Available online at www.sciencedirect.com

ScienceDirect

www.nrjournal.com

Review Article

Reductions in body weight and percent fat mass increase the vitamin D status of obese subjects: a systematic review and metaregression analysis☆,☆☆

Poonam K. Pannu[a], *Yun Zhao*[b], *Mario J. Soares*[a,*]

[a] *Directorate of Nutrition, Dietetics & Food Technology, School of Public Health, Curtin Health Innovation Research Institute–Biosciences, Faculty of Health Sciences, Curtin University, Perth, WA, Australia*

[b] *School of Public Health, Faculty of Health Sciences, Curtin University, Perth, WA, Australia*

ARTICLE INFO

Article history:
Received 10 July 2015
Revised 19 November 2015
Accepted 24 November 2015

Keywords:
Obesity
Weight loss
Vitamin D
25 Hydroxyvitamin D
Sequestration
Dilution

ABSTRACT

The purpose of this review was to confirm a volumetric dilution of vitamin D in obesity. It was based on the hypothesis that weight loss, particularly fat loss, would increase serum 25-hydroxyvitamin D (25OHD) in the obese. We conducted a systematic review of the literature over the last 21 years and included human trials that reported changes in 25OHD, weight, or body composition after weight loss. Study arms were excluded if vitamin D was supplemented, dietary intake exceeded 800 IU/d, or extreme sun exposure was reported. Eighteen of 23 trials that met our criteria documented an increase in vitamin D status with weight loss. Metaregression analyses indicated a marginally significant effect of weight loss on unadjusted weighted mean difference of 25OHD (β = –0.60 [95% confidence interval {CI}, –1.24 to +0.04] nmol/L; P = .06) and after adjustment for study quality (Jadad score ≥3) (β = –0.64 [95% CI, –1.28 to +0.01] nmol/L; P = .05). The effect of percent fat mass on weighted mean difference of 25OHD was also marginally significant before (β = –0.91 [95% CI, –1.96 to +0.15] nmol/L; P = .08) and after adjustment of study quality (β = –1.05 [95% CI, –2.18 to +0.08] nmol/L; P = .06). Collectively, these outcomes support a volumetric dilution of vitamin D. The slopes of the respective regression lines, however, indicate a smaller increase in 25OHD than would be expected from a direct mobilization of stores into the circulation. Hence, sequestration of 25OHD and its conversion to inactive metabolites would also play a role. Future studies could relate changes in body fat compartments to the enzymatic regulation of 25OHD in response to weight loss.

Abbreviations: %FM, percent fat mass; 1,25 dihydroxyvitamin D3, 1,25(OH)2D3; 25OHD, 25-hydroxyvitamin D; AT, adipose tissue; BIA, bioelectrical impedance analysis; BMI, body mass index; CBA, competitive protein binding assays using rachitic rat kidney cytosol; CI, confidence interval; CLIA, chemiluminescence immune assay; DEXA, dual-energy x-ray absorptiometry; ECLIA, electrochemiluminescent immunoassay; ELISA, enzyme-linked immunosorbent assay; FFM, fat free mass; FM, fat mass; LC-MS, liquid chromatography mass spectrometry; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomized controlled trial; RIA, radioimmunoassay; VDR, vitamin D receptor; WMD, weighted mean difference.

☆ Major finding: The data support a volumetric dilution of vitamin D in obesity but do not discount a sequestration effect.

☆☆ Model used: Systematic review of trials on human subjects.

* *Corresponding author at:* Directorate of Nutrition, Dietetics & Food Technology, School of Public Health, Curtin Health Innovation Research Institute-Biosciences, Curtin University, GPO Box U1987, Perth, WA 6845, Australia. Tel.: +61 8 92663220; fax: +61 8 92662958.

E-mail addresses: p.pannu@curtin.edu.au (P.K. Pannu), y.zhao@exchange.curtin.edu.au (Y. Zhao), m.soares@curtin.edu.au (M.J. Soares).

http://dx.doi.org/10.1016/j.nutres.2015.11.013
0271-5317/

1. Introduction

Vitamin D and parathyroid hormone are essential for calcium homeostasis and bone metabolism [1]. There is accumulating evidence that vitamin D plays an important role in extraskeletal health and diseases such as diabetes mellitus, cancers, cardiovascular disease, and autoimmune disorders [2-5]. Serum 25-hydroxyvitamin D (25OHD) is the best clinical indicator of vitamin D status [1], and based on current cutoffs, the prevalence of vitamin D insufficiency worldwide is high. The escalating obesity crisis potentially contributes to this increasing incidence of vitamin D insufficiency because obese individuals have lower levels of 25OHD than their nonobese counterparts [6-8]. In fact, inverse associations among body weight, body mass index (BMI), and measures of body fatness with vitamin D status have been found across the lifespan [4,7,9,10]. Differences in 25OHD levels can be attributed to age, race, geography, skin color, habitual clothing, and sun exposure among other factors [11]. However, as vitamin D is fat soluble, it is commonly considered that the lower levels in the obese could also be due to uptake by adipose tissue (AT) and its clearance from plasma.

Rosenstreich et al [12] were the first to propose that AT was the major storage site of vitamin D and that its release from this tissue was quite slow. Based on the available evidence from animals and man, Heaney et al [13] have confirmed that the distribution of 25OHD was highest in fat mass (FM) (34%), followed by serum (30%) and then muscle (20%). Worstman et al [14] instead referred to "sequestration" of 25OHD for their observation that ultraviolet B radiation resulted in a significant increase in serum vitamin D3 in nonobese compared to obese individuals. This implied that vitamin D "disappeared" into AT and other tissues and was not immediately available in plasma for further metabolic activity. Such a phenomenon would account for the lower bioavailability of the vitamin in the obese [14]; however, the mechanisms controlling the deposition and release of vitamin D from AT are still unknown [15].

Drincic et al [16], however, support the theory of volumetric dilution, which implies that plasma levels of the vitamin decrease as body size and hence fat stores increase. It follows that, if fat stores decrease, there ought to be a greater return of vitamin D into plasma resulting in increased vitamin D status. In a cross-sectional study, Drincic et al [16] identified body weight as the single strongest predictor of 25OHD levels, followed by FM. Their best fitting model relating 25OHD and body weight was a hyperbola, which indicated that body weight explained 13% of the variance in 25OHD. A visual inspection of the regression line shows that the slope is steeper at a body weight less than 90 kg but gets progressively shallower at higher body weights [16]. Hence, an obese individual of 100 kg would need to lose a considerable amount of weight to benefit from an appreciable increase in 25OHD. The results of a clinical trial would support this interpretation because categories of weight loss less than 15% of baseline brought about increases of 5.3 to 8.3 nmol/L in 25OHD, whereas above a value of 15%, there was more than a doubling of this effect [17]. A caveat to such expectations would be the extensive conversion of released vitamin D to metabolites other than 25OHD, which would not be detected by the specific 25OHD assay used (Fig. 1).

It is unclear how 25OHD is handled once taken up by different body tissues such as AT and skeletal muscle. Both tissues are metabolically active, and the vitamin D receptor (VDR) is expressed in them [18,19]. Hence, a paracrine role in these tissues may account for some of the sequestration effect. Alternatively, if these tissues merely act as a store for the vitamin, then a sizeable amount would be available for release into plasma after tissue mobilization in response to weight loss [20]. There is also the possibility that both sequestration and volumetric dilution coexist in obese individuals. In Fig. 1, we schematically depict the basis of this review and the potential storage and release of 25OHD in an obese individual during weight loss. We focused on the larger stores of AT seen in overweight/obese individuals to allow for the best chance for hypothesized effects. We also negated the contribution from external sources of vitamin D by excluding study arms with vitamin D supplementation and those that reported excessive sunlight exposure during their trials. In this systematic review, we embarked on the hypothesis that weight loss without supplementary vitamin D would result in an increase in plasma 25OHD. We entertained the possibility that changes in 25OHD might be explained by volumetric dilution effect, sequestration effects, or other mechanisms (Fig. 1).

1.1. *Systematic review*

The aim of the search was to identify trials with weight loss that measured change in vitamin D status, but without vitamin D supplementation. Accordingly, placebo arms of trials that used vitamin D supplementation were included because we were only interested in relating the change in the 2 variables. Studies were identified through a systematic electronic search of Web of Science and PubMed Central databases over the period January 1994 to October 2015. One author (PP) conducted the search using the following terms: vitamin D, vitamin D-3, 25-hydroxy-vitamin D, 25-hydroxyvitamin D, serum 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D3, 25OHD, cholecalciferol, 25-OH vitamin D, 25-hydroxycholecalciferol, or serum 25OHD, and obese, overweight, caloric restriction, weight loss, fat mass, fat free mass, body mass index, BMI, or adipose tissue. Only articles published in the English language were included.

At the identification stage, the abstract was read, and the articles were selected, according to the following inclusion criteria: human clinical trials, weight loss study (through energy restriction, increased physical activity, or both), measurement of weight loss or body composition, study or placebo arm(s) without vitamin D supplementation, overweight/obese subjects, and change in serum 25OHD. Exclusion criteria included the use of the following terms in the abstract: vitamin D supplementation in all study arms, vitamin D–enriched foods greater than 800 IU/d, animal studies, gastric bypass/bariatric surgery studies, and duplicates of the same article retrieved from the 2 different databases. At the screening stage, the full text was read, and articles were screened based on the following inclusion criteria: change in serum 25OHD measured, included data

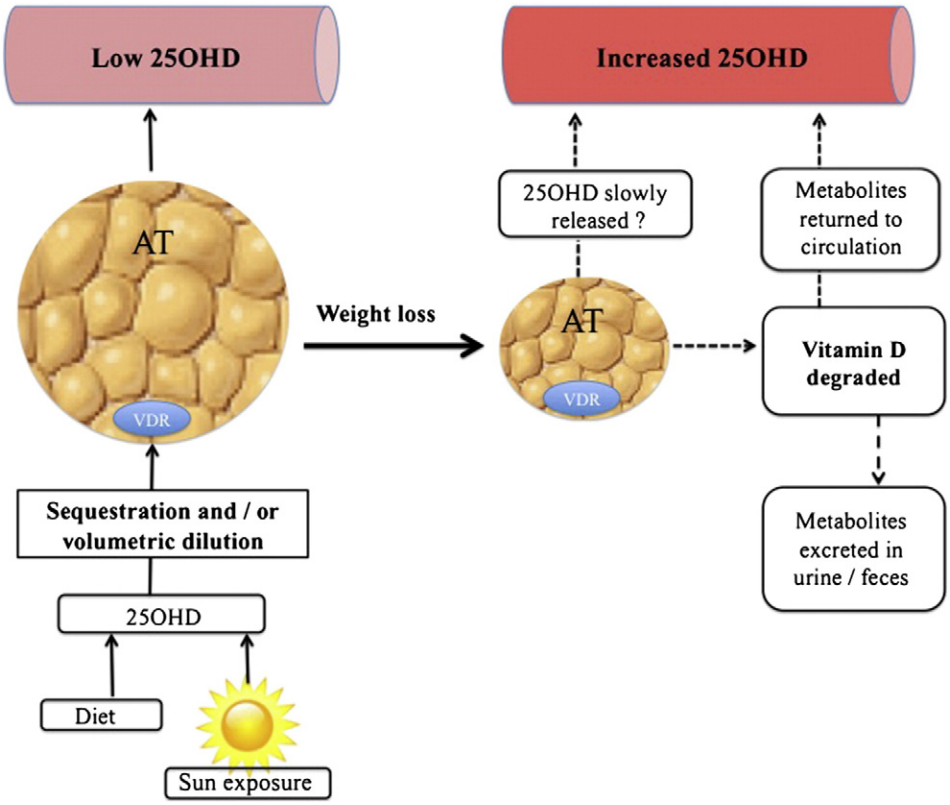

Fig. 1 – The potential pathways influencing 25OHD in obese individuals before and after weight loss. Solid lines in arrows indicate established mechanisms; dashed lines in arrows indicate potential mechanisms.

for at least 1 index of weight change, and weight loss as the primary or secondary outcome. Articles were excluded if vitamin D supplements were used, diets included foods enriched with vitamin D to result in greater than 800 IU/d, or extreme exposure to sunlight was indicated. Additional studies were sourced by manually searching the reference list and included 2 published studies from our laboratory [21,22]. After eligibility was determined, all randomized controlled trials (RCTs) were graded for their quality according to the Jadad score, with values greater than or equal to 3, indicating a high quality study [23], whereas 9 single-stranded studies were graded as zero. The overall process is outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) [24] flow diagram (Fig. 2).

Data extraction was carried out by 1 investigator (PKP) on an excel spreadsheet developed by the statistician (YZ). Another investigator (MJS) cross-checked quality criteria assessment and data entry. Any discrepancies were reviewed and discussed. The change in mean and SD was calculated for body weight, FM, fat free mass (FFM), or BMI, for studies that provided only prevalues and postvalues. Where necessary, vitamin D intake data were converted to international units per day; and 25OHD status, to nanomoles per liter. Fat mass was extracted as percentages; and FFM, as kilograms, as most articles presented their data in this manner. All subjects were overweight or obese at baseline; thus, FM (percentages) is an appropriate measure during weight loss studies. Furthermore, it is common to use FM (percentages) and FFM (kilograms) to evaluate nutrition status [25].

2. Methods and materials

2.1. *Statistical analysis*

2.1.1. *Meta-analysis main effects*

The primary outcome was the relationship of change in vitamin D status and change in weight/obesity status. The change in vitamin D status was calculated as postvalue minus the prevalue where a positive value implied an increase in the 25OHD status. Changes in the 4 main factors of interest in our article, (i) weight (kilograms), (ii) BMI (kilograms per square meter), (iii) FM (percentages), and (iv) FFM (kilograms), were also calculated as postvalue minus the prevalue; hence, a negative value implied a reduction in the 4 main factors. Some RCTs had multiple treatment arms. Each arm was included as a separate study in the meta-analysis. Both fixed-effects and random-effects meta-analysis models were carried out to obtain the weighted mean difference (WMD) of vitamin D status based on the studies included, to extrapolate results to the general population. To test for heterogeneity and identify the potential sources of heterogeneity, I^2 statistics and Galbraith plot were used. Potential publication and small sample size bias were assessed by visual inspections of funnel plots and Egger test.

2.2. *Confounders*

Potential confounders considered for analyses were mean age of subjects, percentage of females in each trial, duration of

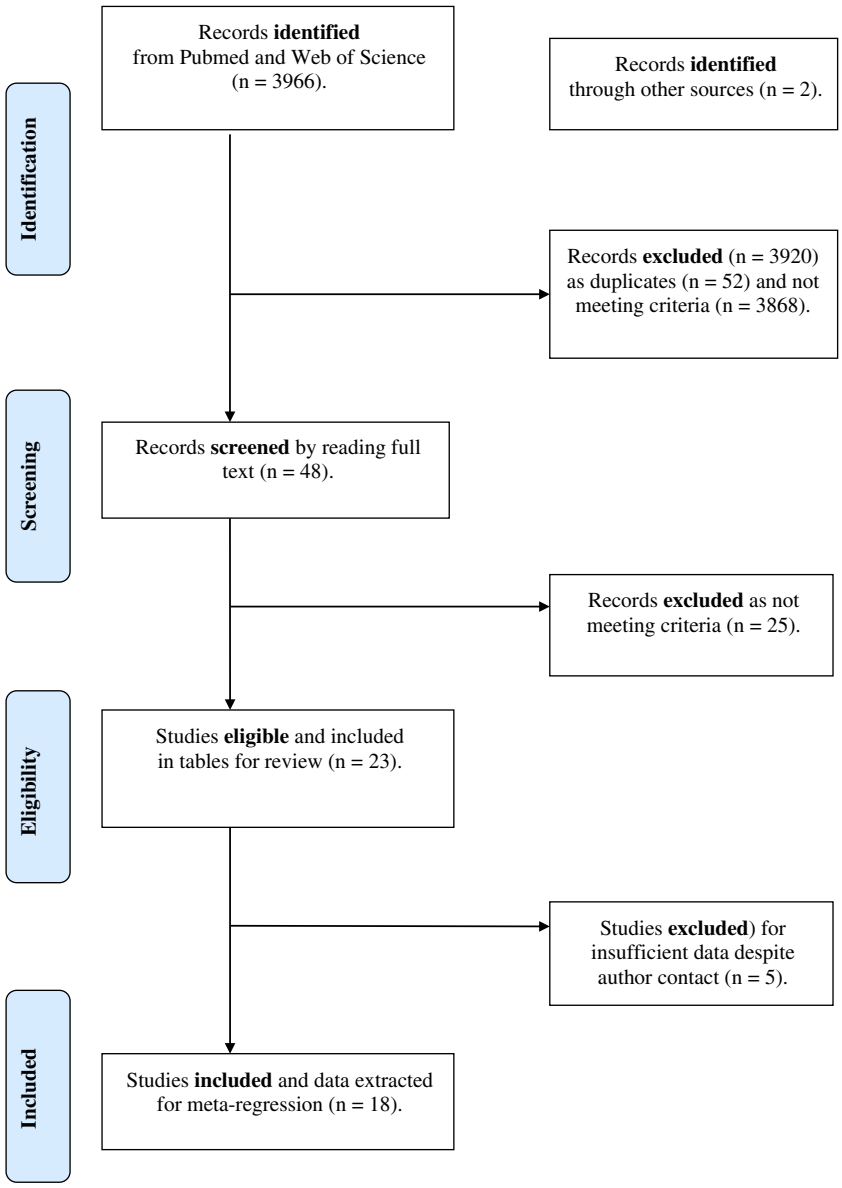

Fig. 2 – PRISMA flow diagram for vitamin D status and weight loss.

trial, vitamin D content in food (international units per day), total vitamin D intake in trial (international units per day × duration of trial), and season [26,27]. In our experience, age and sex (percentage of females) are potential confounders as they worked in opposite directions in regard to the effect of vitamin D supplementation on body weight [26]. In this article, variations in 25OHD between sexes may be due to differences in body composition, with women having a higher percentage of FM [6,28]. Duration of intervention may make a contribution to 25OHD because greater weight loss can be expected over a longer intervention period [29]. An effect of season is potentially intertwined with duration of study. Weight loss studies commencing in winter and lasting over summer may result in an increase in 25OHD due to season that will confound the expected increase due to greater weight loss [30]. However, we could not control for season as this was stated in only 4 studies [22,31-33]. The trials included in this review had also used a range of assays to measure 25OHD. These included radioimmunoassay (RIA) (n = 12), chemiluminescence immune assays (CLIA) (n = 4), competitive protein binding assays using rachitic rat kidney cytosol (CBA) (n = 1), enzyme-linked immunosorbent assay (ELISA) (n = 1), electrochemiluminescent immunoassay (ECLIA) (n = 1), liquid chromatography mass spectrometry (LC-MS) (n = 2), and not reported (n = 2) (Table 1). Potential control for assays was considered but was not carried out due to the limited number of high-quality studies using the same technique (RIA n = 6, CLIA n = 2, ELISA n = 1). Body composition techniques also varied, including dual-energy x-ray absorptiometry (DEXA) (n = 12), bioelectrical impedance analysis (BIA) (n = 6), skinfold thickness measurements, and equations (n = 2), and 3 studies did not report their method. Because of the variation in body composition techniques used and the limited number of high-quality studies using the same

technique (DEXA n = 6, BIA n = 1), no subgroup analysis was attempted.

2.3. Metaregression analysis

Separate unadjusted and adjusted random-effects metaregression analyses were carried out to investigate the independent contribution of the changes in the 4 main factors on the WMD of vitamin D status. A restricted maximum likelihood estimation method with backward elimination regression procedure was used in the metaregression analyses. Bubble plot was obtained with the size of the "bubble" proportional to the precision of the estimate for each of the 4 individual factors. The metaregression analyses were conducted in 3 steps: (1) unadjusted; (2) adjusted for study quality where a Jadad score was treated as a categorical variable ($0 < 3$, $1 \geq 3$); and (3) further adjustment for age, percentage of females, duration, and vitamin D in study diets (international units per day). All data analyses were carried out by Stata version 12 (2011, Stata Statistical Software: Release 12; StataCorp LP, College Station, TX, USA). $P < .05$ was considered as statistically significant.

3. Results

3.1. Systematic review

The search strategy generated 23 studies (14 RCTs and 9 single-stranded studies) whose key features are presented in Table 1. Of these studies, 12 were conducted in Europe [31-33,35-37,39,41,43,46-48]; 5, in the United States [17,34,38,40,45]; 2, in Canada [44,50]; 2, in Australia [21,22]; and 2, in the Middle East [42,49]. The study settings were all outpatient studies in a university setting or outpatient clinics. The 23 studies consisted of 2085 participants, with 74% being female, ages ranging from 12 to 62 years and study duration from 2 weeks to 2 years. All participants were overweight or obese at baseline. We found that, in 17 of 23 eligible studies, a significant increase in 25OHD was observed with a decrease in weight [17,31-33,36-39,41-48,50], a decrease in BMI in 15 studies [11,31-33,36,37,39,41,43-46,48-50], a decrease in percent fat mass (%FM) in 14 studies [17,32,33,37-41,43-47,50], and a decrease in FFM in 4 studies [32,38,44,46] (Table 1). Overall, 5 of these studies reported a significant association ($P < .05$) between 25OHD and any index of weight change [37,46-48,50], and 1 study reported a nonsignificant association [43] (Table 1).

Nine of 23 trials were assessed as high-quality studies (Jadad ≥3) and consisted of 1104 participants, with 80% being female, ages ranging from 32 to 58 years [17,21,22,31,33,34,38,41,42]. Of these 9 studies, a significant increase in 25OHD was observed with a decrease in weight in 5 studies [17,33,38,41,42], a decrease in BMI in 3 studies [17,33,41], a decrease in %FM in 4 studies [17,33,38,41], and a decrease in FFM in 1 study [38].

3.2. Metaregression analysis

Metaregression models were run unadjusted and adjusted for the effect of the confounders. However, none of the confounders was found to make a significant contribution to the change in the WMD of vitamin D when tested individually or in combination. We hence report the results obtained from the unadjusted regression analyses on (1) all weight loss studies (Table 2) and (2) adjusted for study quality (Table 3).

3.3. The effect of weight loss

The metaregression analysis for 34 arms of 17 weight loss studies included 1522 subjects and a mean age of 45 years [17,21,22,31-36,38,39,41,43-45,47,50]. The relationship favored a marginally significant increase of 6.0 nmol/L (95% CI, −12.42 to +0.47) in the WMD of 25OHD for an average weight loss of 10 kg ($P = .06$) (Table 2). When adjusting for quality of study, this association was close to significance ($P = .05$), with an increase of 6.4 nmol/L (95% CI, −12.85 to +0.12) in WMD of 25OHD for weight loss of 10 kg (Table 3).

3.4. The effect of change in %FM

The metaregression analysis for 28 arms of 13 weight loss studies included 1346 subjects, with a mean age of 44 years [17,21,22,31-33,38,39,41,43-45,50]. Results were marginally significant with an increase of 9.1 nmol/L (95% CI, −19.69 to +1.57) in the WMD of 25OHD for a 10% loss in %FM ($P = .08$) (Table 2). This result approached significance when analysis was adjusted for quality of studies where an increase of 10.5 nmol/L (95% CI, −21.87 to +0.85) in the WMD of 25OHD for a 10% decrease in %FM ($P = .06$) was observed (Table 3).

3.5. The effect of change in BMI and FFM

The metaregression analyses failed to find any significant relationship between the change in BMI and in FFM and the WMD of vitamin D in all study arms even when adjusted for quality of study (Tables 2 and 3).

4. Discussion

It is yet to be confirmed whether vitamin D is sequestered or undergoes a volumetric dilution in obesity. We questioned whether weight loss in the absence of vitamin D supplementation would increase circulating 25OHD. In this systematic review, 17 of 23 studies observed an increase in 25OHD with weight loss, but only 5 of these studies reported a significant correlation coefficient between the 2 variables [37,46-48,50]. Our metaregression analysis indicated a near significant association between weight loss and increase in 25OHD, which suggested that, for every 10 kg mean weight loss, there could be an average increase of 6.0 nmol/L in the WMD of 25OHD (Table 2; Fig. 3). When we adjusted the analysis for quality of study (with a Jadad score of ≥3 indicative of high quality), the relationship between change in weight and 25OHD was still near significance with no major change in the regression slope (Table 3). Hence, it would appear that body weight does contribute to a volumetric dilution of 25OHD [16].

After energy restriction, FM loss is a major portion of weight loss [51]. Although FFM is also lost, the precise amount

Table 1 – Human trials on weight loss and change in vitamin D status

First author, year of publication	Study details	Jadad score	Weight loss strategy	Vitamin D in food (IU/d)	Increase in vitamin D status (nmol/L)	Decrease in weight (kg)	Decrease in BMI (kg/m^2)	Decrease in FM (%)	Decrease in FFM (kg)	Assay
Ricci et al 1998 [34]	Age: 60 y Subjects: n = 30 (F) Duration: 24 wk Location: USA Study type: RCT	4	ER	NR	No change	Yes	Yes	Yes	Yes	RIA
Jensen et al 2001 [35]	Age: NR Subjects: n = 52 (F) Duration: 24 wk Location: Denmark Study type: RCT	0	ER	ER: 200 Control: 200	No change	Yes	Yes	NR	NR	CBA
Cummings 2006 [22]	Age: 53 y Subjects: n = 29 (6 M, 23 F) Duration: 12 wk Location: Australia Study type: RCT	3	ER	ER: 78 Control: 78	No change	Yes	Yes	Yes	Yes	RIA
Holecki et al 2007 [36]	Age: 50 y Subjects: n = 62 (F) Duration: 12 wk Location: Poland Study type: Single-stranded study	0	ER and PA	NR	Yes	Yes	Yes	NR	NR	RIA
Reinehr et al 2007 [37]	Age: 12 y Subjects: n = 156 (79 M, 77 F) Duration: 1 y Location: Germany Study type: Single-stranded study	0	ER and PA	ER and PA: 39	Yes	Yes, and significantly associated (r = –0.27; P = .013)	Yes	Yes	NR	CLIA
Riedt et al 2007 [38]	Age: 38 y Subjects: n = 31 (F) Duration: 24 wk Location: USA Study type: RCT	4	ER	NR	No change	Yes	NR	Yes	Yes	RIA
Hoelcki et al 2008 [39]	Age: 49 y Subjects: n = 20 (F) Duration: 12 wk Location: Poland Study type: RCT	0	ER and PA	ER and PA: NR	No change	Yes	Yes	Yes	NR	RIA
Lucey et al 2008 [31]	Age: 32 y Subjects: n = 276 (118 M, 158 F) Duration: 8 wk Location: Iceland, Spain, Ireland Study type: RCT	3	ER	ER 1: 68 ER 2: 56 ER 3: 420 Control: 64	Yes (1 group) Decrease (3 groups)	Yes	Yes	NR	NR	ELISA

Apovian et al 2009 [40]	Age: NR Subjects: n = 40 (12 M, 28 F) Duration: 12 wk Location: USA Study type: Single-stranded study	0	ER	NR	Yes	No change	No change	Yes	NR	NR
Ortega et al 2009 [32]	Age: 27 y Subjects: n = 61 (F) Duration: 2 wk Location: Spain Study type: RCT	1	ER	ER 1: 128 ER 2: 260	Yes	Yes	Yes	Yes	Yes	RIA
Chan She Ping-Delfos 2009 [21]	Age: 57 y Subjects: n = 43 (23 M, 20 F) Duration: 12 w Location: Australia Study type: RCT	3	ER, ER and PA	ER 1: 83 ER 2: 129 ER 3 and PA: 131	No change	Yes	Yes	Yes	Yes	RIA
Zitterman et al 2009 [41]	Age: 48 y Subjects: n = 83 (22 M, 61 F) Duration: 1 y Location: Germany Study type: RCT	5	ER	ER: 80	Yes	Yes	Yes	Yes	NR	RIA
Shahar et al 2010 [42]	Age: 52 y Subjects: n = 126 (M, F) Duration: 2 y Location: Israel Study type: RCT	3	ER	NR	Yes	Yes	NR	NR	NR	CLIA
Tzotzas et al 2010 [43]	Age: 40 y Subjects: n = 62 (F) Duration: 20 wk Location: Greece Study type: Single-stranded study	0	ER	NR	Yes	Yes, and associated ($r = -0.367$; $P = .065$)	Yes, and associated ($r = -0.376$; $P = .059$)	Yes	NR	ECLIA
Josse et al 2011 [44]	Age: 28 y Subjects: n = 81 (F) Duration: 16 wk Location: Canada Study type: RCT	2	ER and PA	ER and PA 1: 28 ER and PA 2: 392 ER and PA 3: 528	Yes (1 group) No change (1 group) Decrease (1 group)	Yes	Yes	Yes	Yes (2 groups) Decrease (1 group)	RIA
Mason et al 2011 [17]	Age: 58 y Subjects: n = 439 (F) Duration: 1 y Location: USA Study type: RCT	3	ER, ER and PA, PA	ER: 540 ER and PA: 538 PA: 595 Control: 447	Yes (1 group [a])	Yes	Yes	Yes	No	CLIA
Van Loan et al 2011 [45]	Age: 32 y Subjects: n = 71 (21 M, 50 F) Duration: 12 wk	2	ER	ER 1: 128 ER 2: 320	Yes (1 group) No change (1 group)	Yes	Yes	Yes	No change	RIA

(continued on next page)

Table 1 *(continued)*

First author, year of publication	Study details	Jadad score	Weight loss strategy	Vitamin D in food (IU/d)	Increase in vitamin D status (nmol/L)	Decrease in weight (kg)	Decrease in BMI (kg/m^2)	Decrease in FM (%)	Decrease in FFM (kg)	Assay
Christensen et al 2012 [46]	Location: USA Study type: RCT Age: 62 y Subjects: n = 175 (33 M, 142 F) Duration: 16 w Location: Denmark Study type: Single-stranded study	0	ER	ER: 382	Yes [a]	Yes, and significantly associated (r = –0.21; P = .006)	Yes	Yes, and significantly associated (r = –0.16; P = .03)	Yes	CLIA
Damms-Machado et al 2012 [47]	Age: 47 y Subjects: n = 32 (4 M, 28 F) Duration: 12 wk Location: Germany Study type: Single-stranded study	0	ER	ER: 200	Yes [a]	Yes	NR	Yes, and significantly associated (r = –0.6369; P < .0001)	NR	RIA
Wamberg et al 2013 [48]	Age: 35 y Subjects: n = 17 (9 M, 8 F) Duration: 8 and 4 wk maintenance Location: Denmark Study type: Single-stranded study	0	ER	NR	Yes	Yes, and significantly associated (% weight loss) (r = 0.67; P = .005)	Yes, and significantly associated (r = –0.67; P = .005)	NR	NR	LC-MS
Albadah et al 2015 [49]	Age: 32 y Subjects: n = 49 (M) Duration: 12 wk Location: Saudi Arabia Study type: Single-stranded study	0	ER	NR	Yes	NR	Yes	NR	NR	NR
Ibero-Baraibar et al 2015 [33]	Age: 57 y Subjects: n = 47 (24 M, 23 F) Duration: 4 wk Location: Spain Study type: RCT	5	ER	ER 1: 142 ER 2: 191	Yes (1 group [a])	Yes	Yes	Yes	NR	RIA
Gangloff et al. 2015 [50]	Age: 48 y Subjects: n = 103 (M) Duration: 1 y Location: Canada Study type: Single-stranded study	0	ER and PA	NR	Yes [a]	Yes, and significantly associated (r = –0.31; P < .005)	Yes, and significantly associated (r = –0.32; P < .005)	Yes, and significantly associated (r = –0.32; P < .005)	NR	LC-MS

Age indicates mean age. P < .05 was considered significant.
Abbreviations: ER, energy restriction; F, female; M, male; NR, not reported; PA, physical activity.
[a] Baseline 25OHD less than 50 nmol/L; after weight loss, it was greater than 50 nmol/L.

Table 2 – Unadjusted metaregression of changes in weight and indices of body composition on vitamin D status

Outcome variable: WMD of vitamin D status	Variable	Estimated coefficient β	95% CI	P
The effect of weight loss				
Model 1	Change in weight (kg)	–0.60	–1.24, 0.04	.06
	Constant	–0.30	–4.24, 4.79	.90
The effect of decrease in BMI				
Model 2	Change in BMI (kg/m^2)	–0.13	–4.67, 4.41	.95
	Constant	2.40	–6.98, 11.78	.60
The effect of %FM loss				
Model 3	Change in FM (%)	–0.91	–1.96, 0.15	.08
	Constant	2.34	–1.22, 5.89	.18
The effect of FFM loss				
Model 4	Change in FFM (kg)	1.28	–1.25, 3.81	.30
	Constant	4.68	1.29, 8.07	.01

$P < .05$ was considered significant.

could vary with protein intake and/or increased physical activity [52], with both generally retarding loss of FFM. As both FM and FFM are major stores for the vitamin [13], we examined the effect of changes in these compartments on circulating 25OHD.

Fourteen of 23 studies observed that, with a loss in %FM, there was an increase in 25OHD [17,32,33,37-41,43-47,50] with 3 of these studies indicating a significant correlation coefficient between the 2 variables [46,47,50]. Metaregression analysis found that decreases in %FM were not significantly related to increases in 25OHD, on examination of the total data set (Table 2). When adjusted for quality of trials, this relationship between %FM loss and increase in 25OHD became marginally significant (Table 3; Fig. 4). The lack of statistical significance may have arisen not only from the smaller number of studies reporting %FM (28 study arms) and the smaller sample size (n = 1346) but also from the larger spread of effects. The β coefficient suggested that, with a 10% loss in %FM, the mean increase in 25OHD would be 10.5 nmol/L; however, the 95% CI were large at 21.8 to –0.8 nmol/L. The amount of vitamin D available in AT is approximately 103 nmol/kg [13] and represents a sizeable store in an obese person. Based on this, a 10% decrease in %FM should have resulted in a much greater increase in 25OHD than predicted by the β coefficient. There are a few potential reasons that may explain our observations.

The detection of changes in 25OHD and %FM loss would be influenced by the sensitivity of the various methods used in these trials. There is substantial interlaboratory variation in detecting 25OHD [53]. Binkley et al [53] observed that there could be up to a 2-fold difference between laboratories assaying the same sample with the same technique. Similarly, body composition techniques have limitations in their calibration, accuracy, and precision [54] dependent on the type of technique used (BIA vs DEXA vs skinfold measurement) [54,55] or within models of the same machine [56]. Dual-energy x-ray absorptiometry is considered to be the criterion standard for body composition; however, variations of up to 6% have been found between instruments from the same manufacturer [57,58]. Moreover, BIA and the skinfold technique appear to be more accurate in nonobese subjects, so there could be substantial variation in the studies of obese

Table 3 – Metaregression of changes in weight and indices of body composition on vitamin D status adjusted for study quality

Outcome variable: WMD of vitamin D status	Variable	Estimated coefficient β	95% CI	P
The effect of weight loss				
Model 1	Change in weight (kg)	–0.64	–1.28, 0.01	.05
	Jadad score (0, 1)	1.57	–2.71, 5.86	.46
	Constant	–0.84	–6.22, 4.55	.75
The effect of decrease in BMI				
Model 2	Change in BMI (kg/m^2)	–0.17	–4.77, 4.42	.93
	Jadad score (0, 1)	0.82	–4.82, 6.46	.76
	Constant	1.88	–8.28, 12.04	.70
The effect of %FM loss				
Model 3	Change in FM (%)	–1.05	–2.18, 0.08	.06
	Jadad score (0, 1)	1.43	–2.45, 5.31	.45
	Constant	1.04	–3.97, 6.05	.67
The effect of FFM loss				
Model 4	Change in FFM (kg)	2.11	–0.55, 4.77	.11
	Jadad score (0, 1)	5.30	–1.35, 11.96	.11
	Constant	1.07	–4.56, 6.69	.69

Jadad score: $0 = 0 < 3$; $1 = 1 \geq 3$. $P < .05$ was considered significant.

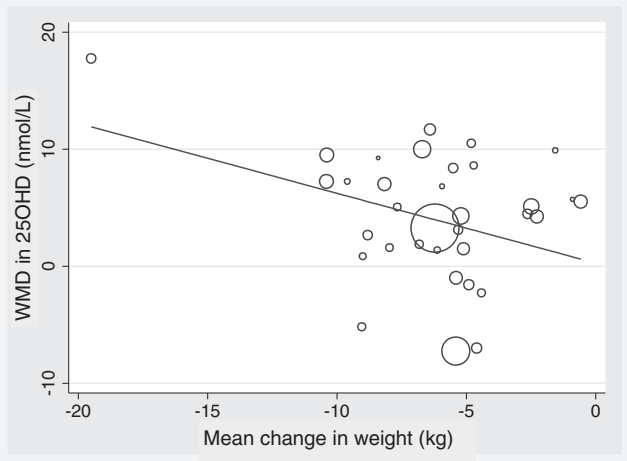

Fig. 3 – Relationship between change in weight (kilograms) and change in vitamin D status (WMD). Bubble plot of fitted metaregression line; the size of the bubbles is proportional to the precision of the estimate; WMD, weighted mean difference (nanomoles per liter) in vitamin D status.

subjects included in this review [31,32,37,39-41,43,47]. Overall, it is possible that changes in 25OHD due to fat loss and changes in %FM may not have been appropriately detected.

A second reason for the small increase in 25OHD on %FM loss is that once taken up into AT, 25OHD is released very slowly back into circulation. The latter may protect the individual from large sudden increases of a potentially toxic nutrient, while acting as a store in times of need [12]. Another further possibility is a negative feedback loop where higher circulating 1,25 dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) in obesity disables the production of 25OHD [59,60]. The mechanism that controls this slow release is uncertain; however, if this is true, then the shorter duration studies in this review may not detect this return of 25OHD. Importantly, vitamin D is involved in both

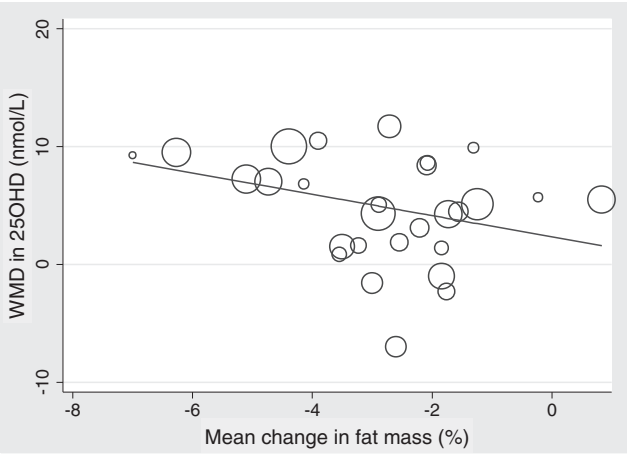

Fig. 4 – Relationship between change in FM (percentages) and change in vitamin D status (WMD). Bubble plot of fitted metaregression line; the size of the bubbles is proportional to the precision of the estimate; WMD, weighted mean difference (nanomoles per liter) in vitamin D status.

paracrine and autocrine actions in AT [61]. A nuclear VDR is expressed in AT [62], and most tissues that express VDR also contain the enzyme CYP27B1 for conversion of the circulating metabolite, 25OHD to $1,25(OH)_2D_3$. Adipose tissue has the ability to synthesize and degrade vitamin D for autocrine and paracrine use, such as in adipogenesis, lipid metabolism, and inflammation in obesity [19,63]. The expanded AT in obesity may hence engender an increased requirement of 25OHD, resulting in less return to the circulation after weight loss.

We now know that there is extensive metabolic conversion of vitamin D in storage depots. Adipose tissue is a dynamic endocrine organ, containing a variety of hydroxylase enzymes. These include the hydroxylase to convert cholecalciferol to 25OHD to $1,25(OH)_2D_3$, as well as the catabolic 24-hydroxylase for degradation of calcitrol to calcitroic acid, and 25OHD to $24,25(OH)_2D_3$ to 1-desoxycalcitroic acid, the major metabolite of 25OHD [19,48,64]. Calcitroic acid and 1-desoxycalcitroic acid are excreted through the bile into feces [65], with limited amounts found in the urine [66]. These metabolites are eliminated from the system and would not be detected in studies that only sampled the plasma compartment. In addition, there are emerging data to indicate that enzyme expression also varies with fat depots (subcutaneous vs visceral) and degrees of fatness (lean vs obese) [48]. Our current understanding is that lean and obese have similar expression of the enzyme CYP27A1 that converts 25OHD to $1,25(OH)_2D_3$ and similar expression of CYP24A1 that degrades 25OHD to calcitroic acid [64]. However, in response to weight loss, obese subjects show an elevation of the catabolic 24-hydroxylating enzyme, CYP2J2 [48], which results in several (almost 30) inactive metabolites [19,64]. Some of these include $1,24,25(OH)_3D_3$, 24-oxo, and/or 23-hydroxy groups [65] which represent pathways for vitamin D elimination [1]. Overall, many of these factors would be operative at the same time during weight loss and would go some way in explaining the smaller increase in 25OHD observed in this review. Perhaps, as Rosenstreich et al [12] opined, this slow return of 25OHD acts to protect against vitamin D toxicity that may occur if a flood of the nutrient became available during weight loss.

There are now many studies that show a positive relationship between 25OHD and muscle mass, growth, and strength/function [67-69]. This would suggest that higher vitamin D status may improve muscle mass and function, relative to those who are vitamin D insufficient. As FFM is a major store for the nutrient, we assumed that during weight loss, mobilization of the protein mass would contribute to an increase in 25OHD. However, we did not obtain a significant relationship between FFM loss and vitamin D status (Table 3). In fact, the slope of the regression line was in the opposite direction to that hypothesized (Table 3; Fig. 5). Because most studies reviewed showed a small to moderate decrease in FFM, our interpretation would be that a loss in FFM decreased circulating 25OHD. We acknowledge that this was a nonsignificant outcome but the slope was similar or greater than that obtained with %FM (Table 3; Fig. 4). Could this observation suggest that the expected positive relation between vitamin D status and muscle mass [67] is possibly bidirectional? Such a phenomenon could have negated the rise in 25OHD seen with loss of %FM (Fig. 4) and perhaps explain why the slope of weight loss change predicted was lesser than that

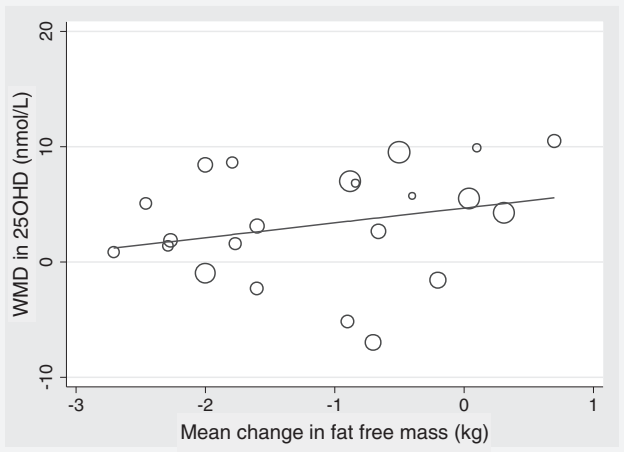

Fig. 5 – Relationship between change in FFM (kilograms) and change in vitamin D status (WMD). Bubble plot of fitted metaregression line; the size of the bubbles is proportional to the precision of the estimate; WMD, weighted mean difference (nanomoles per liter) in vitamin D status.

obtained with %FM (Table 3). It is unclear why a loss in FFM should decrease 25OHD. Fat free mass is composed of lean tissue (mainly skeletal muscle) and bone mineral content. As bone mass is also lost during energy restriction, vitamin D may prevent the expected decrease in fractional bone mass that occurs with weight loss [70]. There is good cross-talk between muscle and bone and AT and bone [70]. So, a decrease in 25OHD or a less than expected increase may also indicate diversion from plasma to other tissues during weight loss.

To the best of our knowledge, there are no other systematic reviews that have specifically addressed our question. Hence, we are unable to compare our results to the existing literature. Our search of the literature was over a long interval but covered only 2 prominent databases. We identified 23 studies, of which only 9 were quality studies with a sample size of 1104. Hence, our metaregression analysis may be limited by adequate numbers, despite contacting the authors of all studies for additional information. Seasonality of 25OHD can amount to 17 nmol/L [30,71] and have a major confounding on the stated outcomes. We were unable to control for this confounder in our analysis because season of start and completion was only mentioned in 3 studies. Moreover, there was a range of assays used in these studies as well as a range of body composition techniques that would have influenced our outcomes.

Longer duration trials of good quality (Jadad ≥3) of at least 6 months duration, which target a substantial amount of weight loss (~20% fat loss), are required. Such data would cement the clinical relevance of weight loss in normalizing vitamin D status of the obese individual. Adipose tissue is an active endocrine organ, expressing numerous receptors including vitamin D [19,72], and vitamin D is required for normal formation and function of AT [73-76]. Hence, what happens to vitamin D status before and after weight loss is important. Further investigation into vitamin D concentration in AT of obese subjects before and after weight loss may provide an insight into the amount of vitamin D and its metabolites at a cellular level. Wamberg et al [48] have provided some pioneering data in the area of vitamin D hydroxylation and catabolizing enzymes in AT. These data need validation in future trials as they provide an understanding of the dynamic influence of AT on vitamin D metabolism. Furthermore, trials on vitamin D need to report detailed body compositional changes, including body fat distribution. Dual-energy x-ray absorptiometry is now globally available and changes in android:gynoid fat can be reported, although more sophisticated determinations of subcutaneous and visceral AT changes based on computed tomography or magnetic resonance imaging scans would be worthwhile inclusions. Lastly, there is a need to report the concentrations of inactive compounds of vitamin D metabolism in both urine and serum. This would assist the evaluation of how much of the vitamin is unavailable for metabolism during weight loss.

In conclusion, this systematic review provides good evidence for an inverse relationship between weight and fat loss and 25OHD in obesity. Although overall in support of a volumetric dilution phenomenon in obesity, the review cannot discount a sequestration effect and possibly extensive degradation of 25OHD after weight loss.

PKP conducted the literature search, assembled the tables, extracted the data, and cowrote the manuscript. MJS generated the idea, conceptualized the review process, cross-checked data extraction, and co-wrote the manuscript. YZ prepared the data extraction template, conducted the statistical analysis, and cowrote the manuscript. All authors contributed to the writing of the final manuscript.

Acknowledgment

The authors sincerely thank Anne Gangloff, Andrea R Josse, Alice J Lucey, Trina A Ricci, Sue A Shapses, and Marta D Van Loan for graciously providing additional data from their trials. The authors acknowledge the useful feedback and insights of the reviewers that shaped this manuscript. PKP is the recipient of an Australian Postgraduate Award. MJS acknowledges the School of Public Health, Curtin University, for research support. There are no conflicts of interest to declare.

REFERENCES

[1] Ross A, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab 2011; 96:53–8.

[2] Pilz S, Kienreich K, Rutters F, de Jongh R, van Ballegooijen AJ, Grubler M, et al. Role of vitamin D in the development of insulin resistance and type 2 diabetes. Curr Diab Rep 2013;13:261–70.

[3] Hollick MF. Vitamin D: importance in the prevention of cancers, type 1 diabetes, heart disease, and osteoporosis. Am J Clin Nutr 2004;79:362–71.

[4] Vimaleswaran KS, Cavadino A, Berry DJ, Jorde R, Dieffenbach AK, Lu C, et al. Association of vitamin D status with arterial blood pressure and hypertension risk: a mendelian

randomisation study. Lancet Diabetes Endocrinol 2014;2:719–29.
[5] Parker J, Hashmi O, Dutton D, Mavrodaris A, Stranges S, Kandala NB, et al. Levels of vitamin D and cardiometabolic disorders: systematic review and meta-analysis. Maturitas 2010;65:225–36.
[6] Lagunova Z, Porojnicu AC, Lindberg F, Hexeberg S, Moan J. The dependency of vitamin D status on body mass index, gender, age and season. Anticancer Res 2009;29:3713–20.
[7] Samuel L, Borrell LN. The effect of body mass index on adequacy of serum 25-hydroxyvitamin D levels in US adults: the National Health and Nutrition Examination Survey 2001 to 2006. Ann Epidemiol 2014;24:781–4.
[8] Mai XM, Chen Y, Camargo Jr CA, Langhammer A. Cross-sectional and prospective cohort study of serum 25-hydroxyvitamin D level and obesity in adults: the HUNT study. Am J Epidemiol 2012;175:1029–36.
[9] Soares MJ, Chan She Ping-Delfos W, Ghanbari MH. Calcium and vitamin D for obesity: a review of randomized controlled trials. Eur J Clin Nutr 2011;65:994–1004.
[10] Earthman CP, Beckman LM, Masodkar K, Sibley SD. The link between obesity and low circulating 25-hydroxyvitamin D concentrations: considerations and implications. Int J Obes 2012;36:387–96.
[11] Mason RS, Sequeira VB, Gordon-Thomson C. Vitamin D: the light side of sunshine. Eur J Clin Nutr 2011;65:986–93.
[12] Rosenstreich SJ, Rich C, Volwiler W. Deposition in and release of vitamin D3 from body fat: evidence for a storage site in the rat. J Clin Invest 1971;50:679–87.
[13] Heaney RP, Horst RL, Cullen DM, Armas LAG. Vitamin D3 distribution and status in the body. J Am Coll Nutr 2009;28:252–6.
[14] Worstman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr 2000;72:690–3.
[15] Malmberg P, Karlsson T, Svensson H, Lonn M, Carlsson NG, Sandberg AS, et al. A new approach to measuring vitamin D in human adipose tissue using time-of-flight secondary ion mass spectrometry: a pilot study. J Photochem Photobiol B 2014;138:295–301.
[16] Drincic AT, Armas LA, Van Diest EE, Heaney RP. Volumetric dilution, rather than sequestration best explains the low vitamin D status of obesity. Obesity 2012;20:1444–8.
[17] Mason C, Xiao L, Imayama I, Duggan CR, Bain C, Foster-Schubert KE, et al. Effects of weight loss on serum vitamin D in postmenopausal women. Am J Clin Nutr 2011;94:95–103.
[18] Pfeifer M, Begerow B, Minne HW. Vitamin D and muscle function. Osteoporos Int 2002;13:187–94.
[19] Ding C, Gao D, Wilding J, Trayhurn P, Bing C. Vitamin D signalling in adipose tissue. Br J Nutr 2012;108:1915–23.
[20] Mawer EB, Blackhouse J, Holamn CA, Lumb GA, Stanbury SW. The distribution and storage of vitamin D and its metabolites in human tissues. Clin Sci 1972;43:413–31.
[21] Chan She Ping-Delfos W. Effects of dairy products and resistance exercise on energy balance. Curtin University: Curtin University; 2009.
[22] Cummings NK. Potential role of calcium in obesity. Curtin University: Curtin University; 2006.
[23] Jadad AR, Moore A, Carroll A, Jenkinson C, Reynolds JM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary. Control Clin Trials 1996;17:1–12.
[24] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1–9.
[25] Kyle UG, Schutz Y, Dupertuis YM, Pichard C. Body composition interpretation. Nutrition 2003;19:597–604.
[26] Pathak K, Soares MJ, Calton EK, Zhao Y, Hallett J. Vitamin D supplementation and body weight status: a systematic review and meta-analysis of randomized controlled trials. Obes Rev 2014;15:528–37.
[27] Zheng Y, Zhu J, Zhou M, Cui L, Yao W, Liu Y. Meta-analysis of long-term vitamin D supplementation on overall mortality. PLoS One 2013;8, e82109. http://dx.doi.org/10.1371/journal.pone.0082109.
[28] Bolland MJ, Grey AB, Ames RW, Mason BH, Horne AM, Gamble GD, et al. The effects of seasonal variation of 25-hydroxyvitamin D and fat mass on a diagnosis of vitamin D sufficiency. Am J Clin Nutr 2007;86:959–64.
[29] Finkler E, Heymsfield SB, St-Onge MP. Rate of weight loss can be predicted by patient characteristics and intervention strategies. J Acad Nutr Diet 2012;112:75–80.
[30] Daly RM, Gagnon C, Lu ZX, Magliano DJ, Dunstan DW, Sikaris KA, et al. Prevalence of vitamin D deficiency and its determinants in Australian adults aged 25 years and older: a national, population-based study. Clin Endocrinol (Oxf) 2012;77:26–35.
[31] Lucey AJ, Paschos GK, Cashman KD, Martinez JA, Thorsdottir I, Kiely M. Influence of moderate energy restriction and seafood consumption on bone turnover in overweight young adults. Am J Clin Nutr 2008;87:1045–52.
[32] Ortega RM, Lopez-Sobaler AM, Aparicio A, Bermejo LM, Rodriguez-Rodriguez E, Perea JM, et al. Vitamin D status modification by two slightly hypocaloric diets in young overweight/obese women. Int J Vitam Nutr Res 2009;79:71–8.
[33] Ibero-Baraibar I, Navas-Carretero S, Abete I, Martinez JA, Zulet MA. Increases in plasma 25(OH)D levels are related to improvements in body composition and blood pressure in middle-aged subjects after a weight loss intervention: longitudinal study. Clin Nutr 2015;34:1010–7.
[34] Ricci TA, Chowdhury HA, Heymsfield SB, Stahl T, Pierson RN, Shapses SA. Calcium supplementation suppresses bone turnover during weight reduction in postmenopausal women. J Bone Miner Res 1998;13:1045–50.
[35] Jensen BL, Kollerup G, Quaade F, Sorensen OH. Bone mineral changes in obese women during a moderate weight loss with and without calcium supplementation. J Bone Miner Res 2001;16:141–7.
[36] Holecki M, Zahorska-Markiewicz B, Janowska J, Nieszporek T, Wojaczynska-Stanek K, Zak-Golab A, et al. The influence of weight loss on serum osteoprotegerin concentration in obese perimenopausal women. Obesity 2007;15:1925–9.
[37] Reinehr T, de Sousa G, Alexy U, Kersting M, Andler W. Vitamin D status and parathyroid hormone in obese children before and after weight loss. Eur J Endocrinol 2007;157:225–32.
[38] Riedt CS, Schlussel Y, von Thun N, Ambia-Sobhan H, Stahl T, Field MP, et al. Premenopausal overweight women do not lose bone during moderate weight loss with adequate or higher calcium intake. Am J Clin Nutr 2007;85:972–80.
[39] Holecki M, Zahorska-Markiewicz B, Wiecek A, Mizia-Stec K, Nieszporek T, Zak-Golab A. Influence of calcium and vitamin D supplementation on weight and fat loss in obese women. Obes Facts 2008;1:274–9.
[40] Apovian C, Bigornia S, Cullum-Dugan D, Schoonmaker C, Radziejowska J, Phipps J, et al. Milk-based nutritional supplements in conjunction with lifestyle intervention in overweight adolescents. Infant Child Adolesc Nutr 2009;1:37–44.
[41] Zittermann A, Frisch S, Berthold HK, Gotting C, Kuhn J, Kleesiek K, et al. Vitamin D supplementation enhances the beneficial effects of weight loss on cardiovascular disease risk markers. Am J Clin Nutr 2009;89:1321–7.
[42] Shahar DR, Schwarzfuchs D, Fraser D, Vardi H, Thiery J, Fiedler GM, et al. Dairy calcium intake, serum vitamin D, and successful weight loss. Am J Clin Nutr 2010;92:1017–22.
[43] Tzotzas T, Papadopoulou FG, Tziomalos K, Karras S, Gastaris K, Perros P, et al. Rising serum 25-hydroxy-vitamin D levels

after weight loss in obese women correlate with improvement in insulin resistance. J Clin Endocrinol Metab 2010;95:4251–7.
[44] Josse AR, Atkinson SA, Tarnopolsky MA, Phillips SM. Increased consumption of dairy foods and protein during diet- and exercise-induced weight loss promotes fat mass loss and lean mass gain in overweight and obese premenopausal women. J Nutr 2011;141:1626–34.
[45] Van Loan MD, Keim NL, Adams SH, Souza E, Woodhouse LR, Thomas A, et al. Dairy foods in a moderate energy restricted diet do not enhance central fat, weight, and intra-abdominal adipose tissue losses nor reduce adipocyte size or inflammatory markers in overweight and obese adults: a controlled feeding study. J Obes 2011;2011, 989657. http://dx.doi.org/10.1155/2011/989657.
[46] Christensen P, Bartels EM, Riecke BF, Bliddal H, Leeds AR, Astrup A, et al. Improved nutritional status and bone health after diet-induced weight loss in sedentary osteoarthritis patients: a prospective cohort study. Eur J Clin Nutr 2012;66:504–9.
[47] Damms-Machado A, Weser G, Bischoff SC. Micronutrient deficiency in obese subjects undergoing low calorie diet. Nutr J 2012;11. http://dx.doi.org/10.1186/1475-2891-11-34.
[48] Wamberg L, Christiansen T, Paulsen SK, Fisker S, Rask P, Rejnmark L, et al. Expression of vitamin D–metabolizing enzymes in human adipose tissue—the effect of obesity and diet-induced weight loss. Int J Obes 2013;37:651–7.
[49] Albadah MS, Dekhil H, Shaik SA, Alsaif MA, Shogair M, Nawaz S, et al. Effect of weight loss on serum osteocalcin and its association with serum adipokines. Int J Endocrinol 2015; 2015, 508532. http://dx.doi.org/10.1155/2015/508532.
[50] Gangloff A, Bergeron J, Pelletier-Beaumont E, Nazare JA, Smith J, Borel AL, et al. Effect of adipose tissue volume loss on circulating 25-hydroxyvitamin D levels: results from a 1-year lifestyle intervention in viscerally obese men. Int J Obes (Lond) 2015;39:1638–43.
[51] Varady KA. Intermittent versus daily calorie restriction: which diet regimen is more effective for weight loss? Obes Rev 2011;12:e593–601.
[52] Stiegler P, Cunliffe A. The role of diet and exercise for the maintenance of fat-free mass and resting metabolic rate during weight loss. Sports Med 2006;36:239–62.
[53] Binkley N, Krueger D, Cowgill CS, Plum L, Lake E, Hansen KE, et al. Assay variation confounds the diagnosis of hypovitaminosis D: a call for standardization. J Clin Endocrinol Metab 2004;89:3152–7.
[54] Erselcan T, Candan F, Saruhan S, Ayca T. Comparison of body composition analysis methods in clinical routine. Ann Nutr Metab 2000;44:243–8.
[55] Neovius M, Hemmingsson E, Freyschuss B, Udden J. Bioelectrical impedance underestimates total and truncal fatness in abdominally obese women. Obesity 2006;14:1731–8.
[56] Pearson D, Horton B, Green DJ. Cross calibration of Hologic QDR2000 and GE lunar prodigy for whole body bone mineral density and body composition measurements. J Clin Densitom 2011;14:294–301.
[57] Ellis KJ, Shypailo RJ. Bone mineral and body composition measurements: cross-calibration of pencil-beam and fan-beam dual-energy x-ray absorptiometers. J Bone Miner Res 1998;13:1613–8.
[58] Covey MK, Berry JK, Hacker ED. Regional body composition: cross-calibration of DXA scanners—QDR4500W and Discovery Wi. Obesity (Silver Spring) 2010;18:632–7.
[59] Bell NH, Epstein S, Greene A, Shary J, Oexmann MJ, Shaw S. Evidence for alteration of the vitamin D-endocrine system in obese subjects. J Clin Invest 1985;76:370–3.
[60] Pourshahidi LK. Vitamin D, and obesity: current perspectives and future directions. Proc Nutr Soc 2015;74:115–24.
[61] Morris HA, Anderson PH. Autocrine and paracrine actions of vitamin D. Clin Biochem Rev 2010;31:129–38.
[62] Salehi-Tabar R, Nguyen-Yamamoto L, Tavera-Mendoza LE, Quail T, Dimitrov V, An B, et al. Vitamin D receptor as a master regulator of the c-MYC/MXD1 network. PNAS 2012; 109:18827–32.
[63] Calton EK, Keane KN, Soares MJ. The potential regulatory role of vitamin D in the bioenergetics of inflammation. Curr Opin Clin Nutr Metab Care 2015;18:367–73.
[64] Jones G, Prosser DE, Kaufmann M. 25-Hydroxyvitamin D-24-hydroxylase (CYP24A1): its important role in the degradation of vitamin D. Arch Biochem Biophys 2012;523:9–18.
[65] Jones G, Strugnell SA, DeLuca HF. Current understanding of the molecular actions of vitamin D. Physiol Rev 1998;78: 1193–231.
[66] Kumar R, Harnden D, DeLuca HF. Metabolism of 1,25-dihydroxyvitamin D3: evidence for side-chain oxidation. Biochemistry 1976;15:2420–3.
[67] Girgis CM, Clifton-Bligh RJ, Hamrick MW, Holick MF, Gunton JE. The roles of vitamin D in skeletal muscle: form, function, and metabolism. Endocr Rev 2013;34:33–83.
[68] Pojednic RM, Ceglia L. The emerging biomolecular role of vitamin D in skeletal muscle. Exerc Sport Sci Rev 2014;42: 76–81.
[69] Sato Y, Iwamoto J, Kanoko T, Satoh K. Low-dose vitamin D prevents muscular atrophy and reduces falls and hip fractures in women after stroke: a randomized controlled trial. Cerebrovasc Dis 2005;20:187–92.
[70] Shapses SA, Sukumar D. Bone metabolism in obesity and weight loss. Annu Rev Nutr 2012;32:287–309.
[71] van der Wielen RPJ, Lowik MRH, van den Berg H, de Groot L, Haller J, Moreiras O, et al. Serum vitamin D concentrations among elderly people in Europe. Lancet 1995;346:207–10.
[72] Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 2004;89:2548–56.
[73] Kamei Y, Kawada T, Kazuki R, Ono T, Kato S, Sugimoto E. Vitamin D receptor gene expression is up-regulated by 1, 25-dihydroxyvitamin d3 in 3 T3-L1 preadipocytes. Biochem Biophys Res Commun 1993;193:948–55.
[74] Kong J, Li YC. Molecular mechanism of 1,25-dihydroxyvitamin D3 inhibition of adipogenesis in 3 T3-L1 cells. Am J Physiol Endocrinol Metab 2006;290:E916–24.
[75] Li J, Byrne ME, Chang E, Jiang Y, Donkin SS, Buhman KK, et al. 1alpha,25-Dihydroxyvitamin D hydroxylase in adipocytes. J Steroid Biochem Mol Biol 2008;112:122–6.
[76] Wong KE, Kong J, Zhang W, Szeto FL, Ye H, Deb DK, et al. Targeted expression of human vitamin D receptor in adipocytes decreases energy expenditure and induces obesity in mice. J Biol Chem 2011;286:33804–10.