Special Article

Adiposity, vitamin D requirements, and clinical implications for obesity-related metabolic abnormalities

Elina Hyppönen and Barbara J. Boucher

This review was conducted to clarify both the complex interrelationship between adiposity and vitamin D and the clinical implications of vitamin D status on metabolic abnormalities associated with obesity. Obesity increases the risk of vitamin D deficiency, a finding consistently reported across all ages and in different population groups. According to genetic studies, this is driven by the effect of higher adiposity, which causes a reduction in circulating concentrations of 25-hydroxyvitamin D [25(OH)D, used as an indicator of vitamin D status]. Conversely, higher concentrations of 25(OH)D do not appear to affect the risk of obesity. Evidence from clinical trials using vitamin D supplementation to achieve weight reduction is limited. Some trials, however, have suggested that concomitant supplementation with vitamin D and calcium potentially reduces central fat deposits, especially in individuals with low dietary calcium intakes. Adiposity has important implications for the efficacy of vitamin D supplementation, and increases in 25(OH)D concentrations are generally lower in obese than in normal-weight individuals. Active hormonal vitamin D has many mechanistic effects, both physiologically and biochemically, that could counteract the harmful effects of obesity on metabolism and reduce the risks of metabolic abnormalities and tissue damage consequent to adiposity. Whether improvements in the overall obesogenic metabolic profile can be achieved by vitamin D supplementation, however, is still unknown.

INTRODUCTION

Obesity increases the risk of vitamin D deficiency, and adipose tissue is of great interest as a determinant of vitamin D requirements and bioavailability. The inverse correlation between adiposity and vitamin D status (serum 25-hydroxyvitamin D [25(OH)D] concentration) is well established[1,2] and has been reported across the life span for various ethnicities and for both men and women,[1–10] although the strength of this association varies between studies. Indeed, as a predictor of vitamin D insufficiency, obesity has been proposed to be second only to low sun exposure.[11,12] This may have important implications for obesity-related health outcomes, given that vitamin D hormone [1α,25$(OH)_2$D; calcitriol] has both physiological and biochemical mechanistic effects as well as the potential to reduce obesity-related risks of tissue damage. The aim of this review was to clarify both the complex interrelationship between adiposity and vitamin D and the clinical implications of vitamin D status on metabolic abnormalities associated with obesity.

LITERATURE SEARCH STRATEGY

The literature search aimed to identify studies of adipose tissue as a determinant of vitamin D nutritional

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status, including studies on the clinical relevance of adipose tissue to obesity-related metabolic abnormalities. The MEDLINE and the Cochrane Library databases were searched for systematic reviews and meta-analyses of studies performed in humans and published in English from January 2010 to January 2018. The search terms used were "vitamin D," "cholecalciferol," "ergocalciferol," "calcitriol," AND "obesity" OR "adiposity" OR "body mass index," along with the expanded MeSH search terms (in titles, abstracts, or keywords). The search was conducted both by limiting the search to reviews, meta-analyses, and clinical trials and by using relevant keywords as search terms, without limiting the type of study. The search limited to certain study types identified 517 publications, and the search based on keywords identified 499. After excluding duplicate entries, 574 publications remained, of which 171 were relevant. These were further scrutinized to identify the most recent relevant systematic review that included meta-analyses of randomized controlled trials (RCTs) on the effects of vitamin D on obesity and related disorders (inflammation, hypertension/blood pressure, dyslipidemia, hyperglycemia, and fatty liver disease). The literature search was complemented by the identification of studies published after the most recent systematic review. Individual studies published in those reviews were scrutinized along with additional mechanistic evidence identified from references within the selected articles or from studies otherwise known to the authors.

VITAMIN D STORAGE IN ADIPOSE TISSUE

In humans, 75% of vitamin D and 35% of 25(OH)D is found in adipose tissue (a further 30% of 25(OH)D is located in the bloodstream and another 20% in skeletal muscle).[13] Adipose tissue also metabolizes vitamin D, thereby initiating each of the steps required for hormonal activation of vitamin D [ie, 25-hydroxylation to form 25(OH)D, and further 1α-hydroxylation to form 1α,25$(OH)_2$D] and degradation by 24-hydroxylation to form 24(OH)D and 1α,24$(OH)_2$D, which take place locally under local homeostatic control.[14] Concentrations of 25(OH)D in both visceral and subcutaneous adipose tissue correlate directly with serum concentrations of 25(OH)D.[15–17] Moreover, the content of intact vitamin D in adipose tissue correlates directly with that measured in the circulation, although concentrations in subcutaneous fat in morbidly obese individuals have been reported to be notably higher than those in the circulation.[18]

Exposure to UV-B radiation leads to smaller rises in the circulating concentrations of intact vitamin D_3 in obese vs normal-weight participants.[19] This may reflect the rapid sequestration of vitamin D in fat, which can also contribute to the lower circulating 25(OH)D concentrations seen in obese individuals and can potentially lead to lower availability of vitamin D metabolites to target tissues for local activation (Figure 1).[19] Alternatively, since serum and adipose tissue 25(OH)D concentrations are closely correlated, obesity may reduce serum 25(OH)D via volumetric dilution and distribution of 25(OH)D into the larger fat volumes. This proposition is supported by a finding demonstrating that the concentrations and distribution of intact vitamin D in subcutaneous and visceral fat are very similar in obese and nonobese individuals, so that the large mass of adipose tissue in obesity forms an enlarged vitamin D reservoir.[20] Hence, a higher amount of vitamin D is required to saturate this larger depot in obese individuals, while this higher storage capacity is also likely to increase the risk of low 25(OH)D concentrations in obesity.[20] Interestingly, in this particular study, in which fat tissue samples were obtained from obese participants undergoing bariatric surgery and compared with samples from normal-weight individuals (who were undergoing elective laparoscopic abdominal surgery for benign gynecologic indications), there were no differences in serum concentrations of 25(OH)D between the groups (or in the concentrations of vitamin D in fat), This likely reflects greater vitamin D intakes by the obese patients, owing to vitamin D supplementation practices that commonly target severely obese patients.[20]

Vitamin D–activating hydroxylases are both present and functional in adipocytes,[21,22] but concentrations of both CYP2J2 and CYP27B1 in white fat are lower in obese than in lean individuals (by up to 70% and 49%, respectively).[21] Hence, activation of vitamin D may be reduced in obesity, and this could be exacerbated by the lower serum 25(OH)D in obesity, since lower serum 25(OH)D reduces the availability of 25(OH)D to all target tissues, including adipose tissue. Additionally, all adipose tissues express the vitamin D receptor, which mediates genomic effects of calcitriol,[21,23] while the vitamin D catabolic CYP24A1 enzyme is present in comparable concentrations in adipose tissue from lean and obese individuals.[21] Thus, adipose tissue can regulate vitamin D activity, including local autocrine and paracrine actions on adipocytes, lipid metabolism, and inflammation.[23] Importantly, this local regulation may also reduce the release of vitamin D metabolites from adipose tissue, potentially reducing the risk of toxicity with high dosages of vitamin D but also potentially maintaining the availability of the metabolites in deficiency.[24] This ability to regulate vitamin D activity contributes to vitamin D homeostasis, since marked weight loss increases serum 25(OH)D just as it increases serum concentrations of

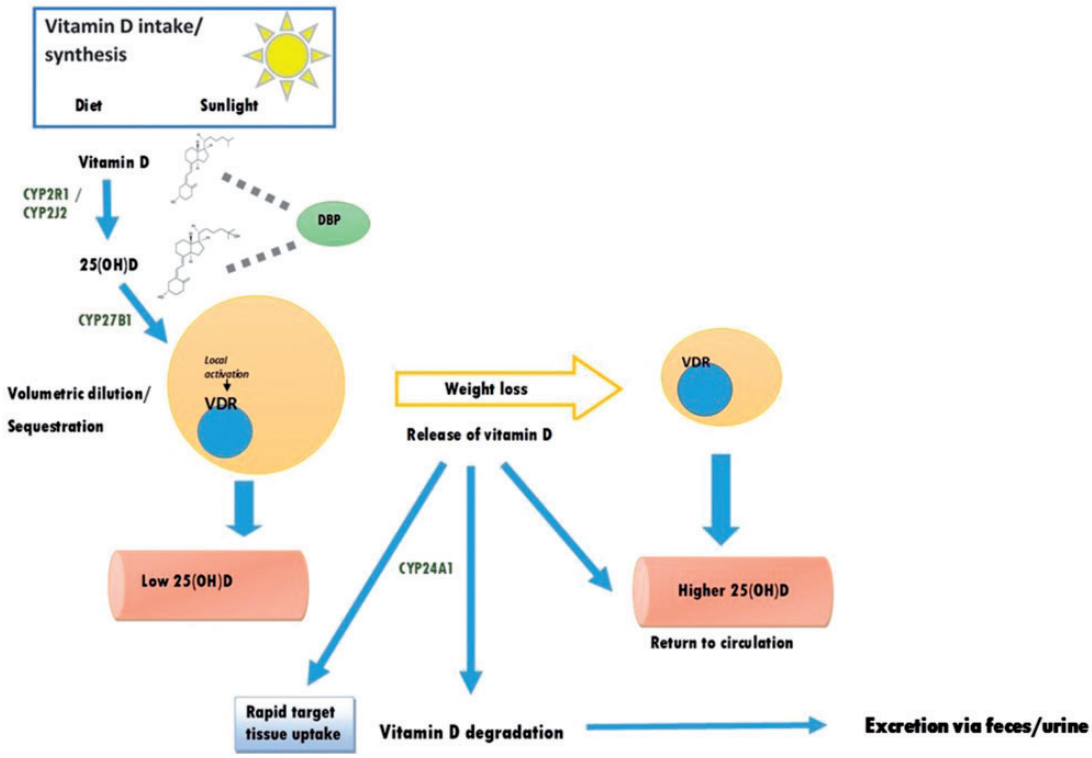

Figure 1 **Simplified schematic representation of vitamin D metabolite storage and release from adipose tissue during weight loss.** Modified from Pannu et al.[12] *Abbreviations*: DBP, vitamin D–binding protein VDR, vitamin D receptor; 25(OH)D, 25-hydroxyvitamin D.

other fat-soluble substances accumulated in fat (eg, dichlorodiphenyltrichloroethane, DDT).[25,26] However, weight loss also increases the expression of vitamin D catabolic enzymes in adipose tissue (by almost 80%), thereby reducing the amount of 25(OH)D released into the circulation, further reducing the risks of vitamin D toxicity during weight loss.[21]

OBESITY, CIRCULATING VITAMIN D–BINDING PROTEINS, AND FREE SERUM 25-HYDROXYVITAMIN D

Up to 99% of 25(OH)D and $1,25(OH)_2D$ in the circulation is bound to vitamin D–binding proteins or albumin. As is the case for other hormones,[27] these binding proteins may act as carrier "reservoirs," regulating the amount of unbound, free 25(OH)D that is bioavailable to target tissues. The importance of free metabolites remains under debate,[28] but if hormonal activity is to any extent reflected by circulating free 25(OH)D rather than total 25(OH)D concentrations,[29] then the effects of obesity on these metabolites must be clarified. Some studies,[30,31] but not all,[32,33] suggest that body mass index (BMI) and obesity correlate directly with circulating vitamin D–binding proteins and that free 25(OH)D may be lower in obesity.[34] However, the functional implications of the possible lowering of serum free 25(OH)D in obesity, if this occurs, remain unknown.[35] In a population-based study of 882 participants, BMI was associated with levels of total 25(OH)D and vitamin D–binding protein, but not with levels of free 25(OH)D.[34] In another study of 223 individuals, circulating concentrations of vitamin D–binding protein and albumin were not associated with obesity.[35] In that study, however, concentrations of both free 25(OH)D and free $1,25(OH)_2D$ were lower in obese than in normal-weight participants,[35] though differences in these values were not associated with reductions in markers of bone health.[35] Monocyte activation is enhanced by knockout of vitamin D–binding protein, suggesting that free 25(OH)D can act as a substrate for hormonal vitamin D activation in the target tissue, which may imply that the availability of free calcitriol might preserve adipose tissue function in hypovitaminosis D.[36] Further work is required to clarify the mechanistic role of free vs bound 25(OH)D, to determine how binding to carrier proteins may affect the bioavailability of vitamin D to target tissues, and to establish what other factors may influence vitamin D metabolism in obesity.[37]

EFFECT OF WEIGHT LOSS ON SERUM 25(OH)D CONCENTRATIONS

If increased adiposity reduces serum 25(OH)D, then significant weight loss due to dieting or gastric banding

should lead to increased serum 25(OH)D (Figure 1). There is substantial evidence to support this supposition, and several studies have reported a positive association between weight loss and serum 25(OH)D concentrations.[38–41] The relative amount of weight loss required to achieve an increase in 25(OH)D has varied between 5% and 10%.[41] Overall, reviews and meta-analyses of weight loss trials have consistently shown increases in serum 25(OH)D to be smaller than might be expected.[12,42] This may reflect an increase in the inactivation of vitamin D metabolites by adipose tissue, but it could also be explained by an increased target tissue uptake of any vitamin D metabolites that have been released, given the state of relative hypovitaminosis D typical in obesity. Although vitamin D metabolites are released into the circulation with nutritional weight loss, this has not been reported to be associated with hypervitaminosis D, likely reflecting the small vitamin D reserves in humans.[13] The local regulation of vitamin D metabolism in adipose tissue may assist in maintaining homeostasis in the vitamin D hormone system, thereby reducing the risks of overt toxicity with excessive intakes.[25,26]

The proportions of fat lost from visceral or subcutaneous fat deposits may affect the resultant increases in circulating vitamin D metabolites, since visceral fat contains approximately 20% more intact vitamin D than subcutaneous fat.[20,43] Recent data from a randomized lifestyle intervention trial in men with central obesity suggest that the loss of intraabdominal fat increases serum 25(OH)D the most, with a 50% reduction in the volume of visceral adipose tissue leading to a concomitant 26% increase in serum 25(OH)D.[39] Increases in serum 25(OH)D following weight loss demonstrate that lifestyle interventions (even when vitamin D intake from diet or supplements is constant) can produce biologically meaningful increases in serum 25(OH)D concentrations.[44] Longitudinal data from a meta-analysis of 14 studies that included 2688 patients who had undergone Roux-en-Y surgery show that reductions in BMI over a period ranging 2 years to more than 5 years led to corresponding long-term changes in 25(OH)D concentrations.[45] Hence, rates of vitamin D deficiency can be expected to fall with reductions in the population prevalence of obesity. In support of this proposition, prospective analyses in the Tromsø study suggested that a reduction in BMI by 1 unit or more over a 14-year follow-up period is associated with an approximately 4.5 nmol/L higher 25(OH)D concentration.[46] In contrast, among the participants who gained weight during the follow-up period, serum 25(OH)D was 2.5 nmol/L lower at the end of the study than at baseline. Weight loss was associated with similar modest increases in 25(OH)D in a recent systematic review and meta-analysis of RCTs that investigated weight reduction in obese participants.[12] Of the 23 trials analyzed, 18 reported increases in 25(OH)D concentrations after weight loss, with related meta-regression analyses finding that a 10-kg weight loss was associated with a 6 nmol/L higher serum 25(OH)D concentration (a 10% loss in fat mass led to an increase of 9 nmol/L).[12] However, statistical evidence was weak, and there was notable heterogeneity between the studies included in these analyses. Further studies, ideally using standardized 25(OH)D assays, are needed to confirm these findings and to improve the precision of the quantification of differences in 25(OH)D concentrations achieved by weight loss.[47]

Patients who undergo surgery for weight loss often have low baseline 25(OH)D concentrations.[48] Bariatric gastric bypass surgery commonly precipitates long-term fat malabsorption, which reduces vitamin D absorption.[49] Vitamin D supplementation is part of the routine management of bariatric surgery patients. Postoperative 25(OH)D concentrations are typically relatively low, and despite varying levels of vitamin D supplementation, patients commonly have serum 25(OH)D concentrations below 75 nmol/L.[48] Randomized controlled trials examining weight loss for causal effects on serum 25(OH)D are complicated by poor participant compliance with weight-reduction interventions and are often confounded by obesity-driven variants in behavior that affect vitamin D intake and/or synthesis in skin, including differences in fat intake and exposure to sunshine.[50]

Dietary weight loss can raise serum 25(OH)D by 27% without altering 25-hydroxylase expression in subcutaneous fat,[12,21] but concomitant increases in catabolic 24-hydroxlase activity in fat make increased 25(OH)D synthesis by fat improbable.[21] Overall, these data suggest that weight loss in obesity increases serum 25(OH)D by reducing the volume of fat in which 25(OH)D is distributed.

EFFECT OF VITAMIN D SUPPLEMENTATION ON OBESITY

There is mechanistic evidence to suggest that vitamin D hormone, ie, calcitriol, could ameliorate obesity, since the effects of calcitriol include increased lipolysis in adipocytes, reduced expression and activity of adipogenic genes, increased expression of lipolytic genes, and reduced lipid content of differentiated 3T3-L1′ adipocytes.[51] Calcitriol is inhibitory against the formation of triacylglyceride in the liver,[52] the accumulation of triacylglyceride in adipocytes, and the maturation of adipocytes from preadipocytes.[53] Hence, vitamin D repletion could have a role in preventing the enlargement of adipose tissue, even if the aforementioned effects would be

unlikely to affect existing fat stores.[15] Furthermore, calcitriol may increase energy consumption in the adipocytes by enhancing the activity of the NAD-SIRT-1 pathway, an important metabolic sensor of cellular energy status.[51] Influences of calcitriol on adipose tissue are generally mediated through expression of the vitamin D receptor. However, calcitriol has also been reported to increase mature adipocyte apoptosis by rapid nongenomic increases in intracellular calcium, which are independent of nuclear vitamin D receptor signaling,[54] despite the similar levels of expression of calcium-sensing receptor (*CaSR*) gene in white fat in individuals with or without obesity, which suggests allosteric regulation of the expression of this gene in obesity.[55]

Despite this mechanistic evidence, RCTs of vitamin D supplementation have not provided evidence of effects on weight loss. Some studies, however, have provided tentative support for an influence of vitamin D on body fat loss.[41] All treatment benefits reported thus far are derived from studies in which vitamin D was administered with calcium or in early life. The largest of the studies was the Women's Health Initiative, a randomized double-blinded placebo-controlled trial in a cohort of 36 282 postmenopausal women that compared 400 IU of vitamin D_3 (+ 1000 mg of calcium) per day with placebo.[56] A small reduction in weight gain was reported in women who received supplementation, while weight gain was reported in women who received placebo (average difference in weight gain between groups, 130 g). However, this difference in weight gain was found only in women with baseline calcium intakes below the daily recommended dietary intake of more than 1200 mg/d, with no benefit observed in those with calcium intakes at or above the recommended dietary intake at baseline.[56] This study design made it impossible to establish effects of supplemental vitamin D and supplemental calcium independently. However, given the low dosage of supplemental vitamin D, the suggested dependence of effectiveness on calcium intake at baseline, and the consumption by participants of up to 1000 IU of vitamin D per day by self-supplementation, the reduced weight gain was unlikely to have been due to vitamin D supplementation. Reanalysis of studies in which individual participant data is available to assess both baseline and achieved vitamin D status using harmonized data for 25(OH)D may provide further understanding.[57,58]

One meta-analysis of 12 trials found vitamin D supplementation to be ineffective in reducing fat mass.[59] Authors reported that the results of 8 of 12 studies were indicative of a reduction in BMI in participants who received supplementation compared with those who received placebo, but the overall effect was not significant (standardized mean difference, −0.10, $P = 0.09$). A later evaluation of 26 RCTs, each containing 50 or more participants,[60] provided no evidence of reductions in obesity or other indices of adiposity in individuals who received vitamin D supplementation vs those who received placebo, or in those who received vitamin D supplementation plus calcium vs those who received calcium alone. Furthermore, this meta-analysis provided no evidence of a dose–response effect of supplemental doses of vitamin D on any measure of adiposity studied.[60] Though evidence to date does not support effects of vitamin D supplementation on weight or BMI, few studies have investigated the effects of vitamin D supplementation on regional fat tissue deposition in obesity. Some evidence of a potential benefit on visceral adiposity was found in 2 RCTs that compared the effects of fortified orange juice (providing total daily vitamin D_3 intake of 300 IU [7.5 μg] + calcium [1050 mg/d]) with those of placebo juice.[61] Visceral adiposity was reduced in the supplemented group compared with the placebo group, with no between-group differences observed for total body weight (the primary outcome), BMI, or waist circumference. These findings are interesting, but, like the findings of the Women's Health Initiative (see above), the effects of calcium and vitamin D cannot be distinguished. Furthermore, it is possible that genetic variation may modify relevant effects, as suggested by one RCT conducted in vitamin D–deficient patients with type 2 diabetes (T2D) that found some reductions in central obesity after vitamin D supplementation, most noticeably in those with the VDR *Cdx-2* genotype.[62]

Genetic studies using variants affecting serum substrate availability (*DHCR7)* or 25(OH)D synthesis (*CYP2R1*) as proxy markers for circulating 25(OH)D concentrations[63] have provided no evidence for a causal effect of higher 25(OH)D concentrations on BMI. Instead, genetic evidence consistently suggests that the observed inverse associations reflect lowering of 25(OH)D concentrations by higher BMIs.[3,64] Variants of genes affecting the synthesis of serum lipids used to mark cardiovascular risk are also reported to affect the responses to vitamin D supplementation.[65] One important limitation of genetic epidemiological studies, as for any RCT of vitamin D supplementation to date, is the lack of data specific to vitamin D–deficient individuals.[66,67]

EFFECT OF OBESITY ON THE EFFICACY OF VITAMIN D SUPPLEMENTATION

Variation in the response of serum 25(OH)D concentrations to vitamin D supplementation in RCTs is common; for example, the estimated 25(OH)D increase

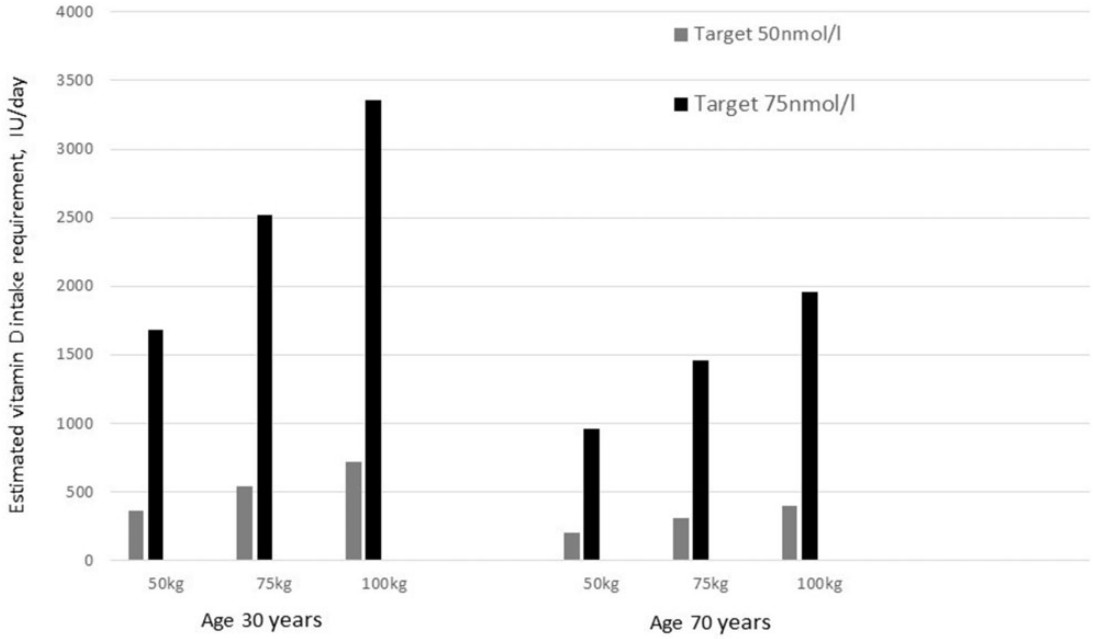

Figure 2 **Daily doses of vitamin D_3 supplementation required for an individual with a baseline concentration of 25 nmol/L to reach target concentrations of 50 nmol/L and 75 nmol/L, by age and body weight.** Data from Zittermann et al.[70]

with specific vitamin D dosages varied 3- to 4-fold in some trials.[68] Differences in the adiposity and body weight of participants explain part of this between-study variation, since substantial evidence suggests that higher dosages are needed to achieve repletion in obese individuals. For example, in one study that used 7 different vitamin D doses (400–4800 IU/d) in normal, overweight, and obese women, increases in serum 25(OH)D were much greater in normal-weight (BMI <25) than in obese women at all doses.[69] Despite this, no evidence of a dose–response effect was found with increases in overweight/obesity. However, existing evidence suggests that flatter dose–response associations in obese vs lean individuals reflect different volumes of distribution, rather than adiposity per se, and that fat mass is no better than other adiposity indices in predicting responses of serum 25(OH)D to vitamin D supplementation.

A comprehensive systematic review and meta-analyses of 94 RCTs showed that the estimated average vitamin D intake required to achieve a given serum 25(OH)D concentration had a nonlinear logarithmic association with body weight (in kilograms).[70] Age was a further independent predictor of response to supplementation, with greater 25(OH)D responses observed in older than younger people, likely owing to the higher baseline 25(OH)D values in younger people or to age-related changes in calcium and vitamin D physiology.[70]

Several predictive formulae have been developed to calculate the dosages needed to achieve specific target 25(OH)D concentrations in people of different weights. In general, supplemental vitamin D intakes are suggested to be 2 to 3 times higher for obese individuals, and 1.5 times higher for overweight individuals, than for lean people.[71] This approximation was based on a community sample of 22 214 participants in a preventative health program that provided advice on vitamin D intake. Participants were self-supplementing with 0 to 50 000 IU of vitamin D per day, and, as a group, they had relatively high basal 25(OH)D concentrations (≈ 90.5 nmol/L). Though vitamin D intakes and 25(OH)D concentrations were higher than in other study populations, 25(OH)D concentrations, as well as the increases seen with supplementation, were lowest in individuals who were obese or overweight.[71] Another study developed predictions for incremental vitamin D_3 dosages suitable for supplementation of vitamin D–deficient individuals weighing 50, 75, or 100 kg, aiming to reach target 25(OH)D concentrations of more than 50 nmol/L or more than 75 nmol/L (Figure 2).[70] According to the calculations used in that study, 50 nmol/L can be reached in all population groups with relatively modest dosages (eg, 540 IU/d for a young individual weighing 75 kg). Notably higher dosages were suggested by another equation developed for clinically obese (BMI, 30–58) but vitamin D–replete individuals [average baseline 25(OH)D = 58 nmol/L]. According to that equation, an estimated 1865 IU/d would be required to raise serum 25(OH)D by 25 nmol/L in an individual weighing 75 kg.[72]

Studies in children and adolescents provide further evidence of the effects of adiposity on serum 25(OH)D

during supplementation, suggesting poor responses in obese individuals.[73,74] For example, in obese 12- to 18-year-olds, responses to vitamin D_3 at a dosage of 2000 IU/d were half of those observed in normal-weight participants,[75] again suggesting the need to double supplemental intakes in obese children, as also suggested for obese adults (see above). There were no adverse events, although 2000 IU/d was associated with small rises in total serum calcium concentrations in normal-weight children but not in obese children. Nevertheless, these data highlight the need to consider body weight when contemplating supplementation in children at dosages above the current recommended daily intakes, which matches the standard practice in prescribing medications for children.

CLINICAL EFFECTS OF VITAMIN D DEFICIENCY ON OBESITY-RELATED METABOLIC DISORDERS

Obesity can have serious effects on health, and many of the consequences of obesity have been linked to poor vitamin D status in cross-sectional and/or prospective studies.[76–78] Indeed, pathophysiological mechanistic studies provide compelling evidence of calcitriol-induced inhibition of many adverse effects of obesity, and the mechanistic effects of low vitamin D status on metabolic disorders are the same as those associated with central obesity (Table 1).[52,79–120] However, evidence demonstrating the ability to reduce or prevent obesity-related abnormalities by targeting vitamin D intakes is largely lacking.[91,102,116,121–123] An ongoing challenge in human studies is to establish whether vitamin D has causal effects on obesity-related diseases; indeed, some studies have suggested that the observed associations with vitamin D status merely reflect confounding by obesity.[124,125] It may be unrealistic to expect notable improvements from vitamin D supplementation (or other primary prevention strategies) for established metabolic abnormalities, since, once metabolic disturbances are evident, much of the related organ damage is already present.

More focus is required to ensure that future trials study appropriate groups of individuals at early stages of disease development and provide optimal supplementation. An important problem is the paucity of trials that have specifically captured participants with true vitamin D deficiency or participants who are yet to develop or who are at the very early stages of metabolic syndrome. A study of supplementation in healthy people with vitamin D deficiency but without prediabetes or T2D showed that pre- and postsupplementation increases in glucose-stimulated insulin secretion were directly correlated.[126] In one RCT, 6 months of supplementation of normoglycemic vitamin D–deficient individuals corrected increased insulin resistance, but only when 25(OH)D concentrations achieved by supplementation suggested repletion. These findings suggest that early supplementation to reduce the risk of metabolic syndrome warrants further study.[103] Furthermore, RCTs conducted to date have typically been short-lived, and many have provided both calcium and vitamin D supplementation or, as in the Women's Health Initiative,[56] have allowed participants to continue relatively high-dose self-supplementation with vitamin D while also providing interventional supplementation. There is also increasing evidence to suggest that relatively modest dosages of vitamin D supplementation may be more effective than larger doses,[57,106,120] highlighting the need for interventions designed to correct deficiency rather than to provide unnecessarily high dosages as part of what are essentially de facto pharmacological experiments.

Low-grade inflammation

Adverse consequences of obesity are mediated in part by the secretion of adipokines, which aggravate inflammation. Mechanistic studies support the potential ability of vitamin D to reduce tissue damage caused by obesity-induced inflammation. This has been confirmed in many tissues[84,85] and by genome-wide data.[127] However, whether adipose tissue–related inflammation is reduced by vitamin D supplementation is uncertain.[15,86] Active calcitriol has well-established immunomodulatory functions. It influences both innate and adaptive immune responses by suppressing the secretion of proinflammatory cytokines and promoting the secretion of anti-inflammatory factors,[84,85] resulting in reduced inflammation both generally and in adipose tissue. Of particular relevance for adipose tissue is the potential for calcitriol to reduce secretion of proinflammatory cytokines by macrophages, which are present in large numbers in enlarged visceral fat deposits.[81–83] Calcitriol suppresses the nuclear factor-κB pathway, thereby inducing anti-inflammatory effects by reducing the secretion of proinflammatory cytokines (eg, interleukin 6) and promoting the secretion of interleukin 10 and other anti-inflammatory cytokines.[36,86,128] Macrophage-derived cytokines also upregulate the vitamin D receptor and induce local and remote inflammation, providing a potential feedback mechanism that could facilitate beneficial effects of calcitriol.

Leptin is a circadian appetite suppressant secreted by adipose tissue. Recombinant leptin therapy reduces food intake and body weight and has the potential to control obesity. A recent meta-analysis of RCTs found no overall effect of vitamin D supplementation on

Table 1 **Examples of obesity-related disorders, including associated metabolic abnormalities, along with mechanistic evidence suggesting possible benefits of optimal vitamin D nutrition**

Abnormality associated with obesity	Relevant actions of calcitriol	Evidence from RCTs indicating value of vitamin D supplementation
Chronic low-grade inflammation Increased adipose tissue mass leads to increased secretion of adipokines, notably (1) proinflammatory cytokines from infiltrating macrophages, and (2) hormonal factors, including leptin, adiponectin, and IGF-1 and its binding proteins[79,80]	Calcitriol suppresses secretion of proinflammatory cytokines and stimulates secretion of anti-inflammatory cytokines from macrophage-infiltrated adipose tissue, as it does in general[81–85] Macrophage-derived cytokines also upregulate vitamin D receptors, providing feedback to reduce obesity-induced inflammatory tissue damage[86] Calcitriol can upregulate adiponectin secretion by adipocytes[87–89] Calcitriol upregulates IGF-1 secretion, and IGF-1 increases vitamin D activation, a feedback mechanism that likely enhances the protective effects of both IGF-1 and vitamin D against metabolic syndrome[79]	Compared with placebo, vitamin D supplementation induces greater reductions in IL-6, but not in other cytokines in obesity[90] Vitamin D supplementation has not been found to have effects on circulating concentrations of leptin[91] or adiponectin[90–92]
Insulin resistance and insulin secretion Obesity leads to hyperinsulinemia and increased adiposity of liver and muscle, causing insulin resistance and leading to nonalcoholic fatty liver disease[93,94]	Calcitriol promotes insulin secretion from healthy islet beta cells by rapidly increasing intracellular calcium (phase 1) and via gene activation after liganding with nuclear vitamin D receptor (phase 2)[95–98] Calcitriol is protective against apoptosis induced by overactivity of uncoupling protein 2 and suppresses overactivity of renin–angiotensin-system in islets induced by hyperglycemia, likely contributing to islet beta cell protection during development of hyperglycemia[99–101]	No beneficial effect of vitamin D supplementation on glucose metabolism in obesity or established T2DM was observed,[102] but increased insulin sensitivity was found in studies of some populations in which vitamin D deficiency was fully corrected, especially in patients with prediabetes and in individuals without diabetes but with increased insulin resistance[103–105] In established T2DM, meta-analyses on vitamin D supplementation with lower doses, but not with very high doses or large bolus doses, was associated with lowering of HbA_{1c} concentrations but had no effect on fasting insulin[106]
Dyslipidemia Obesity leads to dyslipidemia, including increased serum triglycerides and circulating free fatty acids, decreased HDL-C, and increased LDL-C.[107] Furthermore, fatty acids formed in white fat are lengthened by elongases, since long-chain fatty acids induce triacylglycerol (TAG) synthesis and worsen hypertriacylglyceridemia	Calcitriol downregulates elongase (*Elovl3*) via negative-response elements in the gene's promoter region[108,109] Calcitriol reduces hepatic triglyceride synthesis[52]	Some RCTs of vitamin D supplementation in metabolic syndrome, prediabetes, and T2DM reported reductions in dyslipidemia, usually in triacylglyceridemia, without concurrent reductions in LDL-C or increases in HDL-C[110–112]
Hypertension Obesity-associated arterial hypertension is characterized by activation of both the sympathetic nervous system and the renin–angiotensin system, leading to structural changes in the kidney[113] and reductions in vascular wall reactivity that become permanent as atheroma and vascular damage develop[114]	Calcitriol inhibits renin secretion, reducing overactivity of the renin–angiotensin system both in the kidney[115] and more generally (see above regarding insulin secretion and pancreatic islets)	No convincing suggestions of any effect of vitamin D supplementation in established hypertension,[116] but beneficial effects are supported by vitamin D–induced lowering of blood pressure in healthy subjects and by improvements in vascular wall function with supplementation in human studies.[117,118] Furthermore, causality for vitamin D status and blood pressure is supported by data obtained from a meta-analyses of RCTs conducted in individuals with T2DM[119] as well as from a genetic study using a Mendelian randomization approach[3] One trial was suggestive of greater lowering of blood pressure with smaller as compared with larger doses of vitamin D[120]

Abbreviations: HbA_{1C}, hemoglobin A_{1C}; HDL-C, high-density lipoprotein cholesterol; IGF-1, insulin-like growth factor 1; IL-6, interleukin 6; LDL-C, low-density lipoprotein cholesterol; RCT, randomized controlled trial; T2DM, type 2 diabetes mellitus.

serum leptin concentrations, even though changes in leptin were correlated with changes in 25(OH)D concentrations.[91] The effects of calcitriol on leptin secretion are unclear and may be cell selective.[87,129]

Circulating adiponectin concentrations are often inversely correlated with obesity and directly correlated with serum 25(OH)D, with genetic studies providing evidence of causality.[130] Calcitriol can stimulate the secretion of adiponectin by adipocytes in cellular experiments,[87–89] but vitamin D supplementation did not increase total plasma adiponectin concentrations in recent RCTs.[90–92] However, those RCTs were small (only 1 had >100 participants), of short duration, and provided only limited measurements of adipokine profiles. The auxiliary study to the Vitamin D Assessment (ViDA) study investigated the effects of 2000 IU of vitamin D per day (vs placebo) within a lifestyle-based weight loss program over 1 year[90] but found no benefits of vitamin D supplementation for 8 inflammatory biomarkers (or their scores). Secondary stratified analyses, however, suggested benefits in participants who lost the most baseline weight, as supplementation induced larger reductions in interleukin 6 (but not in the other proinflammatory cytokines) compared with placebo in that group.[90] Hypovitaminosis D is associated with an increased risk of gestational diabetes mellitus, and a recent study showed maternal serum 25(OH)D to be inversely associated with maternal serum high-molecular-weight adiponectin in the first trimester.[131] As both 25(OH)D and adiponectin were predictive of gestational diabetes mellitus, with some evidence for an effect of mediation by adiponectin, studies of their joint effects in pregnancy are warranted.

Blood pressure and hypertension

Blood pressure is often inversely associated with vitamin D status.[132] Calcitriol reduces overactivity of the renin–angiotensin system by suppressing renin production,[115] providing a mechanism that would be expected to raise blood pressure and increase damage to various tissues in metabolic syndrome.[133] A previous genetic study that sought to establish the causal association between vitamin D status and blood pressure using a Mendelian randomization approach supported such an effect.[132] In that study, each 10% increase in genetically instrumented 25(OH)D concentration was associated with a modest reduction in blood pressure, with the odds of hypertension reduced by 8%.[3] In contrast, RCTs of vitamin D supplementation rarely report clinically useful reductions in blood pressure.[116,134] These types of discrepancies are not unexpected, given that genetic estimates reflect lifelong differences in vitamin D status, and it is not possible to test this type of long-term influence on vascular function by short-term RCTs.[116] Supplementation is also likely to be ineffective in reducing blood pressure if there is preexisting (and irreversible) arterial wall fibrosis, which is likely to be present in established T2D, metabolic syndrome, hypertension, or atheromatous arterial disease.[118,135] Interestingly, some lowering of blood pressure was seen in one RCT that compared 2 different dosages of vitamin D, with a possible benefit suggested for the lower (400 IU/d) but not the higher (4000 IU/d) dosage.[120] These data might suggest a possible threshold effect for vitamin D dosage. Moreover, in this population, modest daily dosages may have been sufficient to achieve an optimal intake of vitamin D. If optimization of vitamin D status could help reduce overactivity of the renin–angiotensin system in humans, there could be important effects relevant to the prevention of metabolic syndrome. It has also been suggested that overactivity of the renin–angiotensin system drives the development of metabolic syndrome.[133] Regardless of whether this is the case, continuing positive feedback upregulation of the renin–angiotensin system by hypovitaminosis D may contribute to progression of metabolic syndrome and its complications.

Insulin resistance, insulin secretion, and glycemia

Insulin resistance increases with increased adiposity of liver and muscle.[93] Calcitriol promotes insulin secretion from healthy islet beta cells by rapidly increasing intracellular calcium (phase 1) and by gene activation after liganding with nuclear vitamin D receptor (phase 2).[95–98] Prolonged increases in insulin resistance lead to loss of beta cells, islet fibrosis, insulin secretory failure, and T2D.[96] The protective effects of vitamin D on beta cells are likely to be most pronounced before the development of islet damage, and prospective follow-up studies provide support for a beneficial effect of higher serum 25(OH)D concentrations on the risk of metabolic syndrome and T2D.[136,137] A Mendelian randomization study that included up to 58 000 cases of T2D (370 000 noncases) also provided support for a causal effect of genetically instrumented 25(OH)D on T2D, with a 25 nmol/L higher concentration associated with a 14% lower risk of T2D.[138] Overall, evidence from RCTs to support a protective effect of vitamin D supplementation on incident T2D is lacking.[123] A recent systematic review identified 4 RCTs, but none of the individual studies showed evidence of a benefit on incident disease.[139] However, since none of these studies had used baseline serum 25(OH)D as an inclusion criterion, it was not possible to test for the effects of corrected deficiency on the risk of disease.[139]

It is possible that vitamin D could have benefits in individuals with hyperglycemia and/or insulin resistance. There is some experimental evidence to suggest that vitamin D reduces both hepatic lipid formation and glucose output, even under conditions of insulin resistance.[100] Calcitriol protects against cellular apoptosis induced by overactivity of uncoupling protein 2 and suppresses hyperglycemia-induced overactivity of the renin–angiotensin system in pancreatic islets, likely contributing to the protection of islet beta cells as hyperglycemia develops.[99–101] Several RCTs in different populations have sought to identify potential benefits of vitamin D supplementation in insulin resistance or T2D.[103–105] A recent systematic review and meta-analysis of up to 22 studies provided some evidence for vitamin D–related reductions in hemoglobin A_{1C} and fasting blood glucose, but only among T2D patients with low 25(OH)D concentrations at baseline.[140] In line with an earlier meta-analysis,[102] subgroup analyses also suggested that vitamin D supplementation was only effective in lowering hemoglobin A_{1C} concentrations in normal-weight patients (BMI, $<30\ kg/m^2$), with no evidence of any such benefits in obese patients.[102,140]

Dyslipidemia and nonalcoholic fatty liver disease

The formation of long-chain fatty acids induces the synthesis of triacylglycerol and leads to worsening of hypertriacylglyceridemia and inflammation.[141–144] Fatty acids are lengthened by elongases in white fat, and there is evidence to suggest that at least one enzyme (*Elovl3*) is downregulated by calcitriol via negative-response elements in the gene's promoter region.[108,109] However, despite the association between low 25(OH)D concentrations and adverse lipid profiles, there is no evidence that correction of vitamin D deficiency will reliably lead to clinically meaningful changes in lipid profiles in obesity. In a large clinical study, Ponda et al[145] reported a strong inverse correlation between low serum 25(OH)D concentrations and an atherogenic lipid profile in cross-sectional analyses. However, elevations in serum 25(OH)D over time were not associated with notable improvements in serum lipid profiles,[145] and subsequent RCTs of vitamin D supplementation provided no, or only weak, evidence of potential benefits.[146,147]

Inverse associations of 25(OH)D with nonalcoholic fatty liver disease (NAFLD) and its complications—cirrhosis and primary hepatoma—are common.[148–150] In rodents fed a high-fat high-glucose diet and in human hepatocytes in vitro, calcitriol increased hepatic lipid homeostasis (by increasing free fatty acid metabolism, reducing hepatic triacylglyceride formation and steatosis, and reducing hepatic glucose output).[100,151,152] However, a recent systematic review of observational studies did not suggest an association between low vitamin D status and stage of liver fibrosis in patients with NAFLD.[153] In addition, a Cochrane Review summarizing evidence from RCTs that examined the relationship between vitamin D supplementation and liver disease and related mortality (including NAFLD) failed to identify evidence to support a benefit.[154] However, only a few trials, often with insufficient numbers of participants, were included in that review, and the overall quality of the available evidence was judged to be very low.[154] Thus, it is possible that vitamin D could have beneficial effects in NAFLD,[155] but whether long-term repletion could prevent, or reduce the progression of, NAFLD or its serious sequelae (cirrhosis and primary hepatoma) remains uncertain. It is also possible that some of the observational associations in NAFLD could be explained by reverse causality, since liver damage is likely to reduce the 25-hydroxylation of vitamin D. A recent bidirectional Mendelian randomization study that aimed to address this issue found no evidence for a causal association between 25(OH)D and NAFLD in either direction.[156] That genetic study may have been underpowered to detect an effect, and, given the paucity of evidence overall, further investigation of the association between vitamin D and NAFLD is needed.[157]

EFFECT OF EARLY-LIFE VITAMIN D STATUS ON OBESITY OR METABOLIC RISK LATER IN LIFE

Maternal vitamin D metabolism changes during pregnancy.[158] Placental transfer of 25(OH)D is poor,[159] but hydroxylation of 25(OH)D to form calcitriol increases in both the decidua and the placenta, and maternal circulating calcitriol concentrations double early in pregnancy.[160] Concomitantly, calcitriol destruction through epigenetic inactivation of CYP24A1, the catabolic enzyme, is suppressed.[161] These changes in maternal vitamin D metabolism help to ensure adequate maternal calcitriol availability, likely supporting the protection of the developing fetus from the maternal immune system.[158]

Epigenetic effects of poor maternal nutrition are now recognized. Vitamin D inadequacy leads to variable methylation of the promoter region of calcium transporter genes in offspring,[162] with the potential to induce health problems caused by mechanistic defects in vitamin D signaling[162] as well as other epigenetic effects. Thus, early-life vitamin D status could determine many health risks besides those related to bone health,[163] and these may not be identified by RCTs conducted later in life, since epigenetic effects can persist into adulthood.[164] In line with this, children of vitamin D–deficient vs –replete mothers have been reported to be more obese as neonates and infants, with differences

persisting to age 6 years.[161,165,166] Risk for disease is transmitted across generations via epigenetic mechanisms; for example, intrauterine malnutrition, maternal obesity, and maternal T2D all increase offspring risk of adult T2D.[167] Nutritional inadequacy, paternal smoking, and paternal betel chewing each contribute to the risk of metabolic syndrome and T2D in offspring, as may parental vitamin D status,[168–170] with experimental evidence provided by increased weight, fat synthesis, insulin resistance, islet size, and hepatic steatosis in the offspring of vitamin D–deficient mouse dams.[164]

Possible mechanisms of an increased risk of obesity later in life after early-life vitamin D deficiency include increased adipogenesis,[171] reduced adipocyte maturation, hypothalamic appetite dysregulation, and the irreversibility of childhood obesity–induced increases in adipocyte cell numbers/size.[172–174] Furthermore, cytotoxic effects of high, but physiological, tissue calcitriol content on mesenchymal stem cells might prevent undue increases in adipocyte cell numbers in early life.[175]

These associations could be affected by seasonal variations in temperature and UV-B radiation, the so-called winter hypothesis. Thus, low UV-B radiation in winter could lead to reductions in vitamin D synthesized in the skin, signaling energy accumulation with increased body weight, optimization of heat conservation, and survival through winter food shortages.[176] A meta-analysis of 16 studies (18 096 participants) supports the concept that prenatal vitamin D status is associated with offspring birth weight.[177] There is some observational evidence that low maternal 25(OH)D concentrations may also contribute to the longer-term risk of offspring obesity. A recent study reported increases in several adiposity indices in preschool-aged offspring (4 and 6 years) born to mothers with low 25(OH)D concentrations (<37.7 nmol/L).[166] Nevertheless, findings on maternal vitamin D status and offspring adiposity are inconsistent[161,165,166]; for example, a study from the United Kingdom showed low maternal vitamin D status was associated with increased adiposity of offspring at ages 4 and 6 years,[178] but another study from the same region suggested lower adiposity age 9 years.[179] Effects of a Danish food fortification program providing vitamin D showed no differences in body build at age 7 years between children born before vs children born after program implementation.[180] Despite an apparent lack of effect shown in short-term RCTs investigating vitamin D status and risk of obesity, reduced early-life vitamin D status, as well as maternal vitamin D status, has been associated with obesity, inflammation, and dyslipidemia.[181,182] Thus, maintaining repletion over the life span may be protective against the health risks of obesity, while mechanisms underlying the association between obesity in adulthood and vitamin D deficiency could contribute to the programming of later health risks in the offspring of obese mothers. Cross-sectional associations of obesity and related problems with vitamin D insufficiency are similar in children, adolescents, and older people. Obesity-related disorders, including atherosclerotic vascular disease, progress from childhood. Thus, any factor increasing obesity-related risks over time must increase the risks of overt disease.

Despite evidence from one RCT indicating that vitamin D supplementation beginning in infancy is associated with reduced adiposity at age 3 years,[183] evidence of an association between early-life supplementation and reduced adiposity later in life is sparse, and further evaluation of epigenetic risk continues. Eventually, follow-up of offspring after assessment of maternal vitamin D repletory status and analysis of data from RCTs of maternal vitamin D supplementation should clarify the contribution of early-life vitamin D status to later health risks.[184,185] Changing health outcomes once structural damage is present is difficult. Whether long-term vitamin D repletion beginning in early life effectively reduces later health risks is an especially important question. Since childhood obesity is a key determinant of metabolic disorders, it may well be that the reduced serum 25(OH)D induced by obesity contributes to the risk of metabolic syndrome later in life.

CONCLUSION

The larger volume of fat for distribution of 25(OH)D in obesity explains, at least in part, the reduced serum 25(OH)D concentrations and the reduced responses of serum 25(OH)D levels to vitamin D supplementation in obesity. Some studies,[31,33,35] but not all,[34] report lower levels of serum free 25(OH)D in obesity. Further studies should seek to determine whether obesity-related differences in vitamin D status influence obesity-associated health risks over the short or long term. Studies are also needed to establish whether vitamin D inadequacy in obesity causes metabolic abnormalities, reflects confounding by obesity, or results from a vicious cycle owing to the combination of these effects. Compelling mechanistic evidence suggests a need for additional studies to resolve these questions, especially with regard to early-life vitamin D nutrition. A key public health strategy for reducing metabolic syndrome, T2D, and cardiovascular disease remains the prevention of obesity in early life, which may provide potential health benefits from greater tissue availability of vitamin D in addition to all the other well-established benefits of weight control.

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