation, and cell differentiation [35]. Stimulation of most immune cells expresses VDRs, and binding with these VDRs vit-D provides

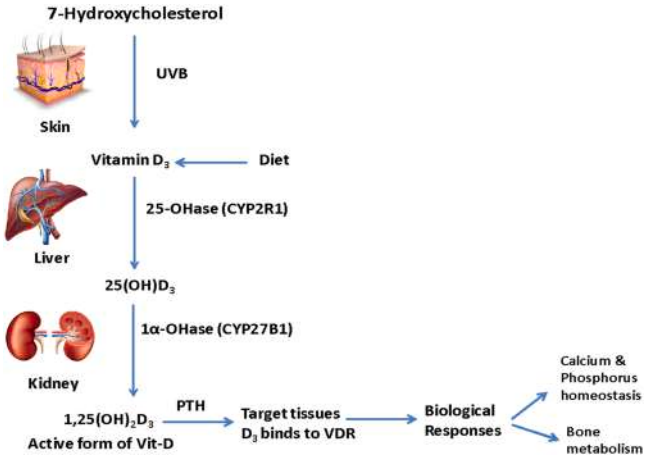

Fig. 2. Synthesis of an active form of vitamin D. Vitamin D3 is synthesized in the skin from 7-hydroxycholesterol which is further metabolized in the liver to 25(OH)D3 by 25-hydroxylase enzyme. Later on 25(OH)D3 is converted into the active form of vit-D, 1, 25(OH)2D3 by 1-α hydroxylase which binds to VDR and exerts its biological functions.

immunomodulatory function by modulating the host's immunity and regulation of inflammatory cascade [6]. Vit-D influences cell proliferation by modulating various key processes including cell cycle progression, apoptosis, and cell differentiation in a cell-specific approach. Direct binding of VDR to the response element in the genes that regulate cell growth or indirect influence on chief transcriptional regulators are involved in vit-D affected cell proliferation. In addition to that vit-D can impact cell proliferation indirectly by influencing cell signaling molecules engaged in the cell cycle, apoptosis, and differentiation [35]. Vit-D has been reported to regulate the differentiation between tumor and normal cells for example it differentiated the cultured mouse myeloid leukemia cells from macrophages; stimulated and differentiated the formation and maturation of an apical microvillus membrane in human intestinal cells (Caco-2) [36]. Experimental and epidemiological evidence revealed that vit-D has a protective effect against cancer, diabetes, hypertension, and cardiovascular diseases [6,8,30]. Vit-D exerts its protective effect against cancer by promoting apoptosis and differentiation of cancer cells or inhibiting the angiogenesis, proliferation, and metastasis of cancer cells [35].

Several studies demonstrated the beneficial effect of vit-D and its analogs on both type 1 diabetes (T1D) and type 2 diabetes (T2D). Vit-D exerts its antidiabetic effect by suppressing the apoptotic destruction of pancreatic-β cells and augmenting insulin secretion as well as IGF-1 (Insulin-like growth factor 1) [37,38]. Vit-D analog, paricalcitol significantly reduced insulin resistance and plasma glucose level through modulation of inflammatory biomarkers including TNF-α, C-peptide, pancreatic IL-2, adiponectin, catalase, and reduction of oxidative stress [35]. Studies have reported that vit-D can regulate the renin-angiotensin system (RAS) and thus, can reduce the risk for hypertension and cardiovascular diseases [39]. Vit-D and its analog exert their beneficial role in cardiovascular diseases through downregulation of prothrombotic factors such as PAR-2, thrombospondin, plasminogen activator inhibitor, etc., suppression of pro-hypertrophic myocyte-enriched calcineurin-interacting protein 1 (MCIP1/ calcineurin/nuclear factor of activated T cells (NFAT) pathway, and inhibition of cardiomyocytes proliferation, and cardiac RAS [35,37]. Previous studies have demonstrated the role of vit-D in adipogenesis which ultimately explicates the association of vit-D deficiency with obesity [16] which has been detailed in Section 6. This section (Section 3), therefore, explains the synthesis of vit-D with an illustration, its metabolism to convert its inactive form to active form and its different biological functions in brief.

4. Prevalence of vit-D deficiency/insufficiency in obese children and clinical manifestations

The overweight, obese, and severely obese pediatric populations are commonly diagnosed with hypovitaminosis, among which vit-D is one of the most significant causes. Thus, the prevalence of vit-D deficiency in obese and severely obese children has been found in a critical stage from many investigations worldwide [21,22,40–42]. Among the European region, the prevalence of vit-D insufficiency among overweight/obese children was the highest (96%) in Germany in 2011 [43]. The second in line was Iran, with 95.6% from the Asia continent in 2016 [44], and Canada from North America was leading next, with 93% in 2010 [45]. As reported in a study in Sweden, hypovitaminosis D prevalence was significantly higher in children with severe obesity (81.1%) and obesity (68.2%) compared to overweight and typically healthy children. In the case of Spanish children, a study reported the prevalence of hypovitaminosis D was 60.4% [40]; whereas another research revealed that vit-D deficiency proportion is slightly higher in pubertal children (70.8%) than the prepubertal children (62.7%) [46]. However, a recent investigation on primary school-going Spanish children showed a lower prevalence of vit-D deficiency, 31.6% (Boys 30.0% and Girls 33.3%). The variance in the prevalence results of same nationality children was due to using different standards for hypovitaminosis D range, and the samples were taken from hospitals for the former two studies [47]. In the

US, the prevalence of vit-D deficiency in severely obese white, Latino, and African-American children were 27% (3–51%), 52% (36%−68%), and 87% (81–93%), respectively [22]. In Saudi Arabia, a study conducted on school-going children of three regions revealed a prevalence of vit-D deficiency of 49.5% [41]. Another survey of Danish children showed that 16.5% of the total mass is suffering from vit-D deficiency [42]. A recent meta-analysis conducted on 41 studies and 18,233 populations for the vit-D status in the south Asian countries reported the overall prevalence of hypovitaminosis D 61% (95% CI: 46–71%). Their country-wise analysis showed the highest prevalence of vit-D deficiency in Afghanistan 96.2% (95% CI: 91–99%) and the lowest was in Sri Lanka 25% (95% CI: 16–36%). Other countries included Pakistan 94% (95% CI: 90–96%), India 64% (95% CI: 46–79%), Bangladesh 35.48% (95% CI: 32–39%) and Nepal 35% (95% CI: 1–83%) [48]. The overview of the global prevalence of vit-D deficiency in obese children is summarized in Table 1. A meta-analysis undertaken on 24,600 children and adolescents worldwide showed the relative risk for the association between obesity and vit-D deficiency was 1.41 (95% CI: 1.26−−1.59) (I 2 = 89%, $p < 0.01$) [49].

Many researchers have recently suggested that the prevalence of vit-D deficiency in obese children may have been linked with the increased risk of clinical health problems like diabetes, cardiovascular diseases, and pulmonary disorders [53–57]. They found a negative correlation of vit-D level with impaired glucose metabolism resulting from loss of β-cell function (BCF) and insulin sensitivity (IS) in non/pre-diabetic obese children and adolescents [58–60]. A systematic review reported that children deficient in vit-D are at higher risk of cardiovascular diseases from childhood [56]. Research conducted on 40 obese children showing its prevalence in obese children supported the same [61]. Saudi Arabian and Tunisian obese children were at an increased risk of metabolic syndrome with vit-D deficiency/ insufficiency [53,57]. Vit-D concentration during the neonatal period had lowered the risk of developing childhood asthma at ages 3–9 years [54]. Hence, pulmonary function compromised obese children have been diagnosed with vit-D deficiency/ insufficiency, indicating its potential to develop obese-asthma phenotype [55]. However, a recent study conducted on the cardiorespiratory fitness (CRF) of overweight and obese school-going children showed that vit-D deficiency has no relation with their body composition and CRF status [47].

The global status of VDD is alarmingly increasing in children which are leading them to critical health risk associated with abnormalities in the metabolic, cardiac and respiratory system. Therefore, this is high time to acknowledge VDD as a potential threat to the well-being of future generations.

5. Requirement of vit-D and recommended nutrient intake for children

Insufficiency of vit-D in children can lead to growth failure and rickets. The recommended daily intake of vit-D in infants, children, and adolescents is set to 400 IU by the American Academy of Pediatrics (AAP) [62], Giving 800 IU of vit-D per day to dark-skinned infants and children who live at higher altitudes is suggested. It is visible that the recommended daily intake of vit-D is not following as expected from most populations. Therefore, an unresolved question is raised: what dose of vit-D should be required in obese subjects to replete vit-D stores and maintain usual 25(OH)D levels after repletion. A randomized study of seven doses of vit-D3 (from 400 IU/d to 4800 IU/d) showed how the response to vit-D supplementations was dependent on body size. After vit-D supplementation to obese and non-obese participants, this study showed that all obese women reached adequate levels of serum 25(OH)D, but women with BMI < 25 kg/m2 reached much higher levels of 25 (OH)D with the same dose. This indicates that one particular vit-D dose is not effective for all subjects with different BMI. The dose depends on the threshold of vit-D to be achieved and body size [62–66]. Therefore, Endocrine Society guidelines suggest taking two to three times more vit-D in obese people for their age group to satisfy their body's vit-D requirement [27]. The dose of vit-D needed to suppress PTH or even the dose required to affect comorbidities associated with obesity is uncertain. Many studies suggested that, in an insufficient vit-D level, a higher dose will be needed to obtain vit-D sufficiency and PTH suppression [67].

Sources of vit-D include its synthesis in the skin from direct sunlight exposures, which can be affected by the skin color, season, and latitude of residence of the subjects or dietary supplements [27,68–71]. Hence, recommended dietary allowance (RDA) for vit-D is insufficient for children who reside in higher altitudes during winter [72]. Giving 800 IU of vit-D per day to dark-skinned infants and children who live at higher altitudes is suggested. The infant formulas' recommendation is to contain 40–100 IU of vit-D per 100 kcal of formula. Moreover, vit-D deficient infants and children can be treated with 1000–5000 IU/day of vit-D [73].

Besides dietary intakes and supplements, food fortification and biofortification strategies will add value to fulfill the RDA [74]. However, quality control of fortified food such as milk and cereals are necessary. Otherwise, it is challenging to meet the vit-D recommendations [75]. It is evident that the daily intake of vit-D for some children is different from others and requires different serum concentrations of 25-hydroxyvitamin D for optimal calcium absorption. Therefore, vit- D intakes and requirements need to be developed for diverse children's populations in the long run.

The standard recommendation for vit-D intake has varied over the last two decades due to age groups, body mass index (BMI), ethnicity, and regional altitudes. AAP first recommended at least 10 μg/ day vit- D for children of all age groups in 2008 [76]. Later, in 2010 Institute of Medicine (IOM) set the lower limit of 15 μg/ day vit- D for children older than one year [25]. The European Food Safety Authority recommended the upper limit of vit-D intake of 25 μg/day for infants, 50 μg/day for children 1–10 years, and 100 μg/ day for children 11–17 years [77]. Moreover, the vit-D supplement has been recommended for pregnant women and infants, and it has been more emphasized in recent years in Europe, specifically in Germany. However, they needed to decrease the recommendation for the older children and adolescents due to the uncertainty of the vit-D status found in randomized controlled trials [78,

Table 1
Summary of the prevalence of vit-D deficiency/insufficiency in children globally.

Prevalence of vit-D deficiency/ insufficiency in children (%)	Country (Year)	References
> 90%	Germany(2011), Iran(2016), Canada(2010), Afghanistan (2022), Pakistan(2022)	[43–45,48]
60–90%	Greece(2021), Sweden(2017), US-African-American children (2013), Spain(2020), India(2022), South Asia(2022)	[22,40, 46–48,50]
30–60%	Turkey(2016), Egypt (2021), US-White-Latino(2013), Saudi Arabia(2017), Spain(2021), Bangladesh(2022), Nepal(2022), Hangzhou(2018)	[22,40,41, 46–48, 50–52]
< 30%	Denmark(2018), Srilanka(2022)	[42,48]

79]. Even after all these recommendations, infants and children in France, the USA, and the UK could not fulfill the vit-D requirements completely. The reasons were reported for taking vit-D from food sources, discontinuation of supplements, and lack of parental education about the child's need for vit-D. Though the recommended dose of vit-D is way far lower than the dose of intoxication, some cases were reported causing vit-D toxicity at the dose of 6000–112,500 μg due to misadministration or accidental ingestion, and another case reported vit-D intoxication of a seven-month-old taking 35–40 μg/day [80]. Hence, parenteral education on dose administration is essential to avoid the risk of overdose. However, considering the potential benefits and low risks of vit-D supplementation, a 10–50 μg /day dose has been recommended to be safe for toddlers, children, and adolescents [81].

The above discussion addresses the non-uniformities in the guideline for the recommended doses of vit-D worldwide due to variables like ethnicity, BMI and geographical conditions. Thus, current researchers in this particular area of interest may focus on establishing a global standard for the recommended dose of vit-D, considering all the existing variability factors.

6. Interrelationship between vit-D levels and obesity

Many studies have shown that low serum 25(OH)D levels may lead to obesity (body mass index (BMI) $\geq$ 30 kg/m^2) [82,83]. After adjusting for age, sex, laboratory batch, and month of measurement, the study showed that each unit increase in BMI is associated with a 1.15% lower concentration of 25(OH)D [84]. The mechanism of low vit-D concentration in obesity is yet to be established, and no single straightforward tool is there by which this consequence could be explained. Several hypotheses behind the mechanism of hypovitaminosis D in obesity have been reported to date. Since vit-D is lipid-soluble, one theory is that the high content of body fat acts as a reservoir for it and increases its sequestration, thus, causing its low bioavailability [85]. Another study showed that fat content is inversely related to serum 25(OH)D concentration which is more robust than the relationship between 25(OH)D and BMI [84].

In obese people, lean body mass also increases with fat mass as an adaptative response to greater body weight. From animal studies, it has been shown that muscle could be another reservoir of vit-D in humans because fat and muscle store 33% and 20% of vit-D, respectively [86]. Other educated guesses demonstrated that obesity is associated with decreased sunlight exposure, limited outdoor activity, or clothing restricting cutaneous vit-D synthesis [87]. One hypothesis is that in obese people, the synthesis of vit-D by the liver may occur at a lower rate due to hepatic steatosis [88]. Another alternative hypothesis explained that when adipose tissue secretes higher levels of leptin and interleukin 6 (IL-6) in blood circulation, they may have inhibitory effects on vit-D synthesis via their receptors [89].

There is a relationship of vit-D with BMI, body size and fat mass. It is evident that endocrine organ-adipose tissue, the main lipid storage depot in the body, secretes various bioactive factors called adipokines [90]. Adipose tissues, derived from different cell lineages are involved in different functions such as white fat stores energy, and brown fat disperses it by utilizing lipids as fuel for thermogenesis. Because of the plastic nature of fat cells, they can expand rapidly in size and number. In obesity, adipocytes increase with high macrophage infiltration and a switch towards the pro-inflammatory phenotype [90,91]. Impairment of addition and differentiation of new adipocytes in individuals occurs with hypertrophic adipose tissue [91]. Differentiation into adipocytes is the crucial transcription factor like the nuclear receptor peroxisome proliferator-activated receptor γ (PPARγ) and the CCAAT enhancer-binding proteins (or C/EBPs) [92]. Moreover, from different studies, it has been proved that the function of adipose tissue largely depends on the function of vit-D [93].

A retrospective cross-sectional study on 229 children (3–18 years) with obesity showed a high prevalence of VDD in them. The analysis revealed that lower levels of vit-D were associated with higher BMI and fat mass. Moreover, a significantly lower level of 25(OH)D was seen in those who had elevated blood pressure [94]. The relationship between vit-D status with obesity and diabetes mellitus was explored in 117 patients in Pakistan. The study showed a statistically significant difference in vit-D status in diabetic versus nondiabetic patients. The BMI was also inversely related to the low level of vit-D [95]. Another investigation on 1660 nine-year-old Korean children resulted in similar output demonstrating low vit-D levels to be associated with obesity and metabolic syndrome [96]. Thomas et al. studied the relationship between parathyroid hormone (PTH) and vit-D in 133 obese children before and after weight loss. He found increasing PTH and decreasing vit-D levels relative to their weight status and this relation went back to normal after weight loss [97]. In North America, 217 children (2–18 years) from a weight management clinic participated in a retrospective study to review their cardio-metabolic, liver, and mental health and vit-D status in relation to obesity. They found that obese children had a high prevalence of vit-D deficiency along with an increased risk for hypertension, insulin resistance, and central obesity [98]. To evaluate the relation between vit-D and BMI, Konradsen et al. conducted a cross-sectional study on 2187 subjects divided according to BMI into five groups (<25, 25–29.9, 30–34.9, 35–39.9, and >39.9 kg/m^2). With the increasing BMI groups, there was a significant decrease in the serum 25-OH-vit D and 1,25-vit D. It was seen that the highest BMI groups (>39.9 kg/m^2) have 24% lower serum 25-OH-vit D levels and 18% lower 1,25-vit D levels than the lowest BMI group (< 25 kg/m^2). The investigation shows that vit-D level in serum is inversely related to the BMI status [99]. Henceforth, most studies on vit-D and fat tissue metabolism indicated a negative trend in their relationship, supported by cross-sectional studies on multinational children worldwide.

7. Mechanism of action of vit-D in obesity

The expression of the VDR, 25-hydroxyvitamin D 1α-hydroxylase (CYP27B1) genes, and the 24-hydroxylase enzyme have been identified in human adipocytes [100]. Some experimental data suggests that vit-D stimulates adiposity, leading to increased PTH, promoting calcium influx into adipocytes, and enhancing lipogenesis [101]. Adipocytes express 1□-hydroxylase and 24-hydroxylase enzymes which are responsible for the activation and deactivation of 25-hydroxyvitamin D (25(OH)D). Obesity might alter the activity of these enzymes which causes a reduction in serum 25(OH)D level [102]. Additionally, 1, 25-hydroxyvitamin D modulates adipogenesis through VDR-dependent inhibition of PPAR [103]. It has been suggested that parathyroid hormone (PTH) is suppressed at a lower serum 25(OH)D in obese women compared to the entire population [104]. There may be a different set-point for the calcium PTH relationship in the obese, as demonstrated in a calcium-citrate clamp that showed an exaggerated PTH response to hypocalcemia compared to normal subjects [105].

Comparing in vitro study with in vivo study, a question has arisen as to whether hypovitaminosis D may contribute to obesity or inhibit weight loss in vivo because of the complex biochemical interactions of adipose tissue with vit-D in vitro. Moreover, few studies showed that vit-D, with or without calcium, does not affect weight when 25(OH)D level was less than 50 nmol/L; however, it was not observed when 25(OH)D was above this threshold [102,104,106,107].

VDR genes are found in many target tissues for which the serum 25 (OH)D is distributed into fat, muscle, and many other tissues [108]. In terms of volumetric dilution of 25(OH)D, all these tissue compartments are increased in obesity. Though obese people receive similar sun exposure to normal-weight people and synthesize the same amount of vit-D the distribution occurs into a larger volume resulting in lower serum 25(OH)D. A similar difference was seen in case the of oral vit-D supplementation in obese and normal-weight people [65]. Thus, the mechanism of the lower level of 25(OH)D can be explained due to the larger tissue volume in obese people compared to normal-weight people.

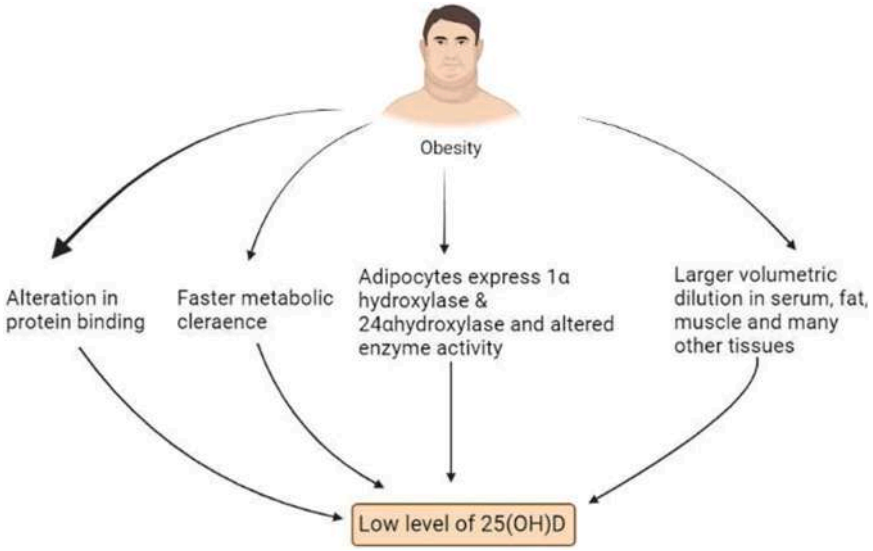

Fig. 3. Mechanism of vit-D in obesity. Obesity causes low levels of 25(OH)D due to alteration in protein binding, faster metabolic clearance, altered enzyme activity and larger volumetric distribution of vit-D in serum,fat, muscle, and all other types of tissues.

Fig. 3 shows the mechanism of vit-D in obesity.

Obesity might be responsible for the alteration of the protein binding and faster metabolic clearance of 25(OH)D which causes the lowering of the serum 25(OH)D level. The experimental evidence showed that in obese people dose-response curve of vit-D is BMI dependent and consistent with volumetric dilution. The data suggest that the dose and the body size with ~2.5 IU/kg are required for every unit increment in 25(OH)D (nanograms per milliliter). The aforementioned mechanism suggests that obesity management and treatment may contribute significantly to overcoming VDD-induced disorders in children.

8. VDR and its importance in the vit-D function

VDR is a member of a nuclear receptor superfamily, ubiquitous and very abundant in the organs [109,110]. VDR has a role in calcium metabolism, absorption of calcium and phosphate, and synthesis of calcitriol (1,25 $(OH)_2$-vit-D_3 or 1,25D) through the PTH. It also plays a vital role in the fibroblast growth factor 23 (FGF-23)/Klotho complex formation, bone turnover and mineralization, cell proliferation, and differentiation [109,111]. In the body, actions of both vit-D and synthetic analogs are mediated via their binding to the VDR. In case of disease or injury, vit-D and any of its metabolites play a compensatory mechanism [109]. Apart from calcium metabolism, the other effects of VDR ligands include antiproliferative, differentiation-inducing, and immunomodulatory effects. There are already VDR agonist drugs used for the treatment of psoriasis (calcipotriol, tacalcitol) with limited systemic absorption, and the use of VDR ligands have been suggested for the treatment of inflammatory diseases (Rheumatoid arthritis, psoriatic arthritis), dermatological conditions (Psoriasis, photoaging), osteoporosis, breast or prostate cancer and autoimmune disorders [112] (Fig. 4).

Vit-D exerts most of its biological actions through the nuclear VDR-mediated control of target genes. It acts as a ligand-inducible transcription factor and forms coactivator complexes proven to be essential for its function [111]. Fig. 4 shows the mechanism of biological action mediated by vit-D. In brief, the hormonal form of vit-D acts as a ligand for VDR. The activated VDR initiates target gene expression at the transcriptional level [113,114]. VDR forms homodimers or heterodimers with three retinoid X receptors (RXRα, RXRβ, RXRγ). Binding with specific enhancer elements, the VDR homodimer or VDR-RXR heterodimer produces vit-D response elements (VDREs) for 1α,25 $(OH)_2$D3 induced transactivation [115]. The coactivators that interact with VDR are essential for forming the initial transcription complex with

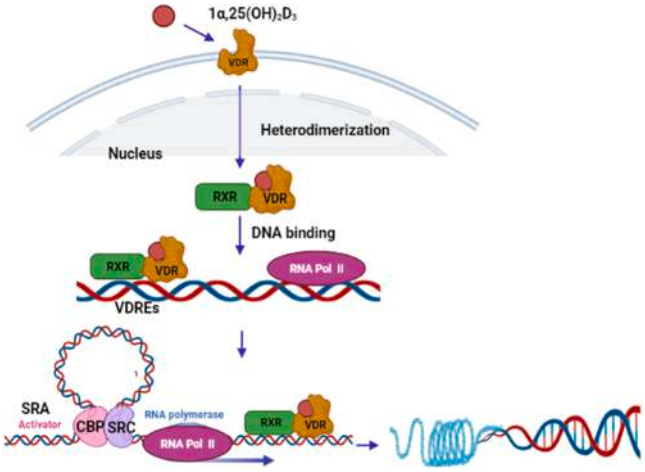

Fig. 4. The hormonal form of vitamin D acts as a ligand for the vitamin D receptor (VDR). The activated VDR forms homodimers or heterodimers with one of three retinoid X receptors (RXRα, RXRβ, RXRγ) and after binding with specific enhancer elements, the VDR homodimer or VDR-RXR heterodimer produces vitamin D response elements (VDREs) for 1α,25$(OH)_2D_3$ induced transactivation. The produced coactivators like SRA, CBP and SRA protein family that interact with VDR are essential for the formation of the initial transcription complex with RNA polymerase II.

RNA polymerase II [116]. They include the SRC-1/TIF2 160 kDa protein family, CBP/p300 protein family, SRA (an RNA coactivator), and these coactivators modulate chromatin structure to activate gene expression [117,118]. Recent findings showed that histone acetylases (HATS) like coactivators are speculated to form a DRIP/TRAP complex (which are ligand-dependent transcription activators of VDR and thyroid receptors (TR), respectively), which has no HAT activity [116,119,120]. However, corepressors; silencing mediator for retinoid and thyroid (SMRT), and nuclear receptor corepressor (NCoR) have been found to correlate with ligand-unbound TR, and all the trans-retinoic acid receptors (RAR) block their ligand-induced transactivation functions [117,121]. It is essential to highlight that these corepressors appear not to interact with ligand unbound VDR [114].

Unexpectedly, vit-D deficiency or VDR null mutant does not show lethality at the beginning. However, in the long run, this may lead to

severe diseases such as rickets with hypocalcemia, hypophosphatemia, and elevated serum levels of alkaline phosphatase (ALP). During the process of embryogenesis, there was no divergence among the VDR null mutant knock-out (KO) mice according to the heterozygous growth rate or behavior. Those mice look as usual after birth up to weaning, and the growth retardation and impaired bone formation were observed three weeks after their birth. Eventually, most of the mice died because of unknown causes. Moreover, typical features of rickets, such as alopecia and poor whiskers, were developed by the VDR null mutant mice within seven weeks. Most strikingly, in vivo studies showed that the numbers of osteoclasts do not occur by VDR inactivation [122,123]. *In vitro* studies proved that vit-D is the most potent inducer of osteoclast differentiation from precursor cells in the spleen [122,123]. Moreover, vit-D acts as a chondrocyte in bone, whereas the mineralization to form bone is an indirect effect of vit-D receptor-mediated through serum minerals. Therefore, the findings of all these studies establish that most vit-D actions are mediated through VDR.

9. Genes involved in the synthesis and metabolism of vit-D

9.1. Vit-D synthesis genes

Two essential genes are involved in the synthesis of vit-D3 (cholecalciferol) from 7-dehydrocholesterol (7-DHC) and are identified as 7-dehydrocholesterol reductase (DHCR7) and cytochrome P450 family 2 subfamily R member 1 / 25-hydroxylase (CYP2R1). DHCR7 is located on chromosome 11q13.4 and is encoded by the DHCR7 gene. 7-hydroxycholesterol (7-DHC) is the substrate for DHCR7 and a precursor of vit-D (D3). The principal function of DHCR7 is the conversion of 7-DHC to cholesterol and the synthesis of vit-D by DHCR7 in the skin, which is facilitated by UVB [124]. On the other hand, CYP2R1 is located on chromosome 11q15.2. CYP2R1 encodes the 25-hydroxylase enzyme in the liver, and this enzyme is responsible for the conversion of D3 to [25 (OH)D] which is the primary circulating form of vit-D [125].

Vit-D2 (ergocalciferol) is gained from plant sources (mushrooms and yeast), while vit-D3 (cholecalciferol) is derived from animal sources (milk, fish, eggs etc.). The existence of a double bond between C22 and C23, and a methyl group side chain at C24 makes the structure of vit-D2 (ergocalciferol) slightly different from vit-D3 (cholecalciferol) which lowers its affinity for vit-D binding proteins. Therefore vit-D2 clearance is faster than vit-D3. Consequently, vit-D2 is not capable of increasing 25 (OH)D levels in blood compared to D3 unless given daily [126].

9.2. Vit-D metabolism genes

Vit-D is metabolized in three steps (25-hydroxylation, 1α-hydroxylation, and 24-hydroxylation) carried out by different cytochrome P450 enzymes. Cytochrome P450 enzymes are mixed-function oxidases (CYPs), and CYP2R1, CYP27B1, and CYP24A1 are three key genes for the metabolism of vit-D. Among these three, however, CYP2R1 plays the most crucial role in vit-D metabolism. These essential genes are discussed below, along with a few others.

9.3. Role of most remarkable genes in 25-hydroxylation of vit-D

CYP2R1, which was first identified in the microsomal fraction of mouse liver [127], has the most crucial role in 25-hydroxylating D2 and D3 with equivalent kinetics converting them to 25(OH)D, which is circulating in plasma. Although this enzyme is mainly expressed in the liver, it is also expressed in the testes. CYP2R1 is stored in the endoplasmic reticulum. This enzyme is also expressed both in visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) [125]. CYP27A1 is another vital enzyme that plays a significant role in metabolizing vit- D [128]. It is the only mitochondrial 25-hydroxylase enzyme and is expressed in SAT and VAT all over the body. Some other 25-hydroxylation enzymes include CYP3A4, CYP2J2, CYP2D25 and CY2C11. CYP3A4, expressed in the liver and intestine, is a major drug-metabolizing enzyme [129,130]. It has a preference to hydroxylate 1αOHD over 25(OH)D. Alternatively, CYP2J2, located primarily in the heart, has decreased 25-hydroxylase activity [131]. However, its CYP2J3 homolog, expressed in the rat liver, has much better 25-hydroxylase properties. CYP2D25, initially isolated from pig liver and kidney, is also a 25-hydroxylase enzyme [132]. CYP2D25 found in the human body does not have a significant role in 25-hydroxylation [133]. CYP2C11, on the other hand, is expressed in the liver of male rats. This enzyme has a 25-hydroxylase activity for both Vit-D3 and Vit-D2 and the 1αOHD analogs, besides having 25-hydroxylase activity for testosterone [134] (Fig. 5).

9.4. Role of the vital genes in 1α-hydroxylation of vit-D

CYP27B1 is the recognized enzyme with 1α-hydroxylase activity for 25-hydroxyvitamin D3 [135]. Regulation of CYP27B1 can be both renal and extrarenal. However, extrarenal regulation of CYP27B1 differs from renal CYP27B1 regulation [136]. Regulation of 1α-hydroxylase is tightly controlled by parathyroid hormone (PTH), fibroblast growth factor 23 (FGF23), and 1,25(OH)2D itself. PTH stimulates the expression of CYP27B1 while fibroblast growth factor 23 (FGF23) and 1,25(OH)2D inhibits CYP27B1 in kidney cells. Elevated calcium and phosphate ions can indirectly inhibit CYP27B1 by suppressing PTH and stimulating FGF23 subsequently. 1,25(OH)2D also functions similarly, limiting CYP27B1 activity by inhibiting PTH and increasing FGF23 production as well as reducing 1,25(OH)2D levels by inducing the catalytic enzyme CYP24A1. 1,25(OH)2D3 also directly inhibits CYP27B1 expression in the kidney through a complex mechanism involving VDR and a vit-D inhibitory receptor (VDIR) that brings both histone deacetylases (HDACs) and DNA methyltransferases to the promoter of CYP27B1 inhibiting its transcription.

Tumor necrosis factor-a (TNF-a) and interferon g (IFN-g) are potent inducers of CYP27B1 activity in the keratinocyte [137,138]. IFN and other cytokines including TNF, interleukin-1 (IL-1), and IL-2 have stimulating effects on the production of 1,25(OH)2D through JAK/-STAT, p38 MAPK, and NFkB pathways [139–141].

9.5. Role of CYP24A1 in 24-hydroxylation of vit-D

The component of cytochrome P450, CYP24A1 catalyzes the conversion of both 25-(OH) D3 and 1,25-(OH)2D3 into 24-hydroxylated products, which further helps to degrade the vitamin D molecule [142]. CYP24A1, the only 24-hydroxylase reported having had both 24-hydroxylase and 23-hydroxylase activities in vit-D metabolism [143, 144]. However, the ratio between these activities is species-dependent [142]. Both 23-hydroxylase and 24-hydroxylase activities can be observed in humans [145]. Mutation of ala 326 to gly 326 in the human CYP24A1 shifts the profile from favoring 24-hydroxylation to 23-hydroxylation [146].

Regulation of CYP24A1 can be related to CYP27B1, especially in the kidney. The expression of CYP24A1 is strongly induced by 1,25(OH)2D, which can also serve as a marker of 1,25(OH)2D response. 50–70 kb downstream of the human CYP24A1 gene binds with H4 acetylases and RNA polymerase II. This complex is a mediator in 1,25(OH)2D induction of CYP24A1 [147].

PTH can partially inhibit the induction of CYP24A1 by 1,25(OH)2D by the deterioration of the CYP24A1 mRNA through the cAMP/PKA pathway [148,149]. However, induction of CYP24A1 is carried out through the same path in osteoblasts by PTH, which suggests that metabolizing enzymes of vit-D might be cell-specific. Although the mechanism is not well defined, CYP24A1 expression in the kidney can be elevated by FGF23 [150]. Some malignancies can also increase CYP24A1 expression [151].

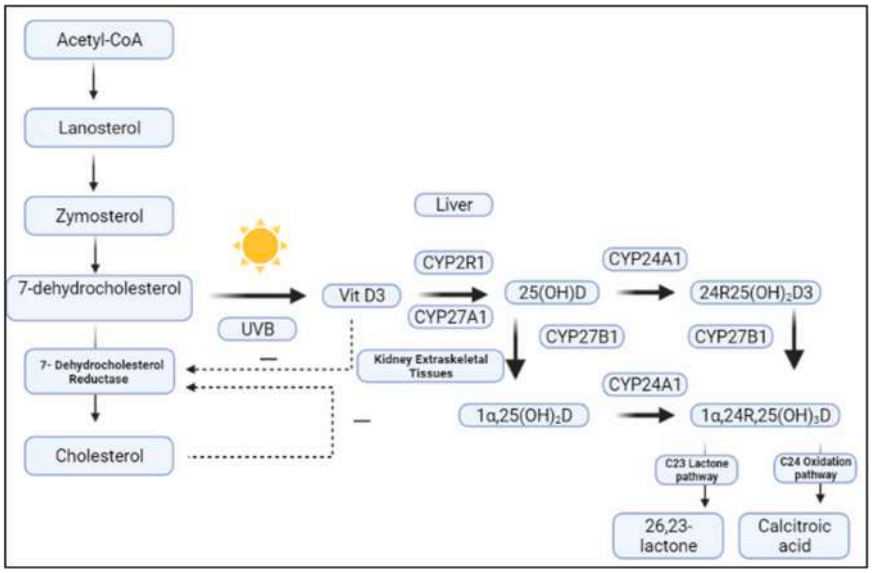

Fig. 5. Role of most remarkable *genes in 25-hydroxylation of vit-D metabolism.* Vit-D is metabolized in three steps (25-hydroxylation, 1α-hydroxylation and 24-hydroxylation) carried out by different cytochrome P450 enzymes. Cytochrome P450 enzymes are mixed-function oxidases (CYPs), and CYP2R1, CYP27B1 and CYP24A1 are three key genes for the metabolism of vit-D. Among these three, however, CYP2R1 plays the most crucial role in vit-D metabolism.

9.6. Role of CYP11A1 in 20-hydroxylation of vit-D

This enzyme carries out 20-hydroxylation of vit-D, especially in keratinocytes. This process serves as an alternate pathway for the metabolism of vit-D. This enzyme also can cleave side chains which is essential for steroidogenesis [152]. It is important to note that it produces 20(OH)D3, 20,23(OH)2D3, 20,22(OH)2D3, 17,20(OH)2D3, and 17,20,23(OH)3D3 metabolites but does not act on 25(OH)D3 [153].

9.7. Role of 3-epimerase in the isomerization of vit-D

Isomerization of vit-D by 3-epimerase was identified in keratinocytes, colon cancer cells (Caco2), parathyroid cells, osteoblasts, and hepatocyte-derived cells (HepG2), but not in kidney cells [126,154]. This gene carries out the isomerization of the C-3 hydroxyl group by changing the A ring from α to β orientation, producing 3-epi-25-hydroxyvitamin D3 (3-epi-25(OH)D3), which is the most abundant form in all-natural vit-D metabolites [154]. However, it is unclear whether this one product is involved since this gene has not been purified or sequenced yet. Interestingly, this process does not restrict CYP24A1 and CYP27B1 in any way [126].

9.8. Role of DBP/GC in the transportation of vit-D

Group-specific component globulin (GC) or vitamin D binding protein (DBD) is a protein that can bind with vit- D and transport it to the target site [155]. A study has been conducted to find out the association between GC genetic variants and serum 25-OHD3 levels. They have found a significant correlation among Chinese Han ethnic groups [156]. On the other hand, DBD transports circulating vit-min D metabolites, which is an essential physiological function [157].

10. Polymorphism of vit-D receptor gene and its consequences

Biological functions of vit-D are mediated through a high-affinity VDR acting as a ligand-activated transcription factor. VDR controls gene transcription via ligand binding, heterodimerization with retinoid X receptor (RXR), binding of the heterodimer to vit-D response elements (VDREs), and recruitment of other nuclear proteins into the transcriptional preinitiation complex. Therefore, genetic alterations in the VDR gene could direct to crucial defects in gene activation and affect cell proliferation, differentiation, calcium metabolism, immune function, etc. [158].

The VDR gene is located on chromosome 12q12–q14 and consists of eleven exons. The 5′ non-coding end of the gene consists of regions of exons 1a, 1b, and 1c [124,159]. The VDR protein is encoded by exons II to IX, with exons VII to IX involved in the binding of VDR to its ligand vit-D [160]. The polymorphisms in the VDR gene are more subtle sequence variations that have been reported to occur more frequently and alter the function of vit-D to varying rates and extents [158]. For instance, alterations in the intron region (non-coding parts of the gene) can affect gene expression along with the stability of mRNA and protein translation efficiency [161,162]. Conversely, alterations in the exonic segment of the DNA can introduce variations in the protein sequence [158]. Synonymous polymorphisms of the VDR gene also occur due to alterations in exonic sequences of the DNA, which do not change protein structure but create or abolish sites for restriction enzymes to cut the DNA. These polymorphisms are termed restriction fragment length polymorphisms (RFLPs) because digestion with the enzyme produces DNA fragments of a different length which can be detected by electrophoresis [158].

The discovery of genetic variants linked with the susceptibility of diseases can be the key to advances in preventive medicine. VDR gene is highly polymorphic with many single nucleotide polymorphisms (SNPs). To date above 200 polymorphisms of the VDR gene have been identified and the most vital polymorphisms have been recognized as *Bsm*I (G>A, rs1544410), *Apa*I (C>A, rs7975232), *Taq*I (T > C, rs731236), *Fok*I (C>T, rs10735810) [166]. All these polymorphisms are mainly RFLPs. The other major types of VDR gene polymorphisms have been detected as *Tru*9I (G>A, rs757343), and *Eco*RV. *Apa*I, *Bsm*I, and *Taq*I polymorphisms can change the binding pattern of VDR with vit-D or its analogs and related signaling pathways [158,160]. *Fok*I and Cdx2 polymorphisms are also reported to alter some physiological functions of vit-D [124]. All these SNPs have been reported to be associated with the increased risk of developing obesity and other metabolic diseases, rickets, osteoarthritis, nephrolithiasis, cardiovascular diseases, cancers, etc. [158] (Fig. 6).

To explore the connection between VDR gene polymorphism with obesity and inflammasome activity in Saudi individuals, three allelic variations of the VDR gene such as *Bsm*I, *Apa*I, and *Taq*I were examined,

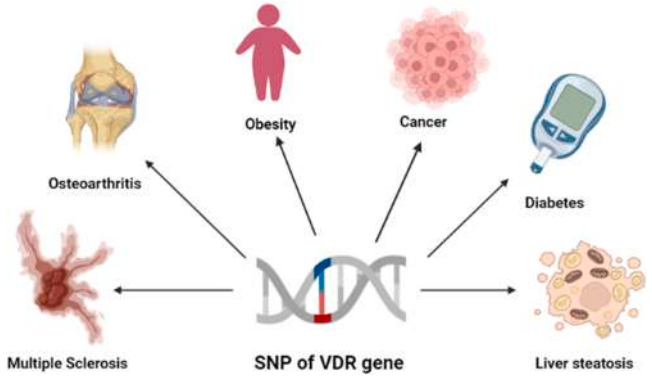

Fig. 6. Consequences of VDR gene polymorphisms. All the SNPs have been reported to increase the risk of developing obesity and other metabolic diseases, rickets, osteoarthritis, nephrolithiasis, cardiovascular diseases, cancers, etc.

and the findings suggested that *Taq*I (G) and *Bsm*I (T) minor allele were more frequent in obese individuals than the non-obese subjects. GTA haplotypes were positively associated with obesity and higher BMI as well as with a reduced VDR expression, higher production of pro-inflammatory cytokines, and up-regulation of inflammasome components. A significant correlation between VDR gene polymorphisms (*Fok*I, *Bsm*I, *Taq*I, and *Apa*I) and urinary tract infection in Iranian children has been reported where the frequency of Bb, bb, Aa, and aa genotypes and the b and a alleles were significantly higher in the case group compared to the healthy group ($P < 0.005$). That indicated a strong correlation of *Apa*I and *Bsm*I SNPs of the VDR gene with UTI in Iranian children [163].

A study was conducted on Nigerian children with rickets to determine whether VDR polymorphism contributes to rickets and the findings demonstrated that the ff genotype in rachitic children was less compared to the community group and the FF genotype was comparatively increased with a 17% f allele increase in rachitic children and a 26% f allele increase in community children [164]. A significant link between *Fok*I polymorphism and low bone mass has been observed in Japanese women, pre-and post-menopausal American women, osteoporosis in postmenopausal Iranian women. In addition, Caucasian postmenopausal osteoporotic women who were at risk of bone mineral density (BMD) in the femoral neck were reported to carry the *Apa*I aa allele whereas women with the low femoral neck carried the *Fok*I Ff allele. This indicates different impacts of different VDR gene polymorphisms on osteoporosis risk and BMD in postmenopausal women [165].

An association of a wide variety of physiological and pathological phenotypes such as changes in body weight, insulin sensitivity, and susceptibility to type 1 or type 2 diabetes in many populations with frequent polymorphisms of the VDR gene has been reported [166]. VDR gene allelic variations have been reported to impact insulin secretion and thus, four SNPs; *Bsm*I, *Apa*I, *Tru*9I, and *Taq*I of the VDR gene were examined in French subjects with T2DM. The results of the study concluded that patients with early-onset T2DM are susceptible to VDR gene polymorphisms [167]. In another study, 50 Egyptian patients with T2DM were investigated to detect any association between VDR gene polymorphism with T2DM, its embolic parameters, and glycemic control. Among three SNPs (*Fok*I, *Bsm*I, and *Taq*I) studied only VDR *Fok*I gene polymorphism was reported to have an association with susceptibility to T2DM in Egyptian patients [168].

A previous study conducted in a cohort of UK children reported that the VDR gene particularly rs2228570 polymorphism was independently associated with liver steatosis in children with non-alcoholic fatty liver [169]. Since multiple sclerosis in adults is the most prevalent autoimmune inflammatory disorder of the CNS a study was carried out on young Mexican adults with MS to find any association between VDR gene polymorphisms and MS. The study findings demonstrated a positive correlation of the SNP *Taq*I and *Bsm*I with MS in the study population [170].

Accumulating research pieces of evidence demonstrated a considerable association between VDR gene polymorphisms and several cancers such as breast, prostate, colorectal, and skin cancers. For instance, *Apa*I, *Fok*I, and *Bsm*I SNPs of the VDR gene have been reported to be associated with breast cancer; *Taq*I, *Fok*I, and *Bsm*I with prostate, colorectal, and skin cancer [171,172].

To date, several studies have been conducted to detect the relationship of VDR gene polymorphisms with cardiovascular diseases. However, no studies have found significant correlations between them.

11. Association of vit-D receptor gene polymorphisms and VDR allelic variation with susceptibility to obesity in children

Obesity is a multifactorial disorder that can be characterized by excessive adipose tissue in an individual, which increases their overall weight. Both environmental and genetic factors influence it. Fat mass and obesity (FTO) associated gene is upregulated in obese subjects confirming genetic factors to be 40% of the etiology behind obesity [161]. An increasing number of studies have uncovered the association of VDR polymorphisms with vit-D concentrations and obesity. Candidate gene analysis has identified five genes, VDR, GC, CYP24A1, CYP2R1, and CYP27B1, whereas genome-wide association studies confirmed the interplay of common genetic variations in GC and CYP2R1 genes [13]. Recently, a substantial upsurge can be observed in the prevalence of obesity. Several studies have found a relationship between obesity and VDR gene polymorphisms, especially among children and adolescents [15,16].

Vit-D receptor gene is expressed in adipose tissue. The VDR steroid nuclear receptor can bind with an active form of vit-D, 1,25(OH)2D3, and its analogs and exert a series of functions [161,173]. However, significantly elevated VDR expression can be observed in the adipose tissue of morbidly obese individuals [174]. Vit-D/VDR signaling suppresses brown adipocyte differentiation and mitochondrial respiration. VDR knockout mice expressed atrophy of the mammary adipose compartment compared to their wild-type littermates, thus suggesting that genetic variations in VDR may affect adiposity [16].

Vit-D has been reported to stimulate and inhibit adipogenesis in humans [175–177]. It stimulates the gene expression of enzymes and nuclear receptors that are involved in adipogenesis. Elevation in the levels of fatty acid-binding protein (FABP), fatty acid synthase (FAS), and peroxisome proliferator activator receptor (PPAR)-γ are responsible for increased adipogenesis [177]. A similar pattern of inhibitory and stimulatory effects on adipogenesis has also been observed in in-vitro studies [161]. VDR polymorphisms may have a crucial role in obesity pathogenesis. More than 200 polymorphisms of the VDR gene have been reported, and the most important of these are *Apa*I, *Bsm*I, *Fok*I, and *Taq*I [163]. Therefore, many studies have been conducted on different populations, including children, concerning the association of VDR gene polymorphisms and VDR allelic variation with susceptibility to obesity in children (Table 2).

A study was conducted on 192 Han Chinese children in a cohort of 6–14-year-olds to identify VDR gene polymorphisms with vit-D deficiency, overweight/obesity, and metabolic syndrome (MetS). Five VDR gene single-nucleotide polymorphisms (SNPs), namely, *Taq*I (rs731236 T > C), *Apa*I (rs7975232 C > A), *Bsm*I (rs1544410 G > A), *Fok*I (rs2228570 G >A), and Cdx2 (rs11568820 G > A), were genotyped and the distributions of different genotypes and alleles were compared among different groups. The study findings revealed that vit-D concentration was significantly lower in overweight/obese children while the AA genotype of *Apa*I SNP exhibited higher frequencies in them. Although not statistically significant A allele was higher in the overweight/obese group of children than the C allele [16].

A cross-sectional study on 234 healthy girls of 7–18 years old in South Brazil was conducted to investigate the correlation of genotype distribution of VDR gene SNPs: *Apa*I, *Bsm*I, and *Taq*I and their

Table 2
Association of VDR gene polymorphisms with childhood obesity.

Study population	Sample size	Age group	SNPs studied	Results	Reference
Han Chinese Children (both sex)	192	6–14 years old	*Taq*I (rs731236 T > C), *Apa*I (rs7975232 C > A), *Bsm*I (rs1544410 G > A), *Fok*I (rs2228570 G >A), and Cdx2 (rs11568820 G > A),	Vit-D concentration was significantly lower in overweight/ obese children while the AA genotype of *Apa*I SNP exhibited higher frequencies	[16]
South Brazilian Healthy girls	234	7–18 years old	*Apa*I, *Bsm*I, and *Taq*I and their haplotypes	Association of *Bsm*I, *Apa*I, and *Taq*I alongside GGT haplotypes with vit-D deficiency	[15]
Brazilian prepubertal and pubertal children	319	–	*Apa*I, *Bsm*I, and *Taq*I	A significant association of *Bsm*I and *Taq*I SNPs with the height in pubertal obese children	[178]
Brazilian schoolchildren	262	Mean age = 8.7 ± 1.3 years	*Apa*I, *Bsm*I, *Fok*I, and *Taq*I	The frequency of the TT allele of *Bsm*I was higher in overweight asthmatic children.	[179]
Egyptian children	110	6–16 years old	*Fok*I, *Apa*I, and *Taq*I	A significantly lower vit-D concentration in the obese group of children compared to the control group and a significant difference in genotype frequencies of VDR-*Taq*I between both groups	[166]
Danish school school-going children	642	8–11-year-old	Eleven SNPs of the vit-D gene; VDR, CYP2R1; DHCR7/NADSYN1; GC	A link of minor allelesYP2R1 rs10500804, and of GC rs4588 and rs7041 with lower serum vit-D levels	[14]
Danish families with their dependent children	201	4-year-old and above	25 SNPs including VDR gene	No correlation was found between SNPs in the VDR gene and vit-D level	[13]

haplotypes with vit-D levels. Findings of the study suggested an association of wild-type genotypes of VDR *Bsm*I, *Apa*I, and *Taq*I alongside GGT haplotypes with vit-D deficiency. The study also suggested haplotype Ht1 as a risk factor, and Ht7 plays a protective role towards vit-D deficits [15]. Another study was conducted in Brazil to examine the impact of allelic variations in the VDR gene on obesity, body height, and glucose tolerance-related features in children and adolescents. This study included 173 prepubertal and 146 pubertal children and three SNPs: rs7975232 (*Apa*I), rs1544410 (*Bsm*I), and rs731236 (*Taq*I) were genotyped. The finding suggested a significant correlation between *Bsm*I and *Taq*I genotypes with height in pubertal children, but not in prepubertal ones. Importantly the height of the homozygous carriers of the minor allele of *Bsm*I was 0.65 z-scores (4 cm) higher than the height of the homozygous carriers of the major allele of *Bsm*I SNP (0.0006). Furthermore, an association of the minor alleles of *Taq*I and *Bsm*I with the increased height in obese children was confirmed by the haplotype analysis [178]. Additionally, a cross-sectional study was conducted to evaluate the association of nutritional status of vit-D and the frequency of VDR gene polymorphisms with overweight and asthma in Brazilian schoolchildren. A total of 262 schoolchildren with a mean age of 8.7 ± 1.3 years were included in the study and four SNPs; *Apa*I, *Bsm*I, *Taq*I, and *Fok*I were identified, and genotypes, alleles, and haplotypes were calculated. The study findings demonstrated the TT allele of the *Bsm*I as a risk factor for overweight asthmatic children since the frequency of the TT allele of the *Bsm*I was higher in overweight asthmatic children compared to the asthmatic eutrophic children and control group [179].

To assess the genetic contribution of VDR gene polymorphisms to the pathogenesis of obesity in 110 Egyptian children 6–16 years old, three SNPs of the VDR gene; *Fok*I, *Apa*I, and *Taq*I, were genotyped using the RFLP technique. This research showed a significantly lower vit-D concentration in the obese group of children compared to the control group and a significant difference in genotype frequencies of VDR-*Taq*I between both groups. The "t" allele distribution in obese children was significantly higher ($p = 0.003$) than in the control group [166].

Associations of VDR gene polymorphisms (SNPs) with serum vit-D levels were investigated in a longitudinal survey of 8–11-year-old Danish school school-going children. In this study, eleven SNPs of the vit-D gene; namely VDR, cytochrome P450 subfamily IIR1 (CYP2R1); 7-dehydrocholesterol reductase/nicotinamide adenine dinucleotide synthetase-1 (DHCR7/ NADSYN1); and group-specific complement (GC) were genotyped for 642 children [14]. The findings revealed the link of minor allelesYP2R1 rs10500804, and of GC rs4588 and rs7041 with lower serum vit-D levels. In contrast, minor allele homozygosity of rs10741657 and rs1562902 in CYP2R1 was correlated with a higher level of vit-D [14].

Nissen et. al. investigated and analyzed the association of vit-D related polymorphisms with serum vit-D levels where 25 SNPs in the VDR gene including others, were genotyped in 201 Danish families with their dependent children. Although four SNPs in CYP2R1 and six SNPs in GC were significantly associated with serum vit-D concentration in children, no correlation was found between SNPs in the VDR gene and vit-D level [13].

Although a few studies have been conducted to investigate the association of VDR gene polymorphisms and their allelic variations with obesity, most studies identified a positive correlation of these parameters with susceptibility to obesity in children.

12. The interplay between vit-D and VDR polymorphism and its contribution to obesity in children

The current increase in obesity in children makes a worldwide concern [180]. This rise is because childhood obesity may trigger metabolic syndromes such as hypertension, dyslipidemia, and insulin resistance [181]. Previous studies have found an association between vit-D deficiency and obesity. However, this relationship can be explained by genetic analysis of vit-D-related genes and obesity patterns [160]. The initial blood circulating form of vit-D is 25- hydroxyvitamin D (25(OH)D), which is converted to its biologically active format, 1, 25-dihydroxy vitamin D (1,25(OH)2D) in the body. The active form of vit-D binds with the vit-D receptor (VDR) in tissues [182]. The location of the VDR gene in the human body is located on chromosome 12q13.11, and it has numerous single-nucleotide polymorphisms (SNPs). Five variants among the SNPs, such as *Taq*I, *Apa*I, *Bsm*I, *Fok*I and Cdx2, are well known [160]. A recent study has found that the mentioned VDR gene polymorphisms correlate with obesity in Han Chinese children [16]. They proved that *Apa*I is positively linked with obesity and *Fok*I polymorphisms are associated with metabolic syndrome in Chinese children.

Another study was done in Malaysia among thirteen-year-old adolescents to know the association between VDR *Bsm*I polymorphism and vitamin D deficiency, obesity, and insulin resistance [183]. They have revealed that only vitamin D deficiency and insulin resistance have significantly correlated with VDR *Bsm*I polymorphism. An Egyptian study examined the role of VDR polymorphisms in causing obesity in children who were 6–16 years old [166]. They assessed that VDR-*Taq*I polymorphism is a risk factor for causing obesity among the study

samples. A Brazilian study involving 8.7 ± 1.3 years old was looking for the association of VDR polymorphism with overweight school children [179] and showed that *Bsm*I polymorphism is responsible for causing Asthma in obese children.

The mechanism of action of vit-D and VDR polymorphism in obesity is not adequately explained and clarified yet. However, vit-D deficiency is vital in causing obesity in humans [182]. VDR is responsible for the function of vit-D inside the body, which networks cell signaling and affects the advancement of obesity [184]. A study conducted in mice found that human VDR has been overexpressed in the adipocytes, resulting in declining energy expenditure and initiation of obesity [185]. Several studies have been conducted to determine the relationship between VDR polymorphism and adulthood obesity in different geographical locations. But a few studies investigated the role of VDR polymorphism in obesity in children. The way vit-D and VDR polymorphism concurrently contribute to obesity in children is an exciting topic in nutrition and obesity. Novel research focused on the genetic VDR polymorphism and its impact on childhood obesity is a demand in the community, which will augment the research for therapeutic intervention to prevent the early onset of obesity in children.

13. Prevention and treatment of vit-D deficiency

When 25(OH)D status in patients is below 20 ng/mL (50 nmol/liter), it is called vit-D deficiency (VDD). This deficiency is a public health concern, and treatment is necessary. If not treated, the patient can face reduced quality of life. VDD could cause rickets, hypocalcemic convulsions, dental problems, general ill health, and poor growth [70,186]. The primary source of vit-D is unprotected sun exposure. But in the absence of sun exposure, dietary sources could get an adequate amount of vit-D [187]. The preventive strategies for VDD are supplementation and food fortification programs [71]. Dietary sources of vit-D are scarce and hardly consumed. Additionally, the food surveillance data from several countries show people's negligence to vit-D intake as recommended. Therefore, the need for addressing the low dietary vit-D consumption is an important concern to minimize the consequences of VDD currently. Clinicians should consider vit-D testing more often for the symptoms associated with VDD such as bone pain, myalgia and other musculoskeletal symptoms which might be misdiagnosed as fibromyalgia, chronic fatigue, age-related weakness, or even depression [188]. VDD treatment involves giving ergocalciferol or cholecalciferol [68] and high-dose bolus therapy [69]. Several pharmacological interventions and scientific evidence-based studies indicated that cholecalciferol efficacy is better than calciferol for the treatment of VDD clinical cases [189]. Daily intake of 400 IU vit-D is recommended for children who are dark-skinned, veiled, exposed to reduced sunlight, or have an underlying medical condition to prevent VDD [72]. The recommended daily vit-D intake for South Asians is 600–1000 IU for healthy adults and 800–2000 IU for high-risk individuals and older adults [73]. A nationwide Turkey program that decreased vit- D-deficient rickets includes free distribution of vit-D drops to all newborns and infants (0–12 months) [76]. They implemented it by visiting health stations with the help of primary care doctors and nurses. The health department in the UK suggests giving vit-D supplementation to children for the first five years of life [75]. Toxicity could occur due to excess vit-D, which manifests in increased urinary or serum concentrations of calcium. When the 25(OH)D is present, a high serum concentration will cause toxic events [182]. It is also evident that there is an increased risk of falls or fractures in those exposed to intermittent high doses of vit-D [190]. Therefore, it is wise to consider the risk/benefits ratio of vit -D supplementation.

Recently, FDA [191] has approved five drugs to treat overweight and obesity for long-term use. These marketed available drugs are orlistat ($C_{29}H_{53}NO_5$, Xenical, Alli), phentermine-topiramate combination ($C_{22}H_{36}N_2O_8S$, Qsymia), naltrexone-bupropion combination ($C_{20}H_{23}NO_4$, Contrave), liraglutide ($C_{172}H_{265}N_{43}O_{51}$, Saxenda), and semaglutide ($C_{187}H_{291}N_{45}O_{59}$, Wegovy). Another drug, setmelanotide (Imcivree) has limited use to the people who have been diagnosed with specific genetic disorders. Fig. 7 below shows the molecular structures of these drugs.

14. Conclusion

Sources of vit-D include photosynthesis in the skin under direct exposure to sunlight and dietary supplements. Factors contributing to vit-D deficiency and childhood obesity comprehend lifestyle changes represented by physical inactivity, decreased outdoor activity, less exposure to sunlight, unhealthy diet, living pattern, socio-economic development, and demographic and epidemiological transition. Several genes: GC, CYP24A1, CYP2R1, CYP27B1, and VDR, have been found to play a vital role in the synthesis, metabolism of vit-D and in exerting its biological effects in the body. As a molecular mechanism, vit-D binds to VDR proteins and acts as a regulator agent in the differentiation and metabolism of adipocytes. The VDR gene has been identified as highly polymorphic with many single nucleotide polymorphisms (SNPs), recognized as *Bsm*I, *Apa*I, *Taq*I, *Fok*I, etc. and these SNPs can change the binding pattern of VDR with vit-D or its analogs and related signaling pathways, thus influencing the differentiation and metabolism of adipocytes. Moreover, VDR gene polymorphisms affect gene expression along with the stability of mRNA and protein translation efficiency and protein sequence as well. Thus, our extensive review suggests that lower serum vit-D levels and VDR gene polymorphisms are associated with susceptibility to adiposity in children and its severe consequences. Since this review has explained the association of obesity with vit-D deficiency and VDR gene polymorphisms, it could help the definition of VDR fingerprints that predict an increased risk of developing obesity and might contribute to identifying novel therapeutic strategies for this metabolic condition. It will further help create awareness among mass people regarding the psychosocial and clinical consequences of vit-D deficiency and VDR gene polymorphisms in obese children.

15. Future recommendations

Only a few studies have been conducted on the correlation of vit-D level and VDR gene polymorphisms with obesity in children; thus, researchers should conduct more research focusing on this area of research taking into consideration of different parts of the world and ethnicity since environmental factors and genetic factors influence vit-D levels and obesity in children.

- Awareness creation among mass people regarding severe consequences of vit-D deficiency and VDR gene polymorphisms in obese children.
- Advising people to provide their children with a healthy lifestyle that facilitates vit-D synthesis in the body.
- Taking immediate and proper measurements when psychosocial and clinical manifestations of obesity in children are observed. For instance, consultation with physicians and measurement of serum vit-D level advised by the physicians followed by vit-D supplementation if required.

Funding

This study did not receive any funds.

Credit authorship contribution statement

Raushanara Akter: Writing – original draft, Writing – review & editing. **Afrina Afrose:** Writing – original draft, Writing – review & editing. **Shahana Sharmin:** Writing – illustrate figures & editing. **Rifat Rezwan**: Writing – review & referencing. **Md. Rashidur Rahman:**

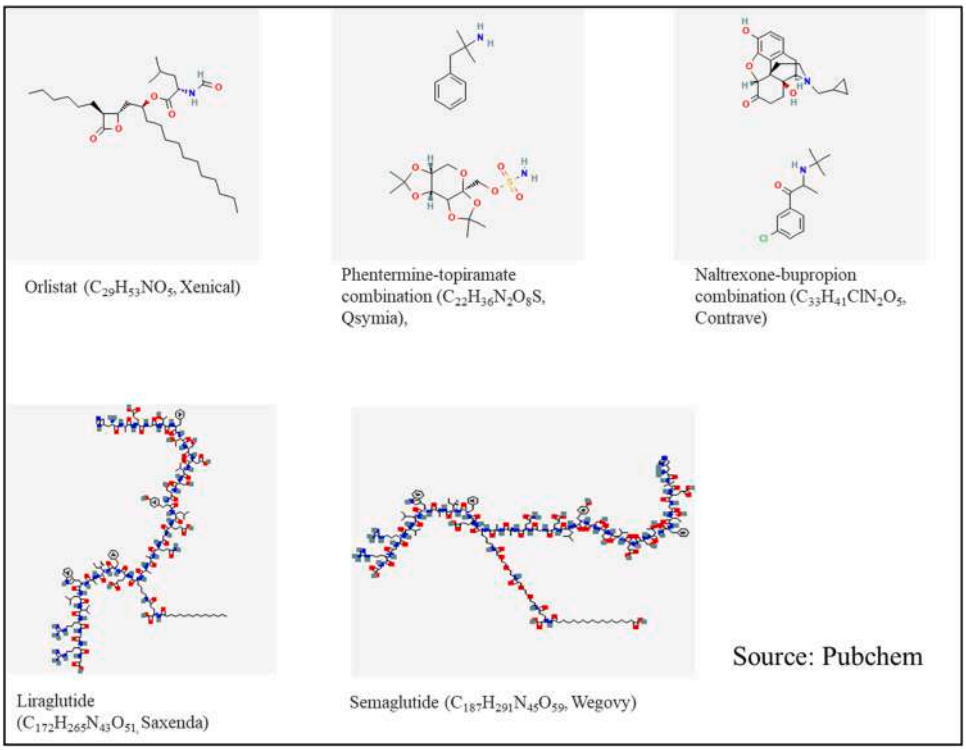

Fig. 7. The structures of the marketed drugs recommended for the treatment of obesity.

Writing – review & editing. **Sharmind Neelotpol:** Writing – original draft, Writing –editing. All authors revised the manuscript, approved the final submitted version, agreed to be personally accountable for their contributions, and will ensure that any concerns regarding integrity or accuracy are investigated and resolved.

Conflict of interest statement

The authors declare no competing interest.

Data Availability

No data was used for the research described in the article.

References

[1] S. Rahman, M.T. Islam, D.S. Alam, Obesity and overweight in Bangladeshi children and adolescents: a scoping review, BMC Public Health 14 (2014) 1–8, https://doi.org/10.1186/1471-2458-14-70.
[2] E. Gün, H. Uzun, S. Bolu, İ. Arslanoğlu, K. Kocabay, Serum 25-hydroxyvitamin D is associated with insulin resistance independently of obesity in children ages 5-17, Prim. Care Diabetes 14 (2020) 741–746, https://doi.org/10.1016/j.pcd.2020.06.006.
[3] X. Liu, Y. Xian, M. Min, Q. Dai, Y. Jiang, D. Fang, Association of 25-hydroxyvitamin D status with obesity as well as blood glucose and lipid concentrations in children and adolescents in China, Clin. Chim. Acta Int. J. Clin. Chem. 455 (2016) 64–67, https://doi.org/10.1016/j.cca.2016.01.023.
[4] M.D. Hawlader, S. Zaman, M. Rahman, M.N. Khan, A. Hossain, G.U. Ahsan, Determinants of vitamin D deficiency among Bangladeshi children: a hospital based case-control study, Epidemiol. Biostat, Public Health 16 (2019) 4, https://doi.org/10.2427/13186.
[5] K.A. da Cunha, E.I. da, S. Magalhães, L.M.R. Loureiro, L.F. da, R. Sant'Ana, A. Q. Ribeiro, J.F. de Novaes, Calcium intake, serum vitamin D and obesity in children: is there an association? Rev. Paul. Pediatr. Orgao . Soc. Pediatr. Sao Paulo 33 (2015) 222–229, https://doi.org/10.1016/j.rpped.2015.03.001.
[6] R. Antonucci, C. Locci, M.G. Clemente, E. Chicconi, L. Antonucci, Vitamin D deficiency in childhood: old lessons and current challenges, J. Pediatr. Endocrinol. Metab. JPEM 31 (2018) 247–260, https://doi.org/10.1515/jpem-2017-0391.
[7] F. Shen, Y. Wang, H. Sun, D. Zhang, F. Yu, S. Yu, H. Han, J. Wang, Y. Ba, C. Wang, W. Li, X. Li, Vitamin D receptor gene polymorphisms are associated with triceps skin fold thickness and body fat percentage but not with body mass index or waist circumference in Han Chinese, Lipids Health Dis. 18 (2019) 1–8, https://doi.org/10.1186/s12944-019-1027-2.
[8] H.T. Hossain, Q.T. Islam, M.A.K. Khandaker, H.N. Ahasan, Study of serum vitamin D level in different socio-demographic population - a pilot study, J. Med. 19 (2018) 22–29, https://doi.org/10.3329/jom.v19i1.34836.
[9] S.Y. Kim, The pleiomorphic actions of vitamin D and its importance for children, Ann. Pediatr. Endocrinol. Metab. 18 (2013) 45–54, https://doi.org/10.6065/apem.2013.18.2.45.
[10] M.F. Holick, Sunlight, UV-radiation, vitamin D and skin cancer: how much sunlight do we need? Adv. Exp. Med. Biol. 624 (2008) 1–15, https://doi.org/10.1007/978-0-387-77574-6_1.
[11] M.F. Holick, T.C. Chen, Vitamin D deficiency: a worldwide problem with health consequences, Am. J. Clin. Nutr. 87 (2008) 1080S–1086SS, https://doi.org/10.1093/ajcn/87.4.1080S.
[12] N.M. Al-Daghri, F.R. Guerini, O.S. Al-Attas, M.S. Alokail, K.M. Alkharfy, H. M. Draz, C. Agliardi, A.S. Costa, I. Saulle, A.K. Mohammed, M. Biasin, M. Clerici, Vitamin D Receptor Gene Polymorphisms Are Associated with Obesity and Inflammosome Activity, PLOS ONE 9 (2014), e102141, https://doi.org/10.1371/journal.pone.0102141.
[13] J. Nissen, L.B. Rasmussen, G. Ravn-Haren, E.W. Andersen, B. Hansen, R. Andersen, H. Mejborn, K.H. Madsen, U. Vogel, Common variants in CYP2R1 and GC genes predict vitamin D concentrations in healthy Danish children and adults, PloS One 9 (2014), e89907, https://doi.org/10.1371/journal.pone.0089907.
[14] R.A. Petersen, L.H. Larsen, C.T. Damsgaard, L.B. Sørensen, M.F. Hjorth, R. Andersen, I. Tetens, H. Krarup, C. Ritz, A. Astrup, K.F. Michaelsen, C. Mølgaard, Common genetic variants are associated with lower serum 25-hydroxyvitamin D concentrations across the year among children at northern latitudes, Br. J. Nutr. 117 (2017) 829–838, https://doi.org/10.1017/S0007114517000538.
[15] B.R. Santos, L.P.G. Mascarenhas, F. Satler, M.C.S. Boguszewski, P.M. Spritzer, Vitamin D deficiency in girls from South Brazil: a cross-sectional study on prevalence and association with vitamin D receptor gene variants, BMC Pedia 12 (2012) 62, https://doi.org/10.1186/1471-2431-12-62.
[16] D. Wang, K. Su, Z. Ding, Z. Zhang, C. Wang, Association of vitamin D receptor gene polymorphisms with metabolic syndrome in Chinese children, Int. J. Gen. Med 14 (2021) 57–66, https://doi.org/10.2147/IJGM.S287205.
[17] Global Atlas on Childhood Obesity, World Obes. Fed. (n.d.). https://www.worldobesity.org/membersarea/global-atlas-on-childhood-obesity (Accessed 15 May 2022).
[18] M. de Onis, M. Blössner, E. Borghi, Global prevalence and trends of overweight and obesity among preschool children, Am. J. Clin. Nutr. 92 (2010) 1257–1264, https://doi.org/10.3945/ajcn.2010.29786.
[19] Y. Zhang, J. Zhao, Z. Chu, J. Zhou, Increasing prevalence of childhood overweight and obesity in a coastal province in China, Pediatr. Obes. 11 (2016) e22–e26, https://doi.org/10.1111/ijpo.12070.

[20] Y. Wang, H. Lim, The global childhood obesity epidemic and the association between socio-economic status and childhood obesity, Int. Rev. Psychiatry Abingdon Engl. 24 (2012) 176–188, https://doi.org/10.3109/09540261.2012.688195.
[21] I. Zakharova, L. Klimov, V. Kuryaninova, I. Nikitina, S. Malyavskaya, S. Dolbnya, A. Kasyanova, R. Atanesyan, M. Stoyan, A. Todieva, G. Kostrova, A. Lebedev, Vitamin D insufficiency in overweight and obese children and adolescents, Front. Endocrinol. 10 (2019) 103, https://doi.org/10.3389/fendo.2019.00103.
[22] C.B. Turer, H. Lin, G. Flores, Prevalence of vitamin D deficiency among overweight and obese US children, Pediatrics 131 (2013) e152–e161, https://doi.org/10.1542/peds.2012-1711.
[23] S. Shuhana, Prevalence and risk factor of childhood overweight and obesity in primary school primary school: children of Dhaka city, (2010). https://www.duo.uio.no/handle/10852/30024 (Accessed 25 April 2022).
[24] R. Zhang, D.P. Naughton, Vitamin D in health and disease: Current perspectives, Nutr. J. 9 (2010) 1–13, https://doi.org/10.1186/1475-2891-9-65.
[25] Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, Dietary Reference Intakes for Calcium and Vitamin D, National Academies Press (US), Washington (DC), 2011. http://www.ncbi.nlm.nih.gov/books/NBK56070/ (Accessed 25 April 2022).
[26] W.D. Fraser, A.M. Milan, Vitamin D assays: past and present debates, difficulties, and developments, Calcif. Tissue Int. 92 (2013) 118–127, https://doi.org/10.1007/s00223-012-9693-3.
[27] M.F. Holick, N.C. Binkley, H.A. Bischoff-Ferrari, C.M. Gordon, D.A. Hanley, R. P. Heaney, M.H. Murad, C.M. Weaver, Evaluation, treatment, and prevention of vitamin D deficiency: an endocrine society clinical practice guideline, J. Clin. Endocrinol. Metab. 96 (2011) 1911–1930, https://doi.org/10.1210/jc.2011-0385.
[28] M.F. Holick, The vitamin D deficiency pandemic: a forgotten hormone important for health, Public Health Rev. 32 (2010) 267–283, https://doi.org/10.1007/BF03391602.
[29] K. Takeyama, S. Kitanaka, T. Sato, M. Kobori, J. Yanagisawa, S. Kato, 25-Hydroxyvitamin D3 1alpha-hydroxylase and vitamin D synthesis, Science 277 (1997) 1827–1830, https://doi.org/10.1126/science.277.5333.1827.
[30] V. Kamale, P. Sharma, Y. Yewale, R. Thamke, Role of Vitamin D in Health and Diseases in Children, New Indian J. Pediatr. (2022). https://nijp.org/role-of-vitamin-d-in-health-and-diseases-in-children/ (Accessed 25 April 2022).
[31] T.L. Clemens, X.Y. Zhou, M. Myles, D. Endres, R. Lindsay, Serum vitamin D2 and vitamin D3 metabolite concentrations and absorption of vitamin D2 in elderly subjects, J. Clin. Endocrinol. Metab. 63 (1986) 656–660, https://doi.org/10.1210/jcem-63-3-656.
[32] G. Jones, Pharmacokinetics of vitamin D toxicity, Am. J. Clin. Nutr. 88 (2008) 582S–586S, https://doi.org/10.1093/ajcn/88.2.582S.
[33] R.W. Gray, A.E. Caldas, D.R. Wilz, J. Lemann, G.A. Smith, H.F. DeLuca, Metabolism and excretion of 3H-1,25-(OH)2-vitamin D3 in healthy adults, J. Clin. Endocrinol. Metab. 46 (1978) 756–765, https://doi.org/10.1210/jcem-46-5-756.
[34] A.G. Turner, P.H. Anderson, H.A. Morris, Vitamin D and bone health, Scand, J. Clin. Lab. Investig. Suppl. 243 (2012) 65–72, https://doi.org/10.3109/00365513.2012.681963.
[35] M. Umar, K.S. Sastry, A.I. Chouchane, Role of Vitamin D Beyond the Skeletal Function: A Review of the Molecular and Clinical Studies, Int. J. Mol. Sci. 19 (2018) 1618, https://doi.org/10.3390/ijms19061618.
[36] A.G. Halline, N.O. Davidson, S.F. Skarosi, M.D. Sitrin, C. Tietze, D.H. Alpers, T. A. Brasitus, Effects of 1,25-dihydroxyvitamin D3 on proliferation and differentiation of Caco-2cells, Endocrinology 134 (1994) 1710–1717, https://doi.org/10.1210/endo.134.4.8137734.
[37] H. Derakhshanian, M.H. Javanbakht, M. Zarei, E. Djalali, M. Djalali, Vitamin D increases IGF-I and insulin levels in experimental diabetic rats, Growth Horm. IGF Res. . J. Growth Horm. Res. Soc. Int. IGF Res. Soc. 36 (2017) 57–59, https://doi.org/10.1016/j.ghir.2017.09.002.
[38] Y. Wang, D. He, C. Ni, H. Zhou, S. Wu, Z. Xue, Z. Zhou, Vitamin D induces autophagy of pancreatic β-cells and enhances insulin secretion, Mol. Med. Rep. 14 (2016) 2644–2650, https://doi.org/10.3892/mmr.2016.5531.
[39] J.R. Wu-Wong, M. Nakane, J. Ma, Vitamin D analogs modulate the expression of plasminogen activator inhibitor-1, thrombospondin-1 and thrombomodulin in human aortic smooth muscle cells, J. Vasc. Res. 44 (2007) 11–18, https://doi.org/10.1159/000097812.
[40] T. Durá-Travé, F. Gallinas-Victoriano, M.J. Chueca-Guindulain, S. Berrade-Zubiri, Prevalence of hypovitaminosis D and associated factors in obese Spanish children, Nutr. Diabetes 7 (2017) e248, https://doi.org/10.1038/nutd.2016.50.
[41] I.M. Kaddam, A.M. Al-Shaikh, B.A. Abaalkhail, K.S. Asseri, Y.M. Al-Saleh, A.A. Al-Qarni, A.M. Al-Shuaibi, W.G. Tamimi, A.M. Mukhtar, Prevalence of vitamin D deficiency and its associated factors in three regions of Saudi Arabia, Saudi Med. J. 38 (2017) 381–390, https://doi.org/10.15537/smj.2017.4.18753.
[42] J.L. Plesner, M. Dahl, C.E. Fonvig, T.R.H. Nielsen, J.T. Kloppenborg, O. Pedersen, T. Hansen, J.-C. Holm, Obesity is associated with vitamin D deficiency in Danish children and adolescents, J. Pediatr. Endocrinol. Metab. JPEM 31 (2018) 53–61, https://doi.org/10.1515/jpem-2017-0246.
[43] C.L. Roth, C. Elfers, M. Kratz, A.N. Hoofnagle, Vitamin D deficiency in obese children and its relationship to insulin resistance and adipokines, J. Obes. 2011 (2011) 531–542, https://doi.org/10.1155/2011/495101.
[44] Y. Motlaghzadeh, F. Sayarifard, B. Allahverdi, A. Rabbani, A. Setoodeh, A. Sayarifard, F. Abbasi, M.-T. Haghi-Ashtiani, A. Rahimi-Froushani, Assessment of vitamin D status and response to vitamin d3 in obese and non-obese Iranian children, J. Trop. Pediatr. 62 (2016) 269–275, https://doi.org/10.1093/tropej/fmv091.
[45] E.E. Delvin, M. Lambert, E. Levy, J. O'Loughlin, S. Mark, K. Gray-Donald, G. Paradis, Vitamin D status is modestly associated with glycemia and indicators of lipid metabolism in French-Canadian children and adolescents, J. Nutr. 140 (2010) 987–991, https://doi.org/10.3945/jn.109.112250.
[46] L. Viana Pires, E.M. González-Gil, A. Anguita-Ruiz, G. Bueno, M. Gil-Campos, R. Vázquez-Cobela, L.A. Moreno, Á. Gil, C.M. Aguilera, R. Leis, Serum 25-hydroxyvitamin D levels and its relationship with sex hormones, puberty and obesity degree in children and adolescents, Child Adolesc. Obes. 3 (2020) 150–169, https://doi.org/10.1080/2574254X.2020.1812964.
[47] L. Villalba-Heredia, C. Comeras-Chueca, A. González-Agüero, D. Domingo-Del-Val, P. Calmarza, G. Vicente-Rodríguez, J.A. Casajús, Á. Matute-Llorente, 25-hydroxyvitamin D and Cardiorespiratory fitness in prepubertal overweight and obese children, Nutrients 13 (2021) 1597, https://doi.org/10.3390/nu13051597.
[48] M.H. Siddiqee, B. Bhattacharjee, U.R. Siddiqi, M.M. Rahman, High burden of hypovitaminosis D among the children and adolescents in South Asia: a systematic review and meta-analysis, J. Health Popul. Nutr. 41 (2022) 10, https://doi.org/10.1186/s41043-022-00287-w.
[49] V.I. Fiamenghi, E.D. de Mello, Vitamin D deficiency in children and adolescents with obesity: a meta-analysis, J. Pediatr. (Rio J.) 97 (2021) 273–279, https://doi.org/10.1016/j.jped.2020.08.006.
[50] G.M. Feketea, I.C. Bocsan, G. Tsiros, P. Voila, L.A. Stanciu, M. Zdrenghea, Vitamin D Status in Children in Greece and Its Relationship with Sunscreen Application, Child. Basel Switz. 8 (2021) 111, https://doi.org/10.3390/children8020111.
[51] M. Demiral, B. Sırmagül, B. Kirel, Endokrin Polik-.-. başvuran çocuklarda D. Vitam. düzeyleri 14 (2016) 60–66.
[52] H.M. Aboulghar, K. AbdElkhalek, S.S.E. Tatawy, Y.M. Shalan, C.G. Salama, Vitamin D deficiency among preschool children and its correlation with nutritional habits and sun exposure, Ann. Rom. Soc. Cell Biol. (2021) 4228–4237.
[53] A.M. Alaklabi, N.A. Alsharairi, Current evidence on vitamin D deficiency and metabolic syndrome in obese children: what does the evidence from Saudi Arabia tell us? Child. Basel Switz. 5 (2018), E11 https://doi.org/10.3390/children5010011.
[54] F. Thorsteinsdottir, I. Cardoso, A. Keller, M. Stougaard, P. Frederiksen, A. S. Cohen, E. Maslova, R. Jacobsen, V. Backer, B.L. Heitmann, Neonatal vitamin D status and risk of asthma in childhood: results from the D-tect study, Nutrients 12 (2020), E842, https://doi.org/10.3390/nu12030842.
[55] L.A. Lautenbacher, S.P. Jariwala, M.E. Markowitz, D. Rastogi, Vitamin D and pulmonary function in obese asthmatic children, Pediatr. Pulmonol. 51 (2016) 1276–1283, https://doi.org/10.1002/ppul.23485.
[56] R. Colak, M. Anil, F. Yasar, A. Rahmi Bakiler, O. Pirgon, M. Helvaci, B. Dündar, Metabolic disturbances and cardiovascular risk factors in obese children with vitamin D deficiency, Arch. Pediatr. Organe . Soc. Fr. Pediatr. 27 (2020) 140–145, https://doi.org/10.1016/j.arcped.2019.12.005.
[57] S. Yahyaoui, L. Jmal, A. Sammoud, M. Abdenebi, A. Jmal, S. Boukthir, Vitamin D deficiency is associated with metabolic syndrome in Tunisian children with obesity, Tunis. Med. 97 (2019) 1353–1356.
[58] D. Corica, C. Zusi, F. Olivieri, M. Marigliano, C. Piona, E. Fornari, A. Morandi, M. Corradi, E. Miraglia Del Giudice, D. Gatti, M. Rossini, R.C. Bonadonna, C. Maffeis, Vitamin D affects insulin sensitivity and β-cell function in obese non-diabetic youths, Eur. J. Endocrinol. 181 (2019) 439–450, https://doi.org/10.1530/EJE-19-0369.
[59] K. Ekbom, C. Marcus, Vitamin D deficiency is associated with prediabetes in obese Swedish children, Acta Paediatr. Oslo Nor. 1992 (105) (2016) 1192–1197, https://doi.org/10.1111/apa.13363.
[60] R. Alemzadeh, J. Kichler, G. Babar, M. Calhoun, Hypovitaminosis D in obese children and adolescents: relationship with adiposity, insulin sensitivity, ethnicity, and season, Metabolism 57 (2008) 183–191, https://doi.org/10.1016/j.metabol.2007.08.023.
[61] I.K. Murni, D.C. Sulistyoningrum, V. Oktaria, Association of vitamin D deficiency with cardiovascular disease risk in children: implications for the Asia Pacific Region, Asia Pac, J. Clin. Nutr. 25 (2016) S8–S19, https://doi.org/10.6133/apjcn.122016.s1.
[62] D. Maggio, A. Cherubini, F. Lauretani, R.C. Russo, B. Bartali, M. Pierandrei, C. Ruggiero, M.C. Macchiarulo, R. Giorgino, S. Minisola, L. Ferrucci, 25(OH)D Serum levels decline with age earlier in women than in men and less efficiently prevent compensatory hyperparathyroidism in older adults, J. Gerontol. A. Biol. Sci. Med. Sci. 60 (2005) 1414–1419, https://doi.org/10.1093/gerona/60.11.1414.
[63] E. Grethen, R. McClintock, C.E. Gupta, R. Jones, B.M. Cacucci, D. Diaz, A. D. Fulford, S.M. Perkins, R.V. Considine, M. Peacock, Vitamin D and hyperparathyroidism in obesity, J. Clin. Endocrinol. Metab. 96 (2011) 1320–1326, https://doi.org/10.1210/jc.2010-2202.
[64] E. Romagnoli, J. Pepe, S. Piemonte, C. Cipriani, S. Minisola, Management of endocrine disease: value and limitations of assessing vitamin D nutritional status and advised levels of vitamin D supplementation, Eur. J. Endocrinol. 169 (2013) R59–R69, https://doi.org/10.1530/EJE-13-0435.
[65] J.C. Gallagher, V. Yalamanchili, L.M. Smith, The effect of vitamin D supplementation on serum 25(OH)D in thin and obese women, J. Steroid Biochem. Mol. Biol. 136 (2013) 195–200, https://doi.org/10.1016/j.jsbmb.2012.12.003.
[66] S. Minisola, L. Colangelo, M. Cilli, C. Cipriani, J. Pepe, E. Romagnoli, Intermittent high doses of vitamin D: a need for further studies, Calcif. Tissue Int. 92 (2013) 487–488, https://doi.org/10.1007/s00223-013-9714-x.
[67] R. Jorde, M. Sneve, P. Torjesen, Y. Figenschau, No improvement in cardiovascular risk factors in overweight and obese subjects after supplementation with vitamin

D3 for 1 year, J. Intern. Med 267 (2010) 462–472, https://doi.org/10.1111/j.1365-2796.2009.02181.x.
[68] A. Sinha, T.D. Cheetham, S.H.S. Pearce, Prevention and treatment of vitamin D deficiency, Calcif. Tissue Int. 92 (2013) 207–215, https://doi.org/10.1007/s00223-012-9663-9.
[69] C. Munns, M.R. Zacharin, C.P. Rodda, J.A. Batch, R. Morley, N.E. Cranswick, M. E. Craig, W.S. Cutfield, P.L. Hofman, B.J. Taylor, S.R. Grover, J.A. Pasco, D. Burgner, C.T. Cowell, Paediatric Endocrine Group, Paediatric Bone Australasia, Prevention and treatment of infant and childhood vitamin D deficiency in Australia and New Zealand: a consensus statement, Med. J. Aust. 185 (2006) 268–272, https://doi.org/10.5694/j.1326-5377.2006.tb00558.x.
[70] L. Muhe, S. Lulseged, K.E. Mason, E.A. Simoes, Case-control study of the role of nutritional rickets in the risk of developing pneumonia in Ethiopian children, Lancet Lond. Engl. 349 (1997) 1801–1804, https://doi.org/10.1016/S0140-6736(96)12098-5.
[71] M. Aguiar, L. Andronis, M. Pallan, W. Högler, E. Frew, Preventing vitamin D deficiency (VDD): a systematic review of economic evaluations, Eur. J. Public Health 27 (2017) 292–301, https://doi.org/10.1093/eurpub/ckw270.
[72] L.M. Gartner, F.R. Greer, Section on breastfeeding and committee on nutrition. American Academy of Pediatrics, Prevention of rickets and vitamin D deficiency: new guidelines for vitamin D intake, Pediatrics 111 (2003) 908–910, https://doi.org/10.1542/peds.111.4.908.
[73] S. Kalra, Vitamin D deficiency: pragmatic suggestions for prevention and treatment, JPMA J. Pak. Med. Assoc. 67 (2017) 1116–1118.
[74] Ş. Hatun, B. Ozkan, A. Bereket, Vitamin D deficiency and prevention: Turkish experience, Acta Paediatr. Oslo Nor. 1992 100 (2011) 1195–1199, https://doi.org/10.1111/j.1651-2227.2011.02383.x.
[75] C.S. Zipitis, G.A. Markides, I.L. Swann, Vitamin D deficiency: prevention or treatment, Arch. Dis. Child. 91 (2006) 1011–1014, https://doi.org/10.1136/adc.2006.098467.
[76] C.L. Wagner, F.R. Greer, American academy of pediatrics section on breastfeeding, american academy of pediatrics committee on nutrition, prevention of rickets and vitamin D deficiency in infants, children, and adolescents, Pediatrics 122 (2008) 1142–1152, https://doi.org/10.1542/peds.2008-1862.
[77] C. Braegger, C. Campoy, V. Colomb, T. Decsi, M. Domellof, M. Fewtrell, I. Hojsak, W. Mihatsch, C. Molgaard, R. Shamir, D. Turck, J. van Goudoever, ESPGHAN committee on nutrition, vitamin D in the healthy European paediatric population, J. Pediatr. Gastroenterol. Nutr. 56 (2013) 692–701, https://doi.org/10.1097/MPG.0b013e31828f3c05.
[78] P. Lips, K.D. Cashman, C. Lamberg-Allardt, H.A. Bischoff-Ferrari, B. Obermayer-Pietsch, M.L. Bianchi, J. Stepan, G. El-Hajj Fuleihan, R. Bouillon, Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society, Eur. J. Endocrinol. 180 (2019) P23–P54, https://doi.org/10.1530/EJE-18-0736.
[79] R.J. Moon, J.H. Davies, C. Cooper, N.C. Harvey, Vitamin D, and maternal and child health, Calcif. Tissue Int. 106 (2020) 30–46, https://doi.org/10.1007/s00223-019-00560-x.
[80] N. Waheed, H.A. Cheema, A. Saeed, M.A. Alvi, Z. Fayyaz, N. Anjum, S. Batool, Vitamin D intoxication in 7-month-old infant with recommended daily intake of vitamin D, J. Ayub Med. Coll. Abbottabad Jamc. 30 Suppl 1 (2018) S673–S675.
[81] S.N. Taylor, Vitamin D in toddlers, preschool children, and adolescents, Ann. Nutr. Metab. 76 (Suppl 2) (2020) 30–41, https://doi.org/10.1159/000505635.
[82] I. González-Molero, G. Rojo-Martínez, S. Morcillo, C. Gutierrez, E. Rubio, V. Pérez-Valero, I. Esteva, M.S. Ruiz de Adana, M.C. Almaraz, N. Colomo, G. Olveira, F. Soriguer, Hypovitaminosis D and incidence of obesity: a prospective study, Eur. J. Clin. Nutr. 67 (2013) 680–682, https://doi.org/10.1038/ejcn.2013.48.
[83] S. Vanlint, Vitamin D and obesity, Nutrients 5 (2013) 949–956, https://doi.org/10.3390/nu5030949.
[84] K.S. Vimaleswaran, D.J. Berry, C. Lu, E. Tikkanen, S. Pilz, L.T. Hiraki, J. D. Cooper, Z. Dastani, R. Li, D.K. Houston, A.R. Wood, K. Michaëlsson, L. Vandenput, L. Zgaga, L.M. Yerges-Armstrong, M.I. McCarthy, J. Dupuis, M. Kaakinen, M.E. Kleber, K. Jameson, N. Arden, O. Raitakari, J. Viikari, K. K. Lohman, L. Ferrucci, H. Melhus, E. Ingelsson, L. Byberg, L. Lind, M. Lorentzon, V. Salomaa, H. Campbell, M. Dunlop, B.D. Mitchell, K.-H. Herzig, A. Pouta, A.-L. Hartikainen, E.A. Streeten, E. Theodoratou, A. Jula, N.J. Wareham, C. Ohlsson, T.M. Frayling, S.B. Kritchevsky, T.D. Spector, J.B. Richards, T. Lehtimäki, W. H. Ouwehand, P. Kraft, C. Cooper, W. März, C. Power, R.J.F. Loos, T.J. Wang, M.-R. Järvelin, J.C. Whittaker, A.D. Hingorani, E. Hyppönen, Causal relationship between obesity and vitamin D status: bi-directional mendelian randomization analysis of multiple cohorts, PLoS Med 10 (2013), e1001383, https://doi.org/10.1371/journal.pmed.1001383.
[85] J. Wortsman, L.Y. Matsuoka, T.C. Chen, Z. Lu, M.F. Holick, Decreased bioavailability of vitamin D in obesity, Am. J. Clin. Nutr. 72 (2000) 690–693, https://doi.org/10.1093/ajcn/72.3.690.
[86] E.B. Mawer, J. Backhouse, C.A. Holman, G.A. Lumb, S.W. Stanbury, The distribution and storage of vitamin D and its metabolites in human tissues, Clin. Sci. 43 (1972) 413–431, https://doi.org/10.1042/cs0430413.
[87] H. Florez, R. Martínez, W. Chacra, N. Strickman-Stein, S. Levis, Outdoor exercise reduces the risk of hypovitaminosis D in the obese, J. Steroid Biochem. Mol. Biol. (2007) 679–681, https://doi.org/10.1016/j.jsbmb.2006.12.032.
[88] G. Targher, L. Bertolini, L. Scala, M. Cigolini, L. Zenari, G. Falezza, G. Arcaro, Associations between serum 25-hydroxyvitamin D3 concentrations and liver histology in patients with non-alcoholic fatty liver disease, Nutr. Metab. Cardiovasc. Dis. NMCD 17 (2007) 517–524, https://doi.org/10.1016/j.numecd.2006.04.002.
[89] C. Ding, V. Parameswaran, L. Blizzard, J. Burgess, G. Jones, Not a simple fat-soluble vitamin: Changes in serum 25-(OH)D levels are predicted by adiposity and adipocytokines in older adults, J. Intern. Med 268 (2010) 501–510, https://doi.org/10.1111/j.1365-2796.2010.02267.x.
[90] T. Romacho, M. Elsen, D. Röhrborn, J. Eckel, Adipose tissue and its role in organ crosstalk, Acta Physiol. Oxf. Engl. 210 (2014) 733–753, https://doi.org/10.1111/apha.12246.
[91] B. Gustafson, A. Hammarstedt, S. Hedjazifar, U. Smith, Restricted Adipogenesis in Hypertrophic Obesity, Diabetes 62 (2013) 2997–3004, https://doi.org/10.2337/db13-0473.
[92] E. Mueller, Understanding the variegation of fat: Novel regulators of adipocyte differentiation and fat tissue biology, Biochim. Biophys. Acta BBA - Mol. Basis Dis. 1842 (2014) 352–357, https://doi.org/10.1016/j.bbadis.2013.05.031.
[93] C.P. Earthman, L.M. Beckman, K. Masodkar, S.D. Sibley, The link between obesity and low circulating 25-hydroxyvitamin D concentrations: considerations and implications, Int. J. Obes. 36 (2012) 387–396, https://doi.org/10.1038/ijo.2011.119.
[94] K.-T. Kao, N. Abidi, S. Ranasinha, J. Brown, C. Rodda, Z. McCallum, M. Zacharin, P.J. Simm, C.G. Magnussen, M.A. Sabin, Low vitamin D is associated with hypertension in paediatric obesity, J. Paediatr. Child Health 51 (2015) 1207–1213, https://doi.org/10.1111/jpc.12935.
[95] S.Y. Hussain Gilani, S. Bibi, A. Siddiqui, S.R. Ali Shah, F. Akram, M.U. Rehman, Obesity and diabetes as determinants of vitamin D deficiency, J. Ayub Med. Coll. Abbottabad Jamc. 31 (2019) 432–435.
[96] S.H. Lee, S.M. Kim, H.S. Park, K.M. Choi, G.J. Cho, B.J. Ko, J.H. Kim, Serum 25-hydroxyvitamin D levels, obesity and the metabolic syndrome among Korean children, Nutr. Metab. Cardiovasc. Dis. NMCD 23 (2013) 785–791, https://doi.org/10.1016/j.numecd.2012.04.013.
[97] T. Reinehr, G. de Sousa, U. Alexy, M. Kersting, W. Andler, Vitamin D status and parathyroid hormone in obese children before and after weight loss, Eur. J. Endocrinol. 157 (2007) 225–232, https://doi.org/10.1530/EJE-07-0188.
[98] K. MacDonald, K. Godziuk, J. Yap, R. LaFrance, M. Ansarian, A. Haqq, D. R. Mager, Vitamin D status, cardiometabolic, liver, and mental health status in obese youth attending a pediatric weight management center, J. Pediatr. Gastroenterol. Nutr. 65 (2017) 462–466, https://doi.org/10.1097/MPG.0000000000001598.
[99] S. Konradsen, H. Ag, F. Lindberg, S. Hexeberg, R. Jorde, Serum 1,25-dihydroxy vitamin D is inversely associated with body mass index, Eur. J. Nutr. 47 (2008) 87–91, https://doi.org/10.1007/s00394-008-0700-4.
[100] J. Li, M.E. Byrne, E. Chang, Y. Jiang, S.S. Donkin, K.K. Buhman, J.R. Burgess, D. Teegarden, 1alpha,25-Dihydroxyvitamin D hydroxylase in adipocytes, J, Steroid Biochem. Mol. Biol. 112 (2008) 122–126, https://doi.org/10.1016/j.jsbmb.2008.09.006.
[101] M.F. McCarty, C.A. Thomas, PTH excess may promote weight gain by impeding catecholamine-induced lipolysis-implications for the impact of calcium, vitamin D, and alcohol on body weight, Med. Hypotheses 61 (2003) 535–542, https://doi.org/10.1016/s0306-9877(03)00227-5.
[102] L. Wamberg, U. Kampmann, H. Stødkilde-Jørgensen, L. Rejnmark, S.B. Pedersen, B. Richelsen, Effects of vitamin D supplementation on body fat accumulation, inflammation, and metabolic risk factors in obese adults with low vitamin D levels - results from a randomized trial, Eur. J. Intern. Med. 24 (2013) 644–649, https://doi.org/10.1016/j.ejim.2013.03.005.
[103] K.V.Q. Luong, L.T.H. Nguyen, Beneficial role of vitamin D3 in the prevention of certain respiratory diseases, Ther. Adv. Respir. Dis. 7 (2013) 327–350, https://doi.org/10.1177/1753465813503029.
[104] S.A. Shapses, E.J. Lee, D. Sukumar, R. Durazo-Arvizu, S.H. Schneider, The effect of obesity on the relationship between serum parathyroid hormone and 25-hydroxyvitamin D in women, J. Clin. Endocrinol. Metab. 98 (2013) E886–E890, https://doi.org/10.1210/jc.2012-3369.
[105] H. Hultin, K. Edfeldt, M. Sundbom, P. Hellman, Left-shifted relation between calcium and parathyroid hormone in obesity, J. Clin. Endocrinol. Metab. 95 (2010) 3973–3981, https://doi.org/10.1210/jc.2009-2822.
[106] M. Sneve, Y. Figenschau, R. Jorde, Supplementation with cholecalciferol does not result in weight reduction in overweight and obese subjects, Eur. J. Endocrinol. 159 (2008) 675–684, https://doi.org/10.1530/EJE-08-0339.
[107] M.J. Soares, W. Chan She Ping-Delfos, M.H. Ghanbari, Calcium and vitamin D for obesity: a review of randomized controlled trials, Eur. J. Clin. Nutr. 65 (2011) 994–1004, https://doi.org/10.1038/ejcn.2011.106.
[108] R.P. Heaney, R.L. Horst, D.M. Cullen, L.A.G. Armas, Vitamin D3 distribution and status in the body, J. Am. Coll. Nutr. 28 (2009) 252–256, https://doi.org/10.1080/07315724.2009.10719779.
[109] D. Zehnder, R. Bland, M.C. Williams, R.W. McNinch, A.J. Howie, P.M. Stewart, M. Hewison, Extrarenal expression of 25-hydroxyvitamin d(3)-1 alpha-hydroxylase, J. Clin. Endocrinol. Metab. 86 (2001) 888–894, https://doi.org/10.1210/jcem.86.2.7220.
[110] J. Bover, J. Egido, E. Fernández-Giráldez, M. Praga, C. Solozábal-Campos, J. V. Torregrosa, A. Martínez-Castelao, Vitamin D, vitamin D receptor and the importance of its activation in patients with chronic kidney disease, Nefrol. Publ. . Soc. Esp. Nefrol. 35 (2015) 28–41, https://doi.org/10.3265/Nefrologia.pre2014.Sep.11796.
[111] S. Kato, The function of vitamin D receptor in vitamin D action, J. Biochem. (Tokyo). 127 (2000) 717–722, https://doi.org/10.1093/oxfordjournals.jbchem.a022662.

[112] S. Nagpal, S. Na, R. Rathnachalam, Noncalcemic actions of vitamin D receptor ligands, Endocr. Rev. 26 (2005) 662–687, https://doi.org/10.1210/er.2004-0002.
[113] H. Darwish, H.F. DeLuca, Vitamin D-regulated gene expression, Crit. Rev. Eukaryot. Gene Expr. 3 (1993) 89–116.
[114] M.R. Haussler, G.K. Whitfield, C.A. Haussler, J.C. Hsieh, P.D. Thompson, S. H. Selznick, C.E. Dominguez, P.W. Jurutka, The nuclear vitamin D receptor: biological and molecular regulatory properties revealed, J. Bone Miner. Res. . J. Am. Soc. Bone Miner. Res. 13 (1998) 325–349, https://doi.org/10.1359/jbmr.1998.13.3.325.
[115] K. Ebihara, Y. Masuhiro, T. Kitamoto, M. Suzawa, Y. Uematsu, T. Yoshizawa, T. Ono, H. Harada, K. Matsuda, T. Hasegawa, S. Masushige, S. Kato, Intron retention generates a novel isoform of the murine vitamin D receptor that acts in a dominant negative way on the vitamin D signaling pathway, Mol. Cell. Biol. 16 (1996) 3393–3400, https://doi.org/10.1128/MCB.16.7.3393.
[116] L.P. Freedman, Increasing the complexity of coactivation in nuclear receptor signaling, Cell 97 (1999) 5–8, https://doi.org/10.1016/s0092-8674(00)80708-4.
[117] H. Chen, R.J. Lin, R.L. Schiltz, D. Chakravarti, A. Nash, L. Nagy, M.L. Privalsky, Y. Nakatani, R.M. Evans, Nuclear receptor coactivator ACTR is a novel histone acetyltransferase and forms a multimeric activation complex with P/CAF and CBP/p300, Cell 90 (1997) 569–580, https://doi.org/10.1016/s0092-8674(00)80516-4.
[118] Y. Kamei, L. Xu, T. Heinzel, J. Torchia, R. Kurokawa, B. Gloss, S.C. Lin, R. A. Heyman, D.W. Rose, C.K. Glass, M.G. Rosenfeld, A CBP integrator complex mediates transcriptional activation and AP-1 inhibition by nuclear receptors, Cell 85 (1996) 403–414, https://doi.org/10.1016/s0092-8674(00)81118-6.
[119] C.X. Yuan, M. Ito, J.D. Fondell, Z.Y. Fu, R.G. Roeder, The TRAP220 component of a thyroid hormone receptor- associated protein (TRAP) coactivator complex interacts directly with nuclear receptors in a ligand-dependent fashion, Proc. Natl. Acad. Sci. U. S. A. 95 (1998) 7939–7944, https://doi.org/10.1073/pnas.95.14.7939.
[120] C. Rachez, B.D. Lemon, Z. Suldan, V. Bromleigh, M. Gamble, A.M. Näär, H. Erdjument-Bromage, P. Tempst, L.P. Freedman, Ligand-dependent transcription activation by nuclear receptors requires the DRIP complex, Nature 398 (1999) 824–828, https://doi.org/10.1038/19783.
[121] A.J. Hörlein, A.M. Näär, T. Heinzel, J. Torchia, B. Gloss, R. Kurokawa, A. Ryan, Y. Kamei, M. Söderström, C.K. Glass, Ligand-independent repression by the thyroid hormone receptor mediated by a nuclear receptor co-repressor, Nature 377 (1995) 397–404, https://doi.org/10.1038/377397a0.
[122] Y. Kawamura, O. Takahashi, T. Ishii, Reevaluating the incidence of pervasive developmental disorders: impact of elevated rates of detection through implementation of an integrated system of screening in Toyota, Japan, Psychiatry Clin. Neurosci. 62 (2008) 152–159, https://doi.org/10.1111/j.1440-1819.2008.01748.x.
[123] N. Takahashi, N. Udagawa, T. Akatsu, H. Tanaka, Y. Isogai, T. Suda, Deficiency of osteoclasts in osteopetrotic mice is due to a defect in the local microenvironment provided by osteoblastic cells, Endocrinology 128 (1991) 1792–1796, https://doi.org/10.1210/endo-128-4-1792.
[124] B.E. Alathari, A.A. Sabta, C.A. Kalpana, K.S. Vimaleswaran, Vitamin D pathway-related gene polymorphisms and their association with metabolic diseases: a literature review, J. Diabetes Metab. Disord. 19 (2020) 1701–1729, https://doi.org/10.1007/s40200-020-00561-w.
[125] M.A. Abbas, Physiological functions of Vitamin D in adipose tissue, J. Steroid Biochem. Mol. Biol. 165 (2017) 369–381, https://doi.org/10.1016/j.jsbmb.2016.08.004.
[126] D.D. Bikle, Vitamin D metabolism, mechanism of action, and clinical applications, Chem. Biol. 21 (2014) 319–329, https://doi.org/10.1016/j.chembiol.2013.12.016.
[127] J.B. Cheng, D.L. Motola, D.J. Mangelsdorf, D.W. Russell, De-orphanization of cytochrome P450 2R1: a microsomal vitamin D 25-hydroxilase, J. Biol. Chem. 278 (2003) 38084–38093, https://doi.org/10.1074/jbc.M307028200.
[128] T. Sakaki, N. Kagawa, K. Yamamoto, K. Inouye, Metabolism of vitamin D3 by cytochromes P450, Front. Biosci. J. Virtual Libr 10 (2005) 119–134, https://doi.org/10.2741/1514.
[129] Z. Wang, E.G. Schuetz, Y. Xu, K.E. Thummel, Interplay between vitamin D and the drug metabolizing enzyme CYP3A4, J. Steroid Biochem. Mol. Biol. 136 (2013) 54–58, https://doi.org/10.1016/j.jsbmb.2012.09.012.
[130] P.B. Watkins, S.A. Wrighton, E.G. Schuetz, D.T. Molowa, P.S. Guzelian, Identification of glucocorticoid-inducible cytochromes P-450 in the intestinal mucosa of rats and man, J. Clin. Invest. 80 (1987) 1029–1036, https://doi.org/10.1172/JCI113156.
[131] J. Zhu, H.F. DeLuca, Vitamin D 25-hydroxylase - Four decades of searching, are we there yet? Arch. Biochem. Biophys. 523 (2012) 30–36, https://doi.org/10.1016/j.abb.2012.01.013.
[132] H. Postlind, E. Axén, T. Bergman, K. Wikvall, Cloning, structure, and expression of a cDNA encoding vitamin D3 25-hydroxylase, Biochem. Biophys. Res. Commun. 241 (1997) 491–497, https://doi.org/10.1006/bbrc.1997.7551.
[133] F. Hosseinpour, K. Wikvall, Porcine microsomal vitamin D(3) 25-hydroxylase (CYP2D25). Catalytic properties, tissue distribution, and comparison with human CYP2D6, J. Biol. Chem. 275 (2000) 34650–34655, https://doi.org/10.1074/jbc.M004185200.
[134] M. Rahmaniyan, K. Patrick, N.H. Bell, Characterization of recombinant CYP2C11: a vitamin D 25-hydroxylase and 24-hydroxylase, Am. J. Physiol. Endocrinol. Metab. 288 (2005) E753–E760, https://doi.org/10.1152/ajpendo.00201.2004.
[135] K. Inouye, T. Sakaki, Enzymatic studies on the key enzymes of vitamin D metabolism; 1 alpha-hydroxylase (CYP27B1) and 24-hydroxylase (CYP24), Biotechnol. Annu. Rev. 7 (2001) 179–194, https://doi.org/10.1016/s1387-2656(01)07037-5.
[136] D.D. Bikle, Extra renal synthesis of 1,25-dihydroxyvitamin D and its health implications, Clin. Rev. Bone Miner. Metab. 7 (2009) 114–125, https://doi.org/10.1007/s12018-009-9033-y.
[137] D.D. Bikle, S. Pillai, E. Gee, M. Hincenbergs, Regulation of 1,25-dihydroxyvitamin D production in human keratinocytes by interferon-gamma, Endocrinology 124 (1989) 655–660, https://doi.org/10.1210/endo-124-2-655.
[138] D.D. Bikle, S. Pillai, E. Gee, M. Hincenbergs, Tumor necrosis factor-alpha regulation of 1,25-dihydroxyvitamin D production by human keratinocytes, Endocrinology 129 (1991) 33–38, https://doi.org/10.1210/endo-129-1-33.
[139] J.S. Adams, M.A. Gacad, Characterization of 1 alpha-hydroxylation of vitamin D3 sterols by cultured alveolar macrophages from patients with sarcoidosis, J. Exp. Med 161 (1985) 755–765, https://doi.org/10.1084/jem.161.4.755.
[140] A.M. Pryke, C. Duggan, C.P. White, S. Posen, R.S. Mason, Tumor necrosis factor-alpha induces vitamin D-1-hydroxylase activity in normal human alveolar macrophages, J. Cell. Physiol. 142 (1990) 652–656, https://doi.org/10.1002/jcp.1041420327.
[141] K. Stoffels, L. Overbergh, A. Giulietti, L. Verlinden, R. Bouillon, C. Mathieu, Immune regulation of 25-hydroxyvitamin-D3-1alpha-hydroxylase in human monocytes,, J. Bone Miner. Res. 21 (2006) 37–47, https://doi.org/10.1359/JBMR.050908.
[142] G. Jones, D.E. Prosser, M. Kaufmann, 25-Hydroxyvitamin D-24-hydroxylase (CYP24A1): its important role in the degradation of vitamin D, Arch. Biochem. Biophys. 523 (2012) 9–18, https://doi.org/10.1016/j.abb.2011.11.003.
[143] G. Jones, S.A. Strugnell, H.F. DeLuca, Current understanding of the molecular actions of vitamin D, Physiol. Rev. 78 (1998) 1193–1231, https://doi.org/10.1152/physrev.1998.78.4.1193.
[144] D.E. Prosser, G. Jones, Enzymes involved in the activation and inactivation of vitamin D, Trends Biochem. Sci. 29 (2004) 664–673, https://doi.org/10.1016/j.tibs.2004.10.005.
[145] T. Sakaki, N. Sawada, K. Komai, S. Shiozawa, S. Yamada, K. Yamamoto, Y. Ohyama, K. Inouye, Dual metabolic pathway of 25-hydroxyvitamin D3 catalyzed by human CYP24, Eur. J. Biochem 267 (2000) 6158–6165, https://doi.org/10.1046/j.1432-1327.2000.01680.x.
[146] D.E. Prosser, M. Kaufmann, B. O'Leary, V. Byford, G. Jones, Single A326G mutation converts human CYP24A1 from 25-OH-D3-24-hydroxylase into -23-hydroxylase, generating 1alpha,25-(OH)2D3-26,23-lactone, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 12673–12678, https://doi.org/10.1073/pnas.0702093104.
[147] M.B. Meyer, P.D. Goetsch, J.W. Pike, A downstream intergenic cluster of regulatory enhancers contributes to the induction of CYP24A1 expression by 1alpha,25-dihydroxyvitamin D3, J. Biol. Chem. 285 (2010) 15599–15610, https://doi.org/10.1074/jbc.M110.119958.
[148] C. Zierold, G.G. Reinholz, J.A. Mings, J.M. Prahl, H.F. DeLuca, Regulation of the procine 1,25-dihydroxyvitamin D3-24-hydroxylase (CYP24) by 1,25-dihydroxyvitamin D3 and parathyroid hormone in AOK-B50 cells, Arch. Biochem. Biophys. 381 (2000) 323–327, https://doi.org/10.1006/abbi.2000.1964.
[149] C. Zierold, J.A. Mings, H.F. DeLuca, Parathyroid hormone regulates 25-hydroxyvitamin D(3)-24-hydroxylase mRNA by altering its stability, Proc. Natl. Acad. Sci. U. S. A. 98 (2001) 13572–13576, https://doi.org/10.1073/pnas.241516798.
[150] F. Perwad, N. Azam, M.Y.H. Zhang, T. Yamashita, H.S. Tenenhouse, A.A. Portale, Dietary and serum phosphorus regulate fibroblast growth factor 23 expression and 1,25-dihydroxyvitamin D metabolism in mice, Endocrinology 146 (2005) 5358–5364, https://doi.org/10.1210/en.2005-0777.
[151] M.G. Anderson, M. Nakane, X. Ruan, P.E. Kroeger, J.R. Wu-Wong, Expression of VDR and CYP24A1 mRNA in human tumors, Cancer Chemother. Pharmacol. 57 (2006) 234–240, https://doi.org/10.1007/s00280-005-0059-7.
[152] A.T. Slominski, Z. Janjetovic, B.E. Fuller, M.A. Zmijewski, R.C. Tuckey, M. N. Nguyen, T. Sweatman, W. Li, J. Zjawiony, D. Miller, T.C. Chen, G. Lozanski, M. F. Holick, Products of vitamin D3 or 7-dehydrocholesterol metabolism by cytochrome P450scc show anti-leukemia effects, having low or absent calcemic activity, PloS One 5 (2010), e9907, https://doi.org/10.1371/journal.pone.0009907.
[153] A.T. Slominski, T.-K. Kim, W. Li, A.-K. Yi, A. Postlethwaite, R.C. Tuckey, The role of CYP11A1 in the production of vitamin D metabolites and their role in the regulation of epidermal functions, J. Steroid Biochem. Mol. Biol. 144 (Pt A) (2014) 28–39, https://doi.org/10.1016/j.jsbmb.2013.10.012.
[154] R.C. Tuckey, E.K.Y. Tang, S.R. Maresse, D.S. Delaney, Catalytic properties of 25-hydroxyvitamin D3 3-epimerase in rat and human liver microsomes, Arch. Biochem. Biophys. 666 (2019) 16–21, https://doi.org/10.1016/j.abb.2019.03.010.
[155] Y. Fang, J.B.J. van Meurs, P. Arp, J.P.T. van Leeuwen, A. Hofman, H.A.P. Pols, A. G. Uitterlinden, Vitamin D binding protein genotype and osteoporosis, Calcif. Tissue Int. 85 (2009) 85–93, https://doi.org/10.1007/s00223-009-9251-9.
[156] W. Xu, J. Sun, W. Wang, X. Wang, Y. Jiang, W. Huang, X. Zheng, Q. Wang, Z. Ning, Y. Pei, M. Nie, M. Li, O. Wang, X. Xing, W. Yu, Q. Lin, L. Xu, W. Xia, Association of genetic variants of vit D binding protein (DBP/GC) and of the enzyme catalyzing its 25-hydroxylation (DCYP2R1) and serum vit D in postmenopausal women, Horm. Athens Greece 13 (2014) 345–352, https://doi.org/10.14310/horm.2002.1484.
[157] J.R. Delanghe, R. Speeckaert, M.M. Speeckaert, Behind the scenes of vitamin D binding protein: more than vitamin D binding, Best. Pract. Res. Clin. Endocrinol. Metab. 29 (2015) 773–786, https://doi.org/10.1016/j.beem.2015.06.006.
[158] J.M. Valdivielso, E. Fernandez, Vitamin D receptor polymorphisms and diseases, Clin. Chim. Acta Int. J. Clin. Chem. 371 (2006) 1–12, https://doi.org/10.1016/j.cca.2006.02.016.

[159] A.A. Al-Eisa, M.Z. Haider, Vitamin D receptor gene *Taq*I and Apal polymorphisms and steroid responsiveness in childhood idiopathic nephrotic syndrome, Int. J. Nephrol. Renov. Dis. 9 (2016) 187–192, https://doi.org/10.2147/IJNRD.S111538.
[160] F.J. Ruiz-Ojeda, A. Anguita-Ruiz, R. Leis, C.M. Aguilera, Genetic Factors and Molecular Mechanisms of Vitamin D and Obesity Relationship, Ann. Nutr. Metab. 73 (2018) 89–99, https://doi.org/10.1159/000490669.
[161] A.H. Faghfouri, E. Faghfuri, V. Maleki, L. Payahoo, A. Balmoral, Y. Khaje Bishak, A comprehensive insight into the potential roles of VDR gene polymorphism in obesity: a systematic review, Arch. Physiol. Biochem. (2020) 1–13, https://doi.org/10.1080/13813455.2020.1788097.
[162] T. Karonova, E. Grineva, O. Belyaeva, A. Bystrova, E.B. Jude, A. Andreeva, A. Kostareva, P. Pludowski, Relationship Between Vitamin D Status and Vitamin D Receptor Gene Polymorphisms With Markers of Metabolic Syndrome Among Adults, Front. Endocrinol. 9 (2018) 448, https://doi.org/10.3389/fendo.2018.00448.
[163] A. Mahyar, P. Ayazi, A. Sarkhosh Afshar, T. Naserpour Farivar, M. Sahmani, S. Oveisi, R. Shabani, S. Esmaeili, Vitamin D receptor gene (*Fok*I, *Taq*I, *Bsm*I, and *Apa*I) polymorphisms in children with urinary tract infection, Pediatr. Res. 84 (2018) 527–532, https://doi.org/10.1038/s41390-018-0092-y.
[164] P.R. Fischer, T.D. Thacher, J.M. Pettifor, L.B. Jorde, T.R. Eccleshall, D. Feldman, Vitamin D Receptor Polymorphisms and Nutritional Rickets in Nigerian Children, J. Bone Miner. Res. 15 (2000) 2206–2210, https://doi.org/10.1359/jbmr.2000.15.11.2206.
[165] A. Szymczak-Tomczak, M. Kaczmarek-Ryś, S. Hryhorowicz, M. Michalak, P. Eder, M. Skrzypczak-Zielińska, L. Łykowska-Szuber, M. Tomczak, R. Słomski, A. Dobrowolska, I. Krela-Kaźmierczak, Vitamin D, vitamin D receptor (VDR) gene polymorphisms (*Apa*I and *Fok*I), and Bone Mineral Density in Patients With Inflammatory Bowel Disease, J. Clin. Densitom. 24 (2021) 233–242, https://doi.org/10.1016/j.jocd.2020.10.009.
[166] M. Saad, E.-A. Ahmad, Vitamin D receptor gene polymorphism among egyptian obese children, Asian J. Clin. Nutr. 9 (2017) 24–29, https://doi.org/10.3923/ajcn.2017.24.29.
[167] W.Z. Ye, A.F. Reis, D. Dubois-Laforgue, C. Bellanne-Chantelot, J. Timsit, G. Velho, Vitamin D receptor gene polymorphisms are associated with obesity in type 2 diabetic subjects with early age of onset, Eur. J. Endocrinol. 145 (2001) 181–186.
[168] H.I.E. Gendy, N.A. Sadik, M.Y. Helmy, L.A. Rashed, Vitamin D receptor gene polymorphisms and 25(OH) vitamin D: lack of association to glycemic control and metabolic parameters in type 2 diabetic Egyptian patients, J. Clin. Transl. Endocrinol. 15 (2019) 25–29, https://doi.org/10.1016/j.jcte.2018.11.005.
[169] P.S. Gibson, A. Quaglia, A. Dhawan, H. Wu, S. Lanham-New, K.H. Hart, E. Fitzpatrick, J.B. Moore, Vitamin D status and associated genetic polymorphisms in a cohort of UK children with non-alcoholic fatty liver disease, Pediatr. Obes. 13 (2018) 433–441, https://doi.org/10.1111/ijpo.12293.
[170] V.H. Bermúdez-Morales, G. Fierros, R.L. Lopez, G. Martínez-Nava, M. Flores-Aldana, J. Flores-Rivera, C. Hernández-Girón, Vitamin D receptor gene polymorphisms are associated with multiple sclerosis in Mexican adults, J. Neuroimmunol. 306 (2017) 20–24, https://doi.org/10.1016/j.jneuroim.2017.01.009.
[171] S. Haddad, Vitamin D receptor (VDR) gene polymorphism *Bsm*I in Syrian breast cancer patients, Meta Gene 26 (2020), 100766, https://doi.org/10.1016/j.mgene.2020.100766.
[172] E. Ergul, T. Simsek, N. Uren, T. Korak, H.U. Simsek, N. Cine, N.Z. Canturk, N. Z. Utkan, Haplotype analysis of vitamin D receptor (VDR) gene in breast cancer patients, Clin. Lab. 67 (2021), https://doi.org/10.7754/Clin.Lab.2020.200931.
[173] A.Y. Belorusova, N. Rochel, Structural studies of vitamin D nuclear receptor ligand-binding properties, Vitam. Horm. 100 (2016) 83–116, https://doi.org/10.1016/bs.vh.2015.10.003.
[174] M. Clemente-Postigo, A. Muñoz-Garach, M. Serrano, L. Garrido-Sánchez, M. R. Bernal-López, D. Fernández-García, I. Moreno-Santos, N. Garriga, D. Castellano-Castillo, A. Camargo, J.M. Fernández-Real, F. Cardona, F. J. Tinahones, M. Macías-González, Serum 25-hydroxyvitamin D and adipose tissue vitamin D receptor gene expression: relationship with obesity and type 2 diabetes, J. Clin. Endocrinol. Metab. 100 (2015) E591–E595, https://doi.org/10.1210/jc.2014-3016.
[175] J. Kong, Y.C. Li, Molecular mechanism of 1,25-dihydroxyvitamin D3 inhibition of adipogenesis in 3T3-L1 cells, Am. J. Physiol. Endocrinol. Metab. 290 (2006) E916–E924, https://doi.org/10.1152/ajpendo.00410.2005.
[176] J.M. Blumberg, I. Tzameli, I. Astapova, F.S. Lam, J.S. Flier, A.N. Hollenberg, Complex role of the vitamin D receptor and its ligand in adipogenesis in 3T3-L1 cells, J. Biol. Chem. 281 (2006) 11205–11213, https://doi.org/10.1074/jbc.M510343200.
[177] C.J. Narvaez, K.M. Simmons, J. Brunton, A. Salinero, S.V. Chittur, J.E. Welsh, Induction of STEAP4 correlates with 1,25-dihydroxyvitamin D3 stimulation of adipogenesis in mesenchymal progenitor cells derived from human adipose tissue, J. Cell. Physiol. 228 (2013) 2024–2036, https://doi.org/10.1002/jcp.24371.
[178] D.A.F. Ferrarezi, N. Bellili-Muñoz, C. Nicolau, N. Cheurfa, I.C. Guazzelli, E. Frazzatto, G. Velho, S.M. Villares, Allelic variations in the vitamin D receptor gene, insulin secretion and parents' heights are independently associated with height in obese children and adolescents, Metab. - Clin. Exp. 61 (2012) 1413–1421, https://doi.org/10.1016/j.metabol.2012.03.018.
[179] T.M. Rodrigues Simões, R. da Silva, B. Bianco, F.L.A. Fonseca, D. Solé, R. Oselka Saccardo Sarni, Vitamin D levels, frequency of vitamin D receptor gene polymorphisms, and associations with overweight and asthma in Brazilian Schoolchildren, Ann. Nutr. Metab. 75 (2019) 238–245, https://doi.org/10.1159/000504872.
[180] P.C. Cheung, S.A. Cunningham, K.M.V. Narayan, M.R. Kramer, Childhood obesity incidence in the united states: a systematic review, Child. Obes. Print. 12 (2016) 1–11, https://doi.org/10.1089/chi.2015.0055.
[181] V. Higgins, K. Adeli, Pediatric metabolic syndrome: pathophysiology and laboratory assessment, EJIFCC 28 (2017) 25–42.
[182] R. Bouillon, G. Carmeliet, Vitamin D insufficiency: definition, diagnosis and management, Best. Pract. Res. Clin. Endocrinol. Metab. 32 (2018) 669–684, https://doi.org/10.1016/j.beem.2018.09.014.
[183] R. Rahmadhani, N.L. Zaharan, Z. Mohamed, F.M. Moy, M.Y. Jalaludin, The associations between VDR *Bsm*I polymorphisms and risk of vitamin D deficiency, obesity and insulin resistance in adolescents residing in a tropical country, PloS One 12 (2017), e0178695, https://doi.org/10.1371/journal.pone.0178695.
[184] A.B. Awad, L. Alappat, M. Valerio, Vitamin d and metabolic syndrome risk factors: evidence and mechanisms, Crit. Rev. Food Sci. Nutr. 52 (2012) 103–112, https://doi.org/10.1080/10408391003785458.
[185] K.E. Wong, J. Kong, W. Zhang, F.L. Szeto, H. Ye, D.K. Deb, M.J. Brady, Y.C. Li, Targeted expression of human vitamin D receptor in adipocytes decreases energy expenditure and induces obesity in mice *, J. Biol. Chem. 286 (2011) 33804–33810, https://doi.org/10.1074/jbc.M111.257568.
[186] Z. Hochberg, A. Bereket, M. Davenport, H.A. Delemarre-Van de Waal, J. De Schepper, M.A. Levine, N. Shaw, E. Schoenau, S.C. van Coeverden, Y. Weisman, Z. Zadik, European Society for Paediatric Endocrinology (ESPE) Bone Club, Consensus development for the supplementation of vitamin D in childhood and adolescence, Horm. Res. 58 (2002) 39–51, https://doi.org/10.1159/000063214.
[187] M.F. Holick, Vitamin D and bone health, J. Nutr. 126 (1996) 1159S–1164SS, https://doi.org/10.1093/jn/126.suppl_4.1159S.
[188] M.F. Holick, High prevalence of vitamin D inadequacy and implications for health, Mayo Clin. Proc. 81 (2006) 353–373, https://doi.org/10.4065/81.3.353.
[189] M. Sosa Henríquez, M.J. Gómez de Tejada Romero, Cholecalciferol or calcifediol in the management of vitamin D deficiency, Nutrients 12 (2020) 1617, https://doi.org/10.3390/nu12061617.
[190] K.M. Sanders, M.J. Seibel, Therapy: New findings on vitamin D3 supplementation and falls - when more is perhaps not better, Nat. Rev. Endocrinol. 12 (2016) 190–191, https://doi.org/10.1038/nrendo.2016.29.
[191] C. for D.E. and Research, FDA approves weight management drug for patients aged 12 and older, FDA. (2021). https://www.fda.gov/drugs/news-events-human-drugs/fda-approves-weight-management-drug-patients-aged-12-and-older (Accessed 15 May 2022).