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Low vitamin D status and obesity: Role of nutritionist

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Abstract Low vitamin D status and obesity have concomitantly reached epidemic levels worldwide. Up to now the direction of the association between low vitamin D status and obesity, the exact mechanisms responsible for this association and the clinical usefulness to increase vitamin D status for reducing adiposity still warrant further evaluation. The aim of the present review was to examine the current evidence linking low vitamin D status and obesity in relation to the role of the nutritionist. On the one side, considering obesity as a causal factor, low sun exposure in obese individuals due to their sedentary lifestyle and less outdoor activity, vitamin D sequestration in adipose tissue, and volumetric dilution of ingested or cutaneously synthesized vitamin D_3 in the large fat mass of obese patients, might represent some of the factors playing a major role in the pathogenesis of the low vitamin D status. On the other side, the expression of both vitamin D_3 receptors and enzymes responsible for vitamin D_3 metabolism in adipocytes depicted a role for the low vitamin D status per se in the development of obesity by modulating adipocyte differentiation and lipid metabolism. Nutritionists need to accurately address the aspects influencing the low vitamin D status in obesity and the vitamin D supplementation in obese individuals.

Keywords Environmental factor · Vitamin D · Obesity · Diet · Nutritionist

1 Text

Low vitamin D status and obesity have concomitantly reached epidemic levels worldwide and research linking these two public health issues has grown extensively over the last number of years. The modern and westernised lifestyles is considered the major responsible on the one side for increasing obesity, on the other side for decreasing the vitamin D status. Although limited by the cross-sectional design of the vast majority of the investigations, a number of clinical studies

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support the role of obesity as a causal risk factor for the development of the low vitamin D status [1]. Indeed, different large epidemiological studies, including the National Health and Nutrition Examination Survey (NHANES) III [2] and the Framingham study [3], have shown increasing prevalence of low vitamin D status with greater body mass index (BMI), also independently of variation in physical activity or vitamin D intake. In particular, it has been calculated that each unit increase of BMI was associated with a 1.15% decrease of 25-hydroxyvitamin D_3 [25(OH)D_3] levels [4]. In addition, circulating levels of 25(OH)D_3 increased after weight loss in the obese individuals through lifestyle interventions without vitamin D supplementation [5]. However, clinical trials investigating the effects of vitamin D supplementation on body weight have not provided consistent data on the possible favourable effects of vitamin D on weight loss [6, 7]. The association between the low vitamin D status and obesity has been analysed in a recent meta-analysis of 15 studies which included 3867 subjects with obesity and 9342 health subjects [8]. In this study, serum 25(OH)D_3 levels >20 ng/mL (>50 nmol/L) were considered adequate according to the Institute of Medicine (IOM), or >30 ng/mL (≥75 nmol/L) according to the Endocrinology Society [9]. On the basis of these classifications, a positive association between low vitamin D status and high risk of obesity incidence was reported, irrespective of geographical areas. In particular, the prevalence of vitamin D deficiency was positively associated with obesity in both Asians and European-Americans, with odd ratios (95% CI) of 3.70 (1.98–6.90) and 3.09 (1.89–5.04), respectively. Nevertheless, it is not clear whether obesity plays a causal role in the development of the low vitamin D status or, alternatively, the low vitamin D status is involved in the development of obesity, as well as of other metabolism-related morbidities [10]. Indeed, the low vitamin D status is likely to contribute per se to the development of overweight/obesity [11] and different genomic and non-genomic mechanisms exerted by vitamin D_3 have been proposed to have a causative role in obesity [12, 13]. A large study based on 42.024 participants of European descent suggested a causal relation for higher BMI on low serum 25(OH)D_3 status, while the effect of serum 25(OH)D_3 on BMI was absent or minimal [4]. In addition, data from three large cohorts, based on repeated measures of anthropometry as well as information on several potential confounders, such as season, geographic latitude, cloudiness and smog, limited sun exposure and outdoor physical activity or low vitamin D intake, evidenced that any causal relationship between 25 (OH)D_3 and annual changes in body weight was either not present or small [14]. Thus, up to now the nature of the association between low vitamin D status and obesity is still debatable, the exact mechanisms responsible for this association remain unclear, and the clinical usefulness to increase vitamin D status for reducing adiposity still warrants further evaluation.

Aim of this paper was to provide at-a-glance overview of the possible bi-directional mechanisms linking the low vitamin D status and obesity and the potential involvement of a nutritional approach as a rational basis to help clinicians decide the appropriate vitamin D replacement doses for obese individuals.

2 Obesity as a causal factor of the low vitamin D status

2.1 Decreased sun exposure

Sunlight exposure provides in humans for more than 90% of the production of vitamin D [15]. In particular, solar ultraviolet (UV)-B radiation (UVB; wavelengths of 290 to 315 nm) stimulates the synthesis of vitamin D_3 from 7-dehydrocholesterol, the vitamin D precursor, in the epidermis of the skin [16]. Obese individuals have a larger body surface area that is available for endogenous synthesis of vitamin D [17]. Nevertheless, obese individuals often conduct a sedentary lifestyle, partake in less outdoor activity, and cover-up more when outdoors compared with their lean or normal-weight counterparts, thus limiting the endogenous production of cholecalciferol in the skin [4, 18–20]. While the content in the skin of 7-dehydrocholesterol was not significantly different between obese and non-obese subjects, it has been calculated that the increase in serum vitamin D_3 concentrations was about one half in the obese than in the non-obese subjects 24 h after the exposure, despite the greater body surface area in the formers [21]. However, in this study the Authors did not provide any data on the amount and location of vitamin D_3 storage in fat tissue and the mechanisms that control the deposition and release of vitamin D_3.

A growing body of evidence proved that air pollution constitutes an independent risk factor in the pathogenesis of both obesity and low vitamin D status, in combination with unhealthy diet and lifestyle. The possible contribution of air pollution on the relationship between low vitamin D status and obesity has been treated elsewhere in this issue [22].

2.2 Sequestration in adipose tissue

Adipose tissue is a major repository of vitamin D_3 in the body [23–25]. Thus, it has also been suggested that the metabolic clearance of vitamin D_3 may increase in obesity, possibly with enhanced uptake by adipose tissue. Nevertheless, the amount and location of vitamin D_3 storage in fat tissue and the mechanisms that control the deposition and release of vitamin D_3 are still unknown. Adipose tissue could function as a vitamin D buffering system that prevents uncontrolled synthesis of 25(OH)D_3 in the liver [25]. The slow release of vitamin D_3 from adipose tissue under fasting conditions could represent

the rate limiting step to protect against the potential toxicity of excess amounts of the vitamin [23]. However, large accrual in adipose tissue depot implies that vitamin D_3 could not be appropriately released into the general circulation to support serum 25(OH)D_3 concentrations. The adipose tissue sequestration was originally suggested by Wortsman et al. [21], who found that obesity-associated vitamin D insufficiency was likely due the decreased bioavailability of cholecalciferol (vitamin D_3) from cutaneous and dietary sources because of its deposition in body fat compartments. According with this hypothesis, Malmberg P et al. [26], by using imaging mass spectrometry techniques, demonstrated that vitamin D_3 and its metabolites 25(OH)D_3, and 1,25-dihydroxyvitamin D_3 [1α,25(OH)$_2D_3$] were located in adipocyte lipid droplets, although the vitamin D_3 concentration is not uniform throughout various fat depots. Heaney RP. et al. have reported as about 17% of orally-administered vitamin D_3 dose was stored in adipose tissue and the rest was consumed or metabolized [27]. However, other factors, such as volumetric dilution, vitamin D_3 intake, and diet composition, may also contribute to low vitamin D status in obese subjects. Thus, more studies are needed to characterize the distribution and metabolism of vitamin D_3 in different fat compartments.

2.3 Volumetric dilution

The sequestration and the inappropriate storage of vitamin D_3 in adipose tissue did not explain the low vitamin D status of obesity, as once the values in obesity are adjusted for body size, there is no longer a difference in 25(OH)D_3 concentrations between normal and obese individuals. Most recently, convincing data suggest that the low vitamin D status of obesity could be simply the consequence of the volumetric dilution of ingested or cutaneously synthesized vitamin D_3 in the large fat mass of obese patients. Drincic et al. [28] reported that the volumetric dilution accounted for essentially all the variability in serum 25(OH)D_3 concentration attributable to obesity. A subsequent article from the same Authors characterized the pharmacokinetics of the 25(OH)D_3 response to 3 different doses of vitamin D_3 in a group of obese subjects to quantify the dose needed to raise 25(OH)D_3 level according to body weight. On this basis, the Authors provided a weight-based equation to estimate the amount of vitamin D_3 needed to raise serum 25(OH)D_3 by any desired amount [29].

2.4 Parathyroid hormone (PTH)

A low vitamin D status is known to induce secondary hyperparathyroidism that causes the overflow of calcium into adipocytes, thereby increasing lipogenesis [30]. Increased intracellular calcium in adipocytes increases the expression of fatty acid synthase, a key regulatory enzyme in the deposition of lipids, and decreases lipolysis [31]. Alternatively, the presence of a negative feedback from elevated 1α,25(OH)$_2D_3$ and parathyroid hormone (PTH) levels on hepatic synthesis of 25(OH)D_3 could be postulated, although the mechanism by which the feedback regulation of the 25(OH)D_3 production occurs has not been established [32]. In this context, it has been reported that normalization of 25(OH)D_3 levels in subjects with low vitamin D could participate to prevent weight gain by reducing the 1α,25(OH)$_2D_3$ production, likely through lowering PTH levels [33].

2.5 Leptin

The satiety hormone leptin, secreted by adipocytes, is positively correlated with the amount of body fat and reflects energy status [34]. Leptin exerts an autocrine–paracrine lipolytic effect on adipocytes by interacting with vitamin D receptor (VDR) to control lipid metabolism through inhibition of lipogenesis and stimulation of lipolysis [35]. Recently, it has been found that 1α,25(OH)$_2D_3$ directly stimulated mRNA expression and secretion of leptin in mouse adipose tissue cultures [36]. Thus, the vitamin D_3 depletion might increase appetite and lead to obesity by directly regulating leptin expression [37]. However, the exact *in vivo* effect of 1α,25(OH)$_2D_3$ on leptin expression in humans needs further investigation.

2.6 Non-alcoholic fatty liver disease

Hepatic steatosis in obese subjects may result in low synthesis of 25(OH)D3 by the liver. Non-alcoholic fatty liver disease (NAFLD) includes a spectrum of disorders of increasing severity from simple fatty liver, non-alcoholic steatohepatitis, cirrhosis, to hepatocellular carcinoma [38]. NAFLD is commonly found among obese individuals, mainly linked to the damage caused by fatty infiltration, oxidative stress and impaired cellular regeneration associated with insulin resistance (IR) and obesity [39]. In this, NAFLD has been defined as the hepatic manifestation of metabolic syndrome [40]. On the other hand, the association between vitamin D levels and NAFLD has been increasingly recognized, with an inverse association with the histologic severity of NAFLD [41]. In particular, a recent meta-analysis reported that low vitamin D status were 26% more common in NAFLD patients than in healthy persons [42]. Although several researches indicated the existence of an independent association between the low vitamin D status and NAFLD, this association could be a consequence of shared risk factors for NAFLD and obesity, such as a sedentary lifestyle or unhealthy dietary pattern, and the loss of vitamin D hydroxylation capacity by the liver has not demonstrated as the cause of hypovitaminosis D in NAFLD patients.

2.7 Insulin resistance

The low vitamin D status is a common problem associated with obesity and IR. In particular, the link between the low vitamin D status and obesity seems to have negative consequences on IR and glucose homeostasis [43]. The negative associations between low vitamin D status and IR have been reported in cross-sectional [44–46], prospective [47], and supplementation studies [48–50]. The underlying mechanisms by which vitamin D decreases the risk of IR have not yet elucidated. Several pathways have been suggested to be involved. Of interest, the negative association between 25(OH)D3 levels and fasting insulin concentrations or IR has been reported also independently of BMI [51]. VitaminVitamin D deficiency has been reported to be associated with an increase in PTH, which in turn is associated with decreased insulin sensitivity [52]. In addition, vitamin D regulates calcium homeostasis and has a role in maintaining adequate intracellular levels of calcium for intracellular process in insulin-responsive tissues, such as muscle cells [53]. Furthermore, VDR are found in pancreatic β-cells, and vitamin D is involved in some of the biological activities of insulin, including physiological insulin secretion, stimulation of the expression of insulin receptors, and increasing insulin responsiveness for glucose transport [54].

3 Low vitamin D status as causal factor of obesity

3.1 Vitamin D/VDR system

VDR is a nuclear steroid hormone receptors which binds to vitamin D_3 with high affinity and specificity [55, 56]. Recent research has demonstrated that adipose tissue expressed VDR and enzymes responsible for vitamin D_3 metabolism, including the 1α-hydroxylase, locally converting 25(OH)D_3 to 1α,25$(OH)_2D_3$ [13]. Thus, adipocytes could be involved in the local synthesis as well as the degradation of biologically active vitamin D_3 and then, the adipose tissue may be a direct target of vitamin D [13]. Vitamin D_3 modulation of adipocyte growth and metabolism could involve both genomic and non-genomic actions [57, 58]. In differentiated 3 T3-L1 cells, low doses of vitamin D_3 inhibited apoptosis, whereas high doses stimulated apoptosis [59]. Although contradicting results were obtained regarding the effect of vitamin D_3 on adipogenesis, many studies supported the involvement of vitamin D/VDR system in modulating adipocyte lipid metabolism [60]. In particular, vitamin D_3 seems to play a central role in adipocyte metabolism via the inhibition of adipogenesis, independently of PTH [61, 62].

VDR is expressed in the earliest stages of adipocyte differentiation, but its expression decreases along with the progress of differentiation. In the presence of vitamin D_3, the VDR blocks the differentiation of pre-adipocytes by down-regulating of a number of transcriptional regulators and functional proteins exerting a key role in adipogenesis, such as PPAR-γ, lipoprotein lipase, protein aP2, a carrier of fatty acids necessary for lipolysis, CCAAT/enhancer-binding protein (C/EBP) and sterol-regulatory element binding protein-1 (SREBP-1) [63]. Therefore, lower vitamin D_3 levels could increase the differentiation of preadipocytes to mature adipocytes. Mature adipocytes do not express VDR. This suggests that vitamin D_3 can affect differentiation if introduced early in the differentiation stage [63, 64]. VDR konckout mice have a lean phenotype and were resistant to diet-induced obesity [61, 65] and also, accumuled less fat with age and high-fat diet [66]. In primary human tissue, vitamin D_3 promoted differentiation of committed subcutaneous preadipocytes through increased expression of some adipogenic markers and lipid filling, suggesting that the local metabolism of vitamin D_3 in adipose tissue may regulate human adipose tissue growth and support the healthy remodelling of human adipose tissue [37]. Also, in the presence of vitamin D_3, mesenchymal cells, derived from human adipose tissue, differentiate in adipocytes with an enhanced lipid accumulation and increased expression of adipogenic marker genes (FASN, FABP4, and PPARγ) [67]. In addition, in human subcutaneous adipocyte, vitamin D_3 modulated a pattern of adipocyte gene expression of human subcutaneous adipocyte which inhibited adipocyte apoptosis and favored adipocyte proliferation [68]. Of interest, the function of VDR in adipose tissue may be gender-specific, as the adipocyte VDR signalling has been reported to affect body weight and fat mass in females but not in males [66]. Recent finding has shown a positive association between *VDR* polymorphisms and adiposity [69]. In particular, *VDR* gene variants with polymorphisms on the 3'UTR region, a site regulating *VDR* gene expression, appeared to suppress the anti-adipogenic effect of vitamin D_3 and to play a role in adiposity phenotypes [69].

3.2 1α,25$(OH)_2$ vitamin D_3

Besides vitamin D_3, also adipose tissue 1α,25$(OH)_2$D3 is able to regulate differently the adipogenesis during the differentiation process. Of interest, adipose tissue 1α-hydroxylase is not regulated by dietary calcium and vitamin D_3 like renal 1α-hydroxylase, and other different factors, including phosphorus, PTH, calcitonin, estradiol, pro-inflammatory cytokines, phytoestrogens have been proposed as regulatory agents [35]. Previous evidence indicated that 1α,25$(OH)_2D_3$ increased intracellular calcium level and subsequently fatty acid synthase activity. Furthermore, 1α,25$(OH)_2D_3$ exerted an inhibitory effect on adipocyte basal lipolysis in human adipocytes culture [70]. The antiadipogenic effect of 1α,25$(OH)_2D_3$ is exerted during preadipocyte differentiation by inhibiting the mRNA expression and phosphorylation of extracellular regulated kinase (ERK), one of the mitogen-activated protein

kinase (MAPK) signalling and through the maintenance of the WNT/b-catenin pathway, which are normally down-regulated during adipogenesis. However, while low doses of $1\alpha,25(OH)_2D_3$ inhibit apoptosis in differentiated 3 T3-L1 cells, high doses stimulate apoptosis through the activation of the Ca2+/calpain-dependent caspase-12 [71]. Of interest, the expression of vitamin D-metabolizing enzymes is different between lean and obese women [72].

3.3 Vitamin D and inflammatory adipokines

Vitamin D metabolites also influence adipokine production and secretion by adipocytes [13]. Several studies demonstrated a negative correlation between vitamin D and leptin or resistin, and a positive association with adiponectin [73–75]. Vitamin D_3 also plays a central role in modulating the inflammatory response in adipose tissue [35]. In obesity, adipose tissue is hypertrophic resulting in blood flow imbalance leading to hypoxia, inflammation, and macrophage infiltration. In addition, the increase in the secretion of interleukins 6 and 8 (IL-6, IL-8), resistin, tumor necrosis factor-alpha (TNF-α) and monocyte chemoattractant (MCP1), and a reduced secretion of adiponectin, are characteristics in hypertrophied adipocytes [76, 77]. Evidence *in vitro* demonstrated that vitamin D_3 exerted an anti-inflammatory action on adipocytes by reducing chemokine and cytokine release by adipocytes and the chemotaxis of monocytes [35]. These anti-inflammatory effects of vitamin D_3 seem mediated by the inhibition of the NFkB and MAPK signalling pathways [35].

3.4 Vitamin D and "winter response"

It has also been suggested that accrual in adipose tissue could result from an excessive adaptive "winter response". According to this hypothesis, the fall in vitamin D skin synthesis in winter entails an increase in body size by the accumulation of fat mass, which reduces heat conductance to the environment, and the induction of a winter metabolism, which increases thermogenic capacity, as result of an anomalous adaptation to a cold climate [78].

In conclusion, the strong scientific evidence for the sequestration [21] and volumetric dilution [28] hypotheses, and more importantly, a lack of contradictory evidence, suggest that both mechanisms are the most probable, either independently or in combination, to explain the low vitamin D status widely reported in obesity. Unravelling the mechanisms underlying the low vitamin D status in subjects with obesity has important therapeutic implications both in deciding on appropriate vitamin D_3 replacement doses for obese individuals and in evaluating potential effects of treatment of vitamin D_3 inadequacy.

4 Role of nutritionist in obese patients with low vitamin D status

4.1 Vitamin D and evaluation of body composition

Fat accumulation plays a major role in the development of the low vitamin D status compared to other body components, such as free fat mass. Therefore, estimating the fat accumulation could be clinically relevant to identify individuals with high risk of low vitamin D status. Nevertheless, in the vast majority of clinical studies evaluating the association between vitamin D status and obesity, obesity has been defined only on the basis of BMI rather than by using a direct estimate of body fat mass. In fact, it is well known that BMI is only a measure of the total adiposity, without discriminating body fat amount and distribution [79], and fails to account for differences in race, gender and age [80]. Waist circumference (WC) is considered a good marker of abdominal fat accumulation [81]. A number of studies evaluated the relationship between vitamin D_3 and WC to better highlights the relationship between abdominal adiposity and serum vitamin D_3 concentration. Rodríguez-Rodríguez et al. [82] evidenced that WC in women with low vitamin D_3 levels was significantly larger than in that in their counterparts with higher vitamin D_3 (86.2 ± 9.3 cm vs 79.4 ± 3.4 cm; $p < 0.05$). It has been calculated that a reduction of 0.29 nmol/L in serum vitamin D for every 1 cm increase in WC ($p = 0.01$) [83]. However, both BMI and WC are weaker anthropometric measurements of adiposity than direct measures of adiposity.

Although it is not considered a "gold standard", biompedeance analysis (BIA) is a validated method providing a useful alternative for measuring body fat in clinical practice, especially to track changes in fat mass along the time [84–86]. In this regard, Looker AC examined the relationship between serum $25(OH)D_3$ and percent body fat calculated from BIA in a large sample of white and black women from the third National Health and Nutrition Examination Survey (NHANES III, 1988–1994) [2]. This Author found that the serum $25(OH)D_3$-% body fat relationship in women varied both by race and age (stronger in whites than blacks and in younger than older persons). Very recently, the relationship between vitamin D status, body composition, and cardiovascular risks has been characterized in Asian population living in Singapore, a sunny tropical region, by measuring by the body fat percentage using different techniques, including BIA [87]. In this study, 42.1% of participants were at risk of vitamin D deficiency (<20 ng/mL), with females (54.5%) showing a higher prevalence of vitamin D deficiency than males (30.5%), likely due to a higher body fat percentage in females than males. Of interest, the difference of vitamin D deficiency between males and females did not persist after adjusting for body fat percentage, suggesting that body fat may be one of the predominant risk factors for vitamin D deficiency.

Anthropometric measures and BIA, however, do not allow to discriminate between the adipose tissue located in the abdominal cavity and retroperitoneal area, which is commonly known as intra-abdominal or visceral adipose tissue (VAT), and the adipose tissue stored subcutaneously (SAT), threatening to underestimated the association between vitamin D status and overall adiposity. The dual-energy x-ray absorptiometry (DEXA), computed tomography (CT) and magnetic resonance imaging (MRI) are considered the gold standard imaging modality for the precise estimation of the location and amount of adipose tissue in various body regions [88]. However, DEXA, CT and MRI imaging are impractical for screening general population, in that they exposure to radiation and require expensive and specialized equipment. Some studies have examined the relation between vitamin D status and adiposity by using volumetric quantification of SAT and VAT compartments. In particular, Young KA et al. [89] showed that a low vitamin D status was associated with higher SAT as well as higher VAT, suggesting that vitamin D_3 levels were associated with both types of adipose tissue. In addition, other investigators reported a strong negative correlation between 25(OH)D_3 concentrations and CT measures of VAT in obese adolescents [90], and with VAT and SAT in young women [91]. Likewise, the third-generation Framingham Heart Study evidenced that higher adiposity were correlated with lower 25(OH)D_3 across different categories of BMI, and the prevalence of vitamin D deficiency (25[OH] D < 20 ng/mL) was threefold higher in those with high SAT and high VAT than in those with low SAT and low VAT, measured by multidetector CT [3]. Moreover, Sulistyoningrum DC et al. [92] reported that VAT, may have a distinct role in determining plasma 25(OH)D_3 concentrations, compared to other adipose tissue compartments. Finally, Rosenblum JL et al. investigated in a study double-blind, placebo-controlled trials conducted in 171 participants for 16-week for evaluated the effect of calcium and vitamin D supplementation on weight loss and reduction of VAT in overweight and obese adults. After 16 week, in the supplementation group, the reduction of VAT was significantly greater than in the control group, after control for baseline VAT. These results suggested that calcium and/or vitamin D supplementation contributes to a beneficial reduction of VAT [93].

4.2 Vitamin D and nutrition

There is universal concern in terms of intake vitamin D, although the concern about vitamin D intakes varies by country, depending on the combined effects of different factors, such as eating pattern, geographical location, available solar UVB doses, pollution, and sun habits. A number of national dietary surveys indicated a widespread prevalence of suboptimal intakes for several micronutrients, including vitamin D_3 [94]. In particular, it has been demonstrated that cholecalciferol (vitamin D_3) is significantly more efficacious than is ergocalciferol (vitamin D_2) not only in increasing serum 25(OH) D concentrations, but also for maintaining serum vitamin D levels and its biological activities [95]. Whereby, vitamin D_3 is the preferred choice for correcting the low vitamin D status and maintenance with oral supplements. The current evidence supports the hypothesis that normal vitamin D status, 25-OH vitamin D above 30 ng/mL (>75 nmol/L), improves the metabolic aspects, such as obesity [96]. Only few foods contain vitamin D_3 and several studies suggest that we may need more vitamin D_3 than presently recommended to prevent chronic non-transmissible diseases [97, 98]. In particular, vitamin D_3 is present in oil-rich fish, sunlight-exposed mushrooms, eggs, and milk [3]. Cod liver oil is a rich natural source of vitamin D_3; nevertheless, there is concern regarding its use at high doses due to its vitamin A content and the possible contamination by heavy metals, such as mercury [99, 100]. The Recommended Dietary Allowances (RDAs) covering requirements of ≥97.5% of the population by life stage are shown in Table 1.

The Mediterranean diet has been described as a healthy eating pattern that promotes good health, a healthy body weight, and disease prevention throughout the lifespan, due to the proportion in which it includes all the food groups (https://health.gov/dietaryguidelines/2015/) [101]. Nevertheless, in the last few years unfavourable changes in the traditional Mediterranean lifestyle (reduction in outdoor physyscal activity, clothing, smog, etc), could have induced changes from the recommended intakes in relation to several nutrients, making difficult to ensure adequate intakes of vitamins and minerals. Accordingly, a recent review on the available evidence on the Nutritional Adequacy of the Mediterranean Diet has recently reported that a greater adherence to the Mediterranean diet has been associated with a higher prevalence of individuals showing adequate intakes of micronutrients, including vitamin D_3 [102]. However, according with the Authors of this study, there is need to increase the knowledge on the nutritional adequacy of the Mediterranean Diet as the first step towards the introduction of correcting measures about the characteristics of the Mediterranean diet which are being lost or, alternatively, should be restored.

Despite sensible exposure to sunlight remains the best, cheapest and the safest way to obtain vitamin D_3, food fortification programs represent a logical approach to solve the global epidemic of vitamin D deficiency [103]. Nevertheless, as it remains difficult to define the proportion that should be obtained from the diet or from conversion through the skin stimulated by UV exposure for each country, it may be advantageous to have country-specific recommendations for vitamin D.

Table 1 Vitamin D dietary reference intakes by life stage

Life-stage group	RDA (intake that covers needs of ≥97.5% of population)		Serum 25OHD level (corresponding to the RDA)[a]
	IU/d	mcg/d	ng/ml
Infants (0–12 months)	400[b]	10[b]	20
1–70 yr	600	15	20
+ 70 yr	800	20	20
Pregnant	600	15	20
Lactating	600	15	20

[a] Measures of serum 25(OH)D_3 levels corresponding to the RDA and covering the requirements of at least 97.5% of the population

[b] Reflects adequate intake reference value rather than RDA. *RDAs have not been established for infants*

The Recommended Dietary Allowances (RDAs) by life stage

RDA Recommended dietary allowance, *IU* International unit

5 Supplementations of vitamin D in obese patients

5.1 Supplementations in obese patients

Some studies have reported that vitamin D supplementation can also be beneficial for obese patients. In a double-blind, randomized clinical trial, placebo-controlled in 77 healthy overweight and obese women, vitamin D supplementation (25 μg *per* day as cholecalciferol) after 12 weeks resulted in a significant reduction in the body fat mass in women who received vitamin D_3 compared with those in the placebo group [104]. The response to vitamin D supplementations is dependent on body weight. A study demonstrated that after supplementation, the increase in serum 25(OH)D_3 levels was lower in overweight or obese women than in women with normal BMI. In particular, the Authors reported that normal weight women reached higher levels of serum 25(OH)D_3 after vitamin D supplementation and suggested that, as the dose response curves are parallel between normal weight and obese people, the difference in serum 25(OH)D_3 levels were probably due to a volume dilution effect; in particular, after vitamin D supplementation in the overweight and obese groups 25(OH)D_3 levels were 7 ng/mL lower than in the group with BMI <25 kg/m^2 [105]. Very recently, Mason C. et al., reported that vitamin D supplementation (2000 IU/day) in women with low vitamin D status at baseline had no effect on body weight or fat loss in postmenopausal women consuming a calorie-restricted diet and following an exercise program [106].

As above mentioned, in obese subjects ~2.5 IU/kg were required for every unit increment in 25(OH)D_3 ng/mL [29]. On this basis, in obese patients, higher doses (two to three times higher; at least 6000–10,000 IU/d) of vitamin D_3 are necessary to treat vitamin D deficiency and to maintain 25(OH)D_3 levels >30 ng/mL, followed by maintenance therapy of 3000–6000 IU/d [9].

5.2 Vitamin D status and bariatric surgery

Considering the high risk for a low vitamin D status in obesity related to the poor quality of the diet and low micronutrient intake, a careful evaluation of vitamin D status as part of the preoperative nutritional screening should be considered in all bariatric surgery candidates in the preoperative setting due the adjunctive impact of the malabsorption of vitamin D induced by bariatric surgery [107]. Low vitamin D status is common in bariatric patients [108], and often requires substantial supplementation to achieve sufficiency [109]. While pure restrictive procedures, such as laparoscopic adjustable gastric band (LAGB), are not necessarily related to vitamin D malabsorption, a low vitamin D status can occur commonly after malabsorptive interventions, including gastric bypass, biliopancreatic diversion with duodenal switch, which preserves the duodenum, and biliopancreatic diversion without duodenal switch, with a growing risk from the first to the last procedures [110]. Consequently, after LAGB current recommendations of the Endocrine Society Clinical Practice Guideline are a minimum of 600 IU/day of vitamin D consistent with established age-specific recommendations for patients at risk for vitamin D deficiency until non obese [9]. After gastric bypass gastric bypass and other malabsorptive, the low vitamin D status should be treated with 50.000 IU once a week for 8 weeks or 6000 IU/day of vitamin D_3, to achieve a blood level of 25(OH)D_3 > 30 ng/ml, followed by maintenance therapy of 1500–2000 IU/day. Severe deficiencies can be treated with doses up to 50.000 IU three times a day or, rarely, with intramuscular injections of ergocalciferol 100.000 IU once a week [9, 111].

6 Conclusions

Several studies reported a positive association between low vitamin D status and obesity, supporting the role for

supplementations of vitamin D in obese patients. Up to now the nature of the bi-directional association between low vitamin D status and obesity, the exact mechanisms responsible for this association, and the clinical usefulness to increase vitamin D status for reducing adiposity still warrant further evaluation. In addition, it is not clear whether obesity plays a causal role in the development of the low vitamin D status or, alternatively, the low vitamin D status is involved in the development of obesity. Residual confounding could exist from factors, such as limited physical activity or low vitamin D_3 intake. Indeed, the low vitamin D status is likely to contribute per se to the development of overweight/obesity and different genomic and non-genomic mechanisms exerted by vitamin D_3 have been proposed to have a causative role in obesity.

Hence, Nutritionists need to accurately address the aspects influencing the low vitamin D status in obesity and the vitamin D supplementation in obese individuals.

$25(OH)D_3$, 25-hydroxyvitamin D3; BMI, body mass index; vitamin D_3, cholecalciferol; $1\alpha,25(OH)_2D_3$, 1,25-dihydroxyvitamin D_3; PTH, Parathyroid Hormone; VDR, Vitamin D Receptor; WC, Waist Circumference; BIA, biompedeance analysis; VAT, Visceral Adipose Tissue, SAT, Adipose Tissue Subcutaneously.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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