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Vitamin D and obesity: current perspectives and future directions

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In recent years, new functional roles of vitamin D beyond its traditional role in calcium homeostasis and bone metabolism have emerged linking the fat-soluble vitamin to various non-communicable diseases. Vitamin D deficiency (25-hydroxyvitamin D (25(OH)D) < 25–30 nmol/l) and sub-optimal status (25(OH)D < 50–100 nmol/l) are increasingly associated with unfavourable metabolic phenotypes, including insulin resistance, type 2 diabetes and CVD; conditions also commonly linked with overweight and obesity. Early studies reported poor vitamin D status in the morbidly obese. More recently, it has been observed that a graded relationship between vitamin D status and BMI, or specifically adiposity, exists in the general population. A number of hypotheses have been proposed to explain the potential mechanisms whereby alterations in the vitamin D endocrine system occur in the obese state. Plausible explanations include sequestration in adipose tissue, volumetric dilution or negative feedback mechanisms from increased circulating 1,25-dihydroxyvitamin D₃. Others hypothesise that heavier individuals may partake in less outdoor activity, may also cover-up and wear more clothing than leaner individuals, thus decreasing sun exposure and limiting endogenous production of cholecalciferol in the skin. Moreover, in some but not all studies, BMI and adiposity have been negatively associated with the change in vitamin D status following vitamin D supplementation. It therefore remains unclear if body size and/or adiposity should be taken into account when determining the dietary requirements for vitamin D. This review will evaluate the current evidence linking vitamin D status and supplementation to overweight and obesity, and discuss the implications for setting dietary requirements.

Vitamin D: Obesity: BMI: Fat mass: Adipose tissue

Traditional roles of vitamin D lie within the musculoskeletal system, maintaining calcium homeostasis and bone metabolism, with deficiency leading to conditions such as rickets in children, or osteoporosis and osteomalacia in adults⁽¹⁾. However, obesity is now frequently cited as a cause of vitamin D deficiency^(2,3), which may in fact lead to other co-morbidities, such as diabetes and CVD, conditions commonly linked to obesity^(4,5).

Indeed, obesity and vitamin D deficiency have concomitantly reached epidemic levels worldwide and research linking the two has grown extensively over the last number of years. It is reasonable to suggest that this nutritional inadequacy may be driven by the increasing obesity rates within the general population, and may

therefore improve with a reversal of the latter. However, despite the plethora of evidence available, the mechanisms remain largely unclear and the area of reverse causality is also commonly debated within the literature: does obesity lead to vitamin D deficiency or vice versa?

Vitamin D is not technically a vitamin, but is better classified as an active circulating pre-hormone within the body. Limited amounts of vitamin D are obtained from dietary sources such as oily fish, liver and fortified foods, such as milks, breakfast cereals and margarines, or dietary supplements. However, the main source is through cutaneous production via the action of UVB irradiation (wavelength 290–315 nm) which converts

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; 1,25(OH)D, 1,25-dihydroxyvitamin D; VDR, vitamin D receptor; FM, fat mass; MHO, metabolically healthy obese.

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7-dehydrocholesterol to previtamin D₃ in the epidermis of the skin^(6,7). Hydroxylation in the liver results in the formation of 25-hydroxyvitamin D₃ (25(OH)D), the status measure of the vitamin, which makes up our stores of the vitamin and being fat-soluble, this storage is mainly in the adipose (fat) tissue^(8,9). When required by the body, a further hydroxylation step forms the biologically active form of the vitamin, 1,25-dihydroxyvitamin D₃ (1,25(OH)D), which exerts its actions *in vivo* via the vitamin D receptor (VDR). As the endogenous production of vitamin D only occurs at a particular sunlight intensity, usually only during the summer months at high latitudes (approximately April–September), this typically gives rise to seasonal variations in vitamin D status throughout the year^(6,7).

Over the course of human evolution, we have developed a more cutaneous phenotype, with depigmented skin manifesting with migration away from the equator^(10,11). The adaptation of a more vitamin D-rich diet, as well as genetic modifications have also been reported with such migration, to further enhance our vitamin D intake from both diet and the sun^(12,13). Unfortunately this ‘vitamin D compromise’ that has occurred over the course of evolution may now have been broken in today’s modern and westernised lifestyles, with increasing obesity rates and more sedentary/indoor lifestyles.

The aims of the present review were to evaluate the current evidence linking vitamin D status and supplementation to overweight and obesity, and discuss the potential implications for setting dietary requirements.

Vitamin D and obesity

Commonly suggested mechanisms

There are four suggested mechanisms that are most commonly cited within the literature which may explain a low vitamin D status in obesity: (1) obese individuals have decreased sun exposure compared with their lean counterparts; (2) negative feedback from an increased 1,25(OH)D concentration in obese individuals decreases 25(OH)D concentrations; (3) vitamin D is sequestered within adipose tissue; (4) lower 25(OH)D concentration is simply due to volumetric dilution.

Decreased sun exposure. While a decreased sun exposure may initially seem counterintuitive because of the larger body surface area in obesity that is available for endogenous synthesis⁽¹⁴⁾, obese individuals reportedly have a limited mobility, they may avoid outdoor activity and may cover-up more when outdoors compared with their lean or normal-weight counterparts^(15–17). Solid evidence for this theory is lacking and may be mainly anecdotal, and although, for example, there may be some evidence that obese individuals partake in less physical activity^(18,19), levels of outdoor physical activity are often not specified so it is difficult to draw definitive conclusions on the subsequent effect on vitamin D status.

Negative feedback from 1,25-dihydroxyvitamin D₃. Evidence for the negative feedback from increased circulating 1,25(OH)D concentrations in obesity is equivocal. As introduced earlier, when required by the

body, 25(OH)D is further hydroxylated to form the active metabolite, 1,25(OH)D, which in turn ‘switches off’ the production of 25(OH)D. Indeed, increased 1,25(OH)D, and therefore decreased 25(OH)D concentration, in obese compared with non-obese subjects was reported in earlier smaller studies^(20,21), but more recently, larger studies show the opposite is true^(22–25). Data supporting this mechanism remain inconclusive.

Sequestration in adipose tissue. The study of Wortsman *et al.*⁽²⁶⁾ was the first to provide strong, convincing evidence that vitamin D (as a fat-soluble vitamin), may become sequestered (i.e. trapped or hidden) within adipose tissue. In their study, nineteen lean and nineteen obese individuals (BMI ≤ 25 and >30 kg/m², respectively) were exposed to UVB irradiation for 24 h. The concentration of circulating cholecalciferol was similar between the groups at baseline, but the obese group had a significantly blunted response to the UVB intervention, resulting in a 57% lower serum cholecalciferol concentration post-intervention, compared with the control (lean) group. Adding support to their theory was the fact that both obese and control groups had similar levels of 7-dehydrocholesterol available in the skin prior to intervention. This suggested that the limitation in the obese group was the bioavailability of the synthesised cholecalciferol in circulation⁽²⁶⁾. This sequestration theory is probably the most supported within the literature and others have since quantified that obese children and adults require 2–5 times more vitamin D to prevent or treat deficiency compared with their lean counterparts, because of such sequestration in adipose tissue⁽²⁷⁾.

The cholecalciferol content of adipose tissue has been quantified^(28–30) and is positively correlated with serum 25(OH)D concentrations in obese subjects⁽²⁹⁾. In a recent pilot study of six females, a significantly lower cholecalciferol and 25(OH)D (but not 1,25(OH)D) content of subcutaneous adipose tissue was observed in obese compared with lean individuals⁽³⁰⁾. Although these data appear to question the sequestration theory suggested by Wortsman *et al.*⁽²⁶⁾, further evidence on the bioavailability of vitamin D from adipose tissue in overweight/obese individuals is required from larger studies (including males and females) before definitive conclusions can be drawn.

Volumetric dilution. Most recently, other convincing data suggest that it is simply volumetric dilution that explains the low vitamin D status of obesity, i.e. putting the same amount into a larger pool, will result in a lower concentration. Drincic *et al.*⁽³¹⁾ showed that the inverse relationship between serum 25(OH)D concentration and body weight was apparent in 686 healthy adults taking minimal supplemental doses of vitamin D (<10 µg/d). Of interest though, in their hyperbolic model (the mathematical expression of dilution), when adjusted for body size, the difference in 25(OH)D concentrations between normal-weight and obese individuals was removed. These authors went on to recommend that the vitamin D dosing regimen for treatment of vitamin D deficiency in obesity should be based on body weight, i.e. ‘one size does not fit all’⁽³¹⁾.



Overall, although these are the four most commonly suggested mechanisms, evidence for the former two is much weaker than that for the latter two theories, where robust evidence is available. Measuring sun exposure in the free-living setting can be problematic and therefore researchers usually rely on more subjective, self-reported measures. Similarly, concentrations of 1,25(OH)D are reported much less frequently within the literature given the relatively short half-life of this active metabolite, its tight metabolic regulation, and the fact that 25(OH)D has been widely accepted as the status measure of the vitamin⁽³²⁾. Taken together, this may contribute to the lack of data supporting the effect of both factors on vitamin D status in obesity.

In contrast, the strong evidence presented earlier for the sequestration⁽²⁶⁾ and volumetric dilution⁽³¹⁾ hypotheses, and more importantly, a lack of contradictory evidence for either, suggest that they are the most probable, either independently or in combination, to explain the low vitamin D status widely reported in overweight and obesity.

Observational evidence

Observational evidence linking vitamin D and obesity stems from the late 1970s when 25(OH)D concentrations were reported to be lower in morbidly obese patients *v.* controls both before and after gastric bypass surgery^(20,33). In these studies, abnormalities in vitamin D metabolism following surgery were attributed to both post-operative complications (e.g. reduced gastric or intestinal absorption) as well as a reduced sun exposure during the recovery period. In the following few years, this was confirmed by other studies^(15,21,34-36), one of which was the first to suggest that secondary hyperparathyroidism may also be contributing to vitamin D deficiency, as they observed significantly higher parathyroid hormone and 1,25(OH)D concentrations in the obese *v.* non-obese group⁽²¹⁾. More recently in support of these findings, a systematic review has quantified that vitamin D deficiencies are critical after obesity surgery and are common in up to two-thirds of cases⁽³⁷⁾. Vitamin D supplementation in such patient groups is successful in treating vitamin D deficiency⁽³⁸⁾ and should be prescribed, or at least recommended to patients, both before and after obesity surgery.

Using baseline data from two randomised, placebo-controlled vitamin D intervention studies, the association between body composition and 25(OH)D concentrations was investigated by the author in both young (age 20–40 years) and older (age ≥64 years) apparently healthy adults. These studies were originally designed to investigate the dietary requirements for vitamin D over the winter months (October–March) and full details have been previously published elsewhere^(39,40). A benefit of this data was that baseline measures were all taken at the end of summer (i.e. when vitamin D status is expected to be at its peak) and therefore the confounding effect of seasonality on 25(OH)D concentrations was removed. In addition, measures of body composition included both the proxy measure of BMI as well as a more robust

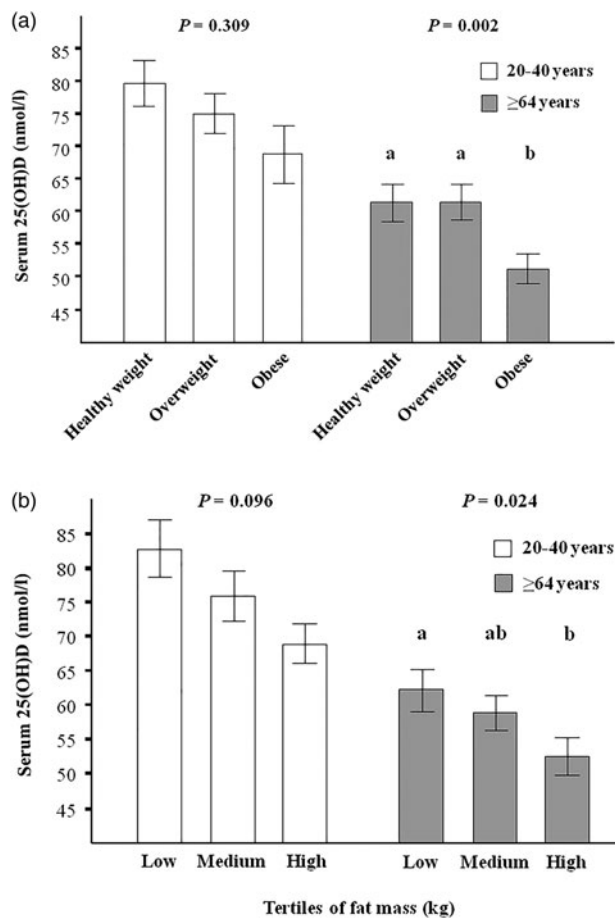


Fig. 1. Association between mean (± 1 SE) serum 25-hydroxyvitamin D (25(OH)D) and (a) BMI categories, (b) tertiles of fat mass in apparently healthy adults aged 20–40 years (n 236) and ≥ 64 years (n 207). Based on data derived from Cashman *et al.*^(39,40) and Forsythe *et al.*⁽⁴¹⁾. BMI categories: healthy weight, BMI ≤ 24.9 kg/m²; Overweight, BMI 25.0–29.9 kg/m²; Obese, BMI ≥ 30.0 kg/m². *P*-value denotes significance between groups from ANOVA. Bars with different letters are significantly different within that age-group (Tukey *post hoc* tests, $P < 0.05$).

measure of fat mass (FM); four-site skinfold thickness measurements. Fig. 1 shows the association between 25(OH)D, BMI and FM in younger and older adults. Although in both age groups an inverse trend is apparent, this is only statistically significant in the older adults, with those in the obese category (BMI > 30 kg/m²) having a significantly lower vitamin D status compared with the healthy and overweight individuals (BMI < 25.0 and ≥ 25.0 kg/m², respectively). A similar pattern was apparent when tertiles of FM were explored, again only significant in the older individuals, in that those with highest levels of FM had the lowest vitamin D status. Of interest within this study, sun exposure habits and levels of outdoor activity could also be compared between the BMI and FM groups and this did not appear to explain the difference in vitamin D status observed (LK Pourshahidi, MBE Livingstone and JMW Wallace, unpublished results). Although this may have suggested that sequestration in adipose tissue and/or volumetric dilution are most likely



causes of the reported associations, data on sun exposure and physical activity were self-reported, and therefore should be interpreted with caution.

These findings have been extended and confirmed by many studies and a plethora of evidence now supports the association between overweight and/or obesity and vitamin D deficiency across all groups of the general population (children to very elderly), including evidence from large cohort studies such as the 1958 British Birth cohort⁽⁴²⁾ and the National Health and Nutrition Examination Survey⁽⁴³⁾. However, the issue of reverse causality still remains, with some reporting that vitamin D deficiency is the cause of obesity⁽⁴⁴⁾, and others suggesting that it is a new form of malnutrition within morbidly obese patients⁽³⁾. Recent evidence from a systematic review and meta-analysis have supported the significant inverse (albeit weak) correlation between 25(OH)D and BMI in adults (4 % reduction in 25(OH)D per each 10 % increase in BMI ($P = 0.005$))⁽⁴⁵⁾. Using a bi-directional genetic approach, others confirm that it is high BMI, which leads to a lower 25(OH)D concentration, and any evidence for the reverse being smaller in effect⁽⁴⁶⁾. The same authors also report that vitamin D pathway genes are unlikely to play any role in obesity-related traits⁽⁴⁷⁾.

Notwithstanding the consistent association shown between overweight and obesity and low vitamin D status, it is noteworthy that the overall strength of the association is usually weak, which is most likely attributable to the significant heterogeneity between studies. This is at least partly owing to a number of methodological differences between studies which can have an impact on both vitamin D synthesis and status. Studies have been conducted worldwide at different latitudes, and many fail to account for seasonality or time of year within their analysis. Furthermore, data from different age and ethnic groups also adds to this heterogeneity as both ageing and skin colour can impact upon vitamin D synthesis and status, as well as body composition. Finally, analytical differences also make the comparison between studies difficult, as for both the assessment of body composition and vitamin D status, studies have used not only different methodologies but have also applied different cut-offs and classifications: both of which are a common debate within the literature.

Despite these limitations, the consistent inverse relationship between vitamin D and obesity is apparent from observational studies; however, by design, these studies cannot prove causality, and researchers began to ask the question, can an improvement in vitamin D status lead to weight loss or alternatively, a prevention of weight gain?

Prospective and intervention studies

Research has shown that the VDR is present in adipocytes (i.e. cells of the adipose tissue), which suggests that vitamin D does in fact play a role in modulating this active metabolic tissue^(48,49). Evidence suggests that 1,25(OH)D plays a central role in adipocyte metabolism via the inhibition of adipogenesis, independently of parathyroid hormone concentrations^(50,51); with lower

vitamin D stores potentially increasing the differentiation of pre-adipocytes to adipocytes (i.e. adipocyte growth)^(51,52). Indeed 25(OH)D has been negatively associated with adipocyte size, albeit only in women to date⁽⁵³⁾ and promising evidence from animal models also supports a protective role for vitamin D in the onset of diet-induced obesity by enhanced fatty acid oxidation⁽⁵⁴⁾ or increased adipose tissue apoptosis⁽⁵⁵⁾.

Secondary analysis of the Women's Health Initiative study concluded that calcium and vitamin D₃ given in combination decreased the risk of postmenopausal weight gain over an average of 7 years⁽⁵⁶⁾ and other prospective studies have shown that weight loss can facilitate an increase in circulating 25(OH)D concentrations over time⁽⁵⁷⁻⁶⁰⁾. Although this evidence appears promising in support of the relationship between vitamin D and weight loss, evidence from intervention studies is less clear⁽⁶¹⁻⁶⁵⁾. Many of these studies give cholecalciferol with or without calcium and show equivocal results. Furthermore, when calcium is given with cholecalciferol, the effects of the vitamin *per se* cannot be distinguished and the evidence from interventions where cholecalciferol is given alone is limited⁽⁵¹⁾.

Overall, the data does not consistently support the role of vitamin D (with or without calcium) in weight or FM loss. It also still remains unclear whether vitamin D acts directly by improving insulin sensitivity to facilitate weight loss, or indirectly through increased calcium absorption from the gut and suppression of circulating parathyroid hormone concentrations⁽⁶⁶⁾. A more recent genetic study suggests that VDR target genes may predict individuals who will not respond to supplementation⁽⁶⁷⁾, and inclusion of such individuals in intervention studies may contribute to the equivocal findings presented earlier. Further randomised controlled trials are required to address these current gaps within the literature.

Obesity, inflammation and 25-hydroxyvitamin D

Obesity is now widely recognised as a state of chronic, low-grade systemic inflammation⁽⁶⁸⁻⁷⁰⁾, with adipocytes shown to actively secrete a number of inflammatory molecules, including both pro- and anti-inflammatory cytokines, hormones, and acute phase reactants, such as C-reactive protein^(68,71-74). Within the adipose tissue, other cells are also present including preadipocytes, mast cells and macrophages^(75,76), which also contribute to this inflammatory milieu^(77,78).

Extensive evidence has demonstrated that adipocytes become enlarged and dysregulated following weight gain, which subsequently produces an imbalance in the inflammatory profile of adipose tissue. Overweight and obesity are commonly linked to an up-regulation of pro-inflammatory molecules, and down-regulation of anti-inflammatory molecules, and this finding has been extensively reviewed⁽⁷⁹⁻⁸³⁾. Moreover, others have shown that levels of obesity-related inflammatory markers can be improved with weight loss⁽⁸⁴⁻⁸⁷⁾.

Vitamin D has been reported to act as an acute phase reactant as a consequence of such an inflammatory

Table 1. Studies investigating the effect of adiposity on the 25-hydroxyvitamin D response to cholecalciferol supplementation in adults

Study	Subjects				Study					
	<i>n</i>	Age (yr)	Sex	Description	Design	Country	Season	Dose (µg/d)	Duration	25(OH)D response
Barger-Lux <i>et al.</i> ⁽⁹⁹⁾	38	20–37	116M; 0F	Healthy	Dose–response intervention study*	USA	Wintertime (Jan–Apr)	2.5 25 1250	8-wk	Inverse association with BMI
Canto-Costa <i>et al.</i> ⁽¹⁰⁰⁾	42	>65	11M; 31F	Housebound	Placebo-controlled intervention study	Brazil	NR	25 (175/wk)	12-wk	No association with body fat
Blum <i>et al.</i> ⁽¹⁰¹⁾	257	>65	122M; 135F	Healthy, ambulatory	Placebo-controlled RCT	USA	Adjusted for in analysis	17.5 (+Ca)	12-mo	Inverse association with BMI and body fat
Nelson <i>et al.</i> ⁽¹⁰²⁾	86	19–35	0M; 86F	Healthy, premenopausal	Placebo-controlled RCT	USA	Wintertime (Oct–Feb)	20	21-wk	No association with body fat
Lee <i>et al.</i> ⁽¹⁰³⁾	17	75 (11) [†]	NR	Patients	Longitudinal study	Australia	Non-summer months (May–Dec)	250	1-wk	Post-intervention 25 (OH)D concentration inversely associated with BMI
Forsythe <i>et al.</i> ⁽⁴¹⁾	118	20–40	58M; 60F	Healthy	Placebo-controlled RCT	UK/ Ireland	Wintertime (Oct–Mar)	15	22-wk	No association with BMI or body fat
Forsythe <i>et al.</i> ⁽⁴¹⁾	109	≥64	45M; 64F	Healthy	Placebo-controlled RCT	UK/ Ireland	Wintertime (Oct–Mar)	15	22-wk	Inverse association with BMI
Drincic <i>et al.</i> ⁽¹⁰⁴⁾	62	19–68	25M; 37F	Obese, in good general health	Randomised dose–response intervention study	USA	Wintertime	25 125 250	21-wk	Inverse association with BMI
Gallagher <i>et al.</i> ⁽¹⁰⁵⁾	147	57–90	0M; 147F	Vitamin D insufficient [‡]	Placebo-controlled, dose–response RCT	USA	NR	10–120 (7 doses + Ca)	1-yr	Higher in those with BMI <25 v. >25 kg/m ²
Waterhouse <i>et al.</i> ⁽¹⁰⁶⁾	385	60–84	206M; 179F	Healthy	Pilot placebo-controlled, dose–response RCT	Australia	Ambient UVR level adjusted for in analysis	750 [§] 1500 [§]	12-mo	Inverse association with BMI

n, Number of subjects; yr, years; 25(OH)D, 25-hydroxyvitamin D; M, male; F, female; wk, week; NR, not reported; RCT, randomised controlled trial; mo, month; UVR, ultraviolet radiation.

* Study also included two additional treatment groups given either supplemental 25(OH)D₃ (*n* 41) or 1,25-dihydroxyvitamin D₃ (*n* 37).

[†] Study only reported mean (sd) age of the group.

[‡] Defined as serum 25(OH)D < 50 nmol/l (20 ng/ml).

[§] Dose administered monthly.

response (e.g. in obesity) which can suppress the concentration of 25(OH)D^(88,89). Polymorphisms affecting the VDR may also play a role in obesity, which may be partly mediated by ongoing inflammation⁽⁹⁰⁾. Indeed, vitamin D has been positively correlated with the protective hormone adiponectin in obese individuals⁽⁹¹⁾ and an improvement in 25(OH)D concentrations has been reported to enhance the beneficial effects of weight loss, which may be at least partly owing to the anti-inflammatory effect of vitamin D^(62,92). Data from metabolically healthy but obese (MHO) individuals add further support to this hypothesis. Individuals that present with the MHO phenotype, despite having a high FM, have a healthier metabolic profile compared with the typical metabolically unhealthy obese⁽⁹³⁾. Although a number of different definitions exist, MHO individuals commonly have higher insulin sensitivity and low inflammation for example, compared with the metabolically unhealthy obese group^(93–95). Recently it has been suggested that vitamin D may offer a protective metabolic effect in the MHO group⁽⁹⁶⁾. In a group of 4391 obese adults, Esteghamati *et al.*⁽⁹⁷⁾ clearly demonstrated that, irrespective of the definition used to define MHO, 25(OH)D concentrations were significantly higher in the MHO individuals compared with the metabolically unhealthy obese group. Further research is warranted to confirm this finding and elucidate the anti-inflammatory or other underlying mechanisms to explain vitamin D's apparent protective metabolic effect in this unique subgroup of obese individuals.

Effect of obesity on the response to supplementation

It has long been recognised that the response to vitamin D supplementation is dependent on baseline 25(OH)D concentrations, i.e. those with a higher vitamin D status display an attenuated response compared with those with the lowest status^(27,98). However, given the decreased bioavailability of vitamin D in obesity, and the purported effect of volumetric dilution discussed earlier^(26,31), it is reasonable to assume that the typical response to supplementation may be different in overweight/obese individuals, albeit that they are usually starting from a lower baseline value.

Table 1 shows nine studies, which have tested the hypothesis that adiposity can attenuate the 25(OH)D response to cholecalciferol supplementation^(41,99–106). In the majority of these studies, a significant inverse relationship was apparent between BMI and/or FM, and this occurred irrespective of population group and across a wide range of supplemental doses of cholecalciferol given for varying durations (1 week to 1 year)^(41,99,101,103–106). For example, in the study by Forsythe *et al.*⁽⁴¹⁾, the mean adjusted change in 25(OH)D among older adults (≥ 64 years) decreased by approximately 6.5 nmol/l with every 5 kg/m² increase in BMI at baseline. These data suggest that such individuals may require a larger dose of vitamin D or a longer supplemental period to achieve a desired vitamin D status, compared with their lean counterparts and independent of

baseline concentrations. Similarly to the associations shown at baseline between vitamin D status, BMI and FM (Fig. 1), adiposity only attenuated the response to supplementation (15 µg cholecalciferol daily) in the older adults. The effect was NS in the younger adults (20–40 years)⁽⁴¹⁾, which may suggest that the effect of adiposity on vitamin D status may become more prominent with increasing age. Moreover, another study has demonstrated that obese individuals are 2–3 times more likely to be deficient after prescribed ergocalciferol (vitamin D₂) replacement⁽¹⁰⁷⁾. Therefore, the effect of adiposity on the 25(OH)D response to supplementation is not only specific to cholecalciferol.

Overall, only two of the nine studies failed to replicate this finding. The first of these was relatively short in duration, uniquely opted for a weekly rather than daily supplementation regime and did not appropriately adjust for seasonality in their analysis⁽¹⁰⁰⁾. Similarly to the study by Forsythe *et al.*⁽⁴¹⁾, the other showed no effect in younger premenopausal females⁽¹⁰²⁾. It is also noteworthy that in the studies by Canto-Costa *et al.*⁽¹⁰⁰⁾ and Nelson *et al.*⁽¹⁰²⁾, the analysis was only carried out using FM, without considering simpler measures of body weight or BMI. This may suggest vitamin D is not being sequestered within the fat tissue, but that it is more likely volumetric dilution, and therefore body size (reflected by BMI) rather than FM *per se* that is influencing 25(OH)D concentrations in obesity.

Implications for setting dietary requirements

A recent meta-analysis by Zittermann *et al.*⁽¹⁰⁸⁾ has concluded that body weight is an important predictor of the variation in 25(OH)D in cohorts taking supplements. From their analysis of ninety-four studies, including over 20 000 subjects and a wide range of supplemental doses, the authors calculated different daily required intakes of vitamin D based on age (30 v. 70 years), baseline and target 25(OH)D concentrations (from 25 up to 50 or 75 nmol/l), across different body weights (50–100 kg). These intake recommendations ranged from 5 µg to 84 µg daily depending on the combination of factors mentioned earlier⁽¹⁰⁸⁾ and, similarly others have quantified this using other calculations and statistical approaches^(27,109,110), with the common theme that 'one size does not fit all'.

Although the evidence consistently supports a negative relationship between adiposity, vitamin D status and the 25(OH)D response to supplementation, it remains unclear if such evidence is relevant in the context of setting dietary requirements. Notwithstanding the fact that dietary requirements are derived to meet the needs of the majority of the general population, and not specific subgroups (e.g. the obese) over and earlier stage of the life-cycle, such recommendations must be cognisant of the increasing obesity prevalence among the general population. Indeed, in the Institute of Medicine's recent revision of the vitamin D dietary references intakes in the USA⁽³²⁾, adiposity was recognised as a cofounder affecting 25(OH)D concentrations. The challenge of



interpreting 25(OH)D concentrations in overweight and obese individuals was noted and the report also stated that the influence of body weight and body composition on 25(OH)D was a future research need to assist in the process of establishing requirements.

Conclusions

Overall, a large amount of evidence supports an inverse (albeit sometimes weak) association between adiposity and vitamin D status in adults, most likely attributable to volumetric dilution, and perhaps sequestration in adipose tissue to a lesser extent. Optimal vitamin D status or high vitamin D intakes also appear to be protective against future weight gain and/or diet-induced obesity, albeit the evidence for this in human subjects is not strong. On the other hand, little evidence currently supports a direct causal link between vitamin D and weight or FM loss and this merits further investigation. Future research should include well-designed, randomised controlled longer-term studies that robustly measure both body size (i.e. body weight or BMI) and body composition (i.e. FM). Notwithstanding the many practical challenges, such studies should also adequately control for time of year (seasonality), sun exposure and dietary intakes. Further mechanistic studies are also warranted to determine if vitamin D interacts with adipose tissue metabolism by anti-inflammatory or other mechanisms. Studies exploring the effects of adiposity on vitamin D status in groups 'at-risk' of vitamin D deficiency, such as pregnant women, other patient groups (e.g. chronic obstructive pulmonary disease patients), ethnic minorities and elite athletes are also needed.

Despite the somewhat formidable challenge of establishing a direct causal link between vitamin D and obesity, the evidence clearly shows that body weight and/or adiposity does negatively influence the 25(OH)D response to supplemental vitamin D. Although it remains to be elucidated if the same relationship is apparent in response to other dietary sources (e.g. fortified foods), such evidence does have implications for both setting dietary requirements and in the clinical setting to prevent and/or treat deficiency. Finally, recent insights from genetic analyses show promise for the use of personalised nutrition in the area of vitamin D and obesity, whereby certain VDR profiles may use to predict an individual's response to supplementation or indeed the risk of developing obesity in the future. Research in this area is particularly timely as the development of public health strategies to decrease the prevalence and/or impact of overweight and obesity are urgently required.

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Authorship

L. K. P. reviewed the literature and wrote the manuscript.

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