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A systematic review of the interrelation between diet- and surgery-induced weight loss and vitamin D status

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Abstract

Obesity is a major global health problem and has been associated with vitamin D deficiency. Intentional weight loss may alter vitamin D status and, conversely, vitamin D supplementation has been hypothesized to aid in weight loss. A systematic literature search in PubMed/Medline identified 3,173 articles of which 37 studies (randomized controlled trials (RCT) (n=17), non-RCTs (n=20)) are summarized as effect of: (I) diet-induced weight loss on vitamin D status (n=7), (II) vitamin D supplementation on diet-induced weight loss (n=11), (III) surgery-induced weight loss on vitamin D status (n=15), and (IV) vitamin D supplementation after surgery-induced weight loss on vitamin D status (n=5). While all studies on the effect of diet-induced weight loss on vitamin D status have consistently reported increased vitamin D levels, the targeted percentage of weight loss that is necessary for an increase has varied between 5% and >10%. N=11 RCTs testing the effect of vitamin D supplementation observe that vitamin D supplementation does not result in increased weight loss, but may affect body fat loss. Vitamin D deficiency and subsequent hyperparathyroidism have been detected in post-surgery patients, and there is evidence that vitamin D supplementation improves these post-surgery complications.. We review the current evidence addressing the role of vitamin D status and supplementation in diet- and surgery induced weight loss. Subsequently, we highlight gaps in current research and suggest directions for future research including differences in vitamin D supplementation dosages, indoor vs. outdoor exercise, and the assessment of vitamin D status in different body pools.

Keywords

obesity; weight loss; diet; bariatric surgery; vitamin D; cancer

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1. Introduction

Obesity is a major health problem worldwide and will likely continue expanding over the next decades [1]. Recent data show that in the United States 20% of the general population are obese (BMI ≥ 30 kg/m²) with 45 states having obesity rates over 25%, 22 states being above 30%, and in 3 states the obesity rates are now exceeding 35% (Arkansas, West Virginia and Mississippi) [2, 3]. Obesity is associated with many comorbidities such as dyslipidemia, insulin resistance, hypertension and cardiovascular disease [4, 5]. In addition, obesity is a well-established risk factor for multiple cancer types, and mechanistic underpinnings (e.g. chronic inflammation, oxidative stress, altered gene expression) of these associations have been reviewed [6–10].

There is consistent evidence on an inverse association between vitamin D status as reflected by plasma 25-hydroxy-vitamin D (25(OH)D) concentrations and obesity [11–13]. Based on obesity-related changes in metabolism and lifestyle, various mechanisms have been hypothesized that may explain the correlation between obesity and low vitamin D status (see Figure 1): a) altered metabolism in obese individuals that results in reduced synthesis and increased degradation (e.g. reduced 1-alpha-hydroxylase (1 α -OHase) activity, increased vitamin D catabolism in cells, b) reduced sun exposure, c) reduced cutaneous synthetic capacity, d) sequestration in body pools (e.g. adipose tissue), and d) volumetric dilution [14].

An understanding of how weight loss in obese individuals may affect vitamin D status and the distribution of vitamin D body pools (e.g., storage and mobilization from adipose tissue) has been identified as an important area for future research according to the 2010 published report on dietary references intakes (DRI) for calcium and vitamin D [15].

Vitamin D is a fat-soluble vitamin and an essential nutrient (e.g., cheese, butter, fish, fortified milk and meat) [16]. In general 80 to 90% of vitamin D concentrations are assigned to dermal synthesis [13], however, sunlight-induced vitamin D synthesis varies considerably with skin pigmentation, time spent outdoors, clothing worn, use of sunblock, latitude, season of year, and other factors. For example, a more recent publication suggests that the UVB related vitamin D synthesis may be only 10–25% and hypothesized that dietary intake is a more significant contributor to vitamin D input [17]. Findings of animal studies indicate that 33% of vitamin D are stored in fat and 20% in muscle, suggesting that muscle tissue could be another important reservoir of vitamin D storage in humans [11]. Besides the control of calcium homeostasis and metabolism, vitamin D regulates the intestinal absorption of different minerals (e.g., zinc, phosphate, magnesium, iron) [18] and important key players of the immune system [19, 20]. Vitamin D has a variety of cancer-preventive effects including apoptosis and cell differentiation, and further inhibition of proliferation and angiogenesis [21–28].

Clinically relevant concentrations of circulating vitamin D can be measured in blood as 25(OH)D. A consensus statement by the American Geriatrics Society Workgroup (AGSW) on vitamin D supplementation defined serum 25(OH)D concentrations of ≥ 30 ng/mL (75 nmol/L) as sufficient for adults [29]; while 25(OH)D insufficiency is defined as serum

concentrations between 21 and 29 ng/mL (72 nmol/L) and deficiency as concentrations < 20 ng/mL (50 nmol/L) [30, 31].

Lower serum 25(OH)D concentrations have been consistently linked to increasing body mass index (BMI) [11–13]. Pereira-Santos et al. demonstrated in a recent meta-analysis of n=65,445 individuals that the prevalence of vitamin D deficiency was 35% higher in obese individuals compared to the eutrophic weight group [13]. Furthermore, obesity-caused vitamin D deficiency may be associated with an increased risk for obesity-induced inflammation, insulin resistance, dyslipidemia and obesity-related diseases (e.g. metabolic syndrome, diabetes, cardiovascular disease) [32, 33]. Prior studies also demonstrated that the loss of adiposity is associated with a proportional increase in circulating vitamin D levels [12, 34]. Several explanations for this inverse relationship between obesity and vitamin D status have been discussed [4, 13]. For example, obese individuals may reduce their exposure to sunlight for reasons of social acceptance, including covering up body parts or undertaking less activity outdoors. However, in the large US based Framingham Heart Study, the association between obesity and low vitamin D status remained even after adjusting for outdoor physical activity [35]. Thus, it appears plausible that other mechanisms may underlie the inverse association between vitamin D and obesity. These include sequestration in adipose tissue, volumetric dilution or negative feedback mechanisms from increased circulating 1,25-dihydroxyvitamin D3 [36]. Moreover, the stimulation of whole body fat oxidation and the increase in faecal energy loss are two established mechanisms by which vitamin D is changing energy balance and may affect weight loss [4, 37]. In support of this, recent data show that vitamin D metabolism in obese individuals is altered during and after weight loss [10]. In contrast, vitamin D supplementation during weight reduction is hypothesized to be associated with even greater weight loss. To date, only few studies have investigated the direct effect of diet-induced weight loss on vitamin D status in obese individuals.

Hence, there is significant interest in the effect of (I) weight loss on vitamin D status and (II) vitamin D supplementation on weight loss. In addition to dietary induced weight loss, bariatric surgery is impacting vitamin D status. Bariatric surgery is the most effective treatment and gold standard for morbid obesity [38]. Since the first bariatric surgery in the 1950s, safe and successful surgical management has progressed and the number of patients who are undergoing bariatric surgery is paralleling the trend of obesity incidence [39]. Weight loss induced by bariatric surgery has shown to induce vitamin D insufficiency [40]. Consequently, the effect of vitamin D supplementation after bariatric surgery has been studied to reduce post-surgery metabolic complications (e.g. Vitamin A, C, D deficiency, drug malabsorption) [41]. To date, medical guidelines for clinical practice of bariatric surgery of the American Association of Clinical Endocrinologists (AACE), The Obesity Society, and American Society for Metabolic & Bariatric Surgery (ASMBS) recommend a daily intake of 400–800 IU vitamin D, besides other nutrient supplementation [42]. In addition, biochemical surveillance of nutritional status every 3–6 months in the first year after surgery and annually thereafter is advised [42]. A recently performed retrospective chart review confirmed the effectiveness of the recommended supplementation doses, but also reported the patient's compliance as substantial effect modifier [43]. Compliance could be an explanation for studies that have presented that the current recommendations for post-

bariatric surgery vitamin D supplementation fails to raise 25(OH)D above the level of 30 ng/ml, that has been defined as sufficient for adults [40, 44].

To assess the association between vitamin D and weight loss either induced by lifestyle change or surgery, we conducted a systematic literature search covering literature from January 1946 to September 2016. Two researchers (CH and MD) searched the database PubMed/Medline, using the keywords: (vitamin D OR 25(OH)D) AND (weight loss OR caloric restriction OR weight control OR obesity OR bariatric surgery).

Abstracts were read, and the articles were selected according to the following inclusion criteria: articles written in English, human studies, prospective studies and a study population of adult men or adult, non-pregnant women. Articles were screened based on the following criteria: change in 25(OH)D levels in response to weight loss from diet or surgery (with or without an exercise component), or the use of vitamin D supplementation either after bariatric surgery or during a weight loss program.

Among the 3,173 articles identified, 37 met the inclusion criteria for this review. The selected studies were classified into four groups: effect of (I) diet-induced weight loss on vitamin D status (n=6), (II) vitamin D supplementation on diet-induced weight loss (n=11), (III) surgery-induced weight loss on vitamin D status (n=15), or (IV) vitamin D supplementation after surgery-induced weight loss on vitamin D status (n=5). Studies were excluded for aims I and III if the main focus of the intervention was exercise, rather than diet or surgery.

A data extraction form was developed and used by two authors (CH and MD). Details on study design, study population, interventions, measurements and results were recorded. Disagreements relating to data extraction were discussed and solved between authors. The overall process is outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) flow diagram (Figure 2) [45].

The aim of the present review is to summarize the state-of-the-art evidence on the role of vitamin D status and vitamin D supplementation in dietary- and surgery-induced weight loss. We performed a systematic review, specifically of randomized-controlled trials or intervention studies and highlight gaps in the current standard of knowledge on this relationship.

2. Diet-induced weight loss and vitamin D

2.1 The effect of diet-induced weight loss on vitamin D

Six studies have investigated the effect of diet-induced weight loss on vitamin D status between 2010 and 2012 (see Table 1) [46–49]. Three randomized controlled trials (RCT), two with large female study populations (n = 350), were conducted [46, 49, 50], and three intervention studies [47, 48, 51] of which only one recruited men and women [47].

To examine the potential for race-specific, adverse responses to weight loss, the most recent RCT performed a 4-week weight loss program in 64 African American (AA) and European American (EA) premenopausal women [50]. Given that haemoglobin may also experience

changes under caloric restriction and shows race-specific differences, it was included in the study assessments. Vitamin D status at baseline was documented as lower in AAs compared to EAs (AA, 35.7 ± 12.9 vs EA, 57.0 ± 20.0 , $p < 0.01$) [50]. 25(OH)D levels increased in both groups (AA, 43.4 ± 14.0 vs. EA, 68.2 ± 24.3 ; $p < 0.01$) while the difference between the races was not significant (AA, $+7.8 \pm 13.5$ vs EA, $+11.2 \pm 16.7$; $p = 0.37$) [50]. Participants reaching $>15\%$ weight loss and the largest increased 25(OH)D level presented the smallest decrease in haemoglobin [50].

Another RCT recruited 383 women (>18 years). Participants were enrolled in a 24 month weight loss program and more than half of the women lost at least 5% of baseline weight [49]. Serum 25(OH)D levels were elevated at the end of the intervention period, showing a linear trend towards greater increases in serum concentrations in women who achieved greater weight loss [49]. Women who lost more than 10% of their baseline weight showed an average increase of 5.0 ng/ml compared to an average increase of 2.7 ng/ml in women who lost 5–10 % of their baseline weight [49]. The majority of overweight or obese women [64% ($n = 230$)] and 83% ($n = 20$) of those who achieved a normal BMI due to weight loss had at least serum concentrations of 20 ng/ml, [49]. These findings suggest that among overweight or obese women, weight loss, presumably with a simultaneous reduction in body fat, increases 25(OH)D levels [49]. Behavioural counselling as part of this intervention also led to an increase in physical activity, likely associated with increased sun exposure due to outdoor activities; however, observed associations remained after adjusting for physical activity [49].

In 2011, Mason et al performed a RCT in 439 obese postmenopausal women that were randomly assigned to four different groups: I) diet modification (1200–2000 kcal/d, $<30\%$ of daily energy intake from fat), II) exercise, III) exercise + diet, or IV) control. The authors observed that serum 25(OH)D increased slightly more in women with baseline concentrations ≥ 20 ng/mL ($+1.9$ ng/mL) than in women with baseline concentrations <20 ng/mL ($+2.5$ ng/mL) (p for interaction = 0.04). Nevertheless, women who lost between 5–15% of their baseline weight had a significant increase in 25(OH)D concentrations proportional to the increasing weight loss (p for trend = 0.002) [46].

A non-randomized intervention study with a small population size of 38 men, followed participants up to 6 months in either a weight loss program or weight maintenance [51]. The weight loss program was designed based on a standard behavior modification nutrition education weight loss program including an individualized caloric intake (500–600 kcal deficit/day) [51]. 25(OH)D level increased similar in both groups ($p < 0.005$) [51].

We identified one non-randomized intervention study that enrolled both men and women (age > 50 years) diagnosed with knee osteoarthritis [47]. All participants underwent a formula-based weight loss diet (415–810 kcal/day), followed by 8 weeks on hypo-energetic 1200 kcal/day diet with a combination of normal food and defined formula products that contained vitamin D [47]. The authors noted that this intensive weight loss program increased 25(OH)D concentrations and improved bone mineral density [47]. Yet, the impact on 25(OH)D may have been either attributable to the supplementation with vitamin D as part

of the formula, or vitamin D may have been liberated from fat tissue during the weight loss [52].

Another non-randomized intervention study enrolled obese women (n=44) in an 18–20 weeks low-calorie diet intervention and compared their vitamin D status with that of healthy controls (n=25) [48]. They reported that a weight loss of 10% was associated with significantly increased 25(OH)D concentrations and improved insulin resistance [48].

Prior studies have consistently reported an association between weight loss and increased vitamin D levels. However, the percentage of baseline weight loss that is mandatory for a significant effect on vitamin D levels has varied between 5% and >10% [46, 49] and Mallard et al report no clear dose-response as part of a meta-analysis of weight loss vs weight maintenance among vitamin D-supplemented individuals [53].

2.2 The effect of vitamin D supplementation on diet-induced weight loss

Numerous RCTs have tested the influence of vitamin D supplementation on weight loss with a variety of different doses and dosages. (see Table 2) [54–64].

No significant effect of vitamin D supplementation on weight loss has been reported in any of these studies with comparable weight changes in the supplementation compared to the control groups (see Table 2) [54–63]. Some examples are given below. A recent double-blind RCT, compared 12 months of vitamin D supplementation with placebo intake on weight loss, body composition, insulin, and C-reactive protein (CRP). Two hundred eighteen postmenopausal women (age: 50 to 75 years) were enrolled in a weight loss-intervention, and received either 2000 International Unit (IU; vitamin D = 0,025 µg vitamin D) or oral vitamin D per day or daily placebo [54, 57, 64]. There were no significant differences in weight loss comparing women in the intervention group to the control group. However, a proportional increase in vitamin D with weight loss was observed: women who lost <5%, 5–9.9%, 10–14.9%, or 15% of their initial weight experienced mean increases in 25(OH)D levels of 2.1, 2.7, 3.3, and 7.7 ng/mL, respectively (p for trend= 0.002). The extent of fat loss (kg) was significantly associated with an increase in 25(OH)D levels (p= 0.035) while this was not observed for the change in lean mass (p= 0.73). [54, 57, 64]

Another 12 month follow-up study randomized 200 overweight individuals in a weight reduction program to an additional intake of either 83µg vitamin D per day or placebo [63]. Vitamin D supplementation did not significantly increase weight loss. [63]. While greater weight loss could not be linked to vitamin D supplementation, nevertheless it may augment body fat and visceral fat loss, as supported by data from prior studies [56, 58, 59, 62]. For example, Salehpour et al noted in 2012 that supplementation with vitamin D triggered a significant decrease in body fat mass in the vitamin D intervention group compared to the placebo group (-2.7 ± 2.1 kg compared to -0.47 ± 2.1 kg; $p<0.001$) [59].

Overall, the data of nine RCTs suggest that supplementation of vitamin D during weight loss programs stimulates changes in fat mass distribution and several circulating biomarker profiles (e.g., CRP), while it has not been associated with increased weight loss [54–63].

3. Surgery-induced weight loss and vitamin D

3.1. The effect of surgery-induced weight loss on vitamin D

Bariatric surgery is the gold standard for the treatment of morbid obesity [38]. Six month and 12 month post-surgery patients have been shown to lose in average 60%, respectively 77% of excess weight [39]. Surgery treatment in obese individuals has shown to reduce patient's risk of premature death by 30–40% [39]. Different surgical procedures have been developed: Roux-en-Y gastric bypass (RYGB), laparoscopic sleeve gastrectomy, adjustable gastric band, and biliopancreatic diversion. The most common used procedure is RYGB [65].

Despite multiple beneficial effects of bariatric surgery, this type of weight loss intervention is fairly extreme and has been shown to alter the absorption of dietary vitamin D [66]. Subsequently, patients have a high rate of vitamin D deficiency after surgery, which can cause calcium malabsorption, osteoporosis, enhanced bone resorption, and an increased risk of fractures [67]. The complication rates depend on several related factors (e.g., age, gender, pre-surgery 25(OH)D level) that are recommended to be closely monitored in clinical routine [68].

The systematic literature search resulted in 15 studies including one RCT [69–83]. Most of them have been intervention studies recruiting patients undergoing RYGB surgery (follow-up from 6 months up to 12 months) [69–80, 83] and one observational study [82] (see Table 3). Temporarily, after surgery, vitamin D status appears to improve (approximately one month; [73, 74, 76, 77, 79, 82]). However, after long-term follow-up all studies have consistently shown a vitamin D deficiency in this patient groups [69, 74, 78–80, 82, 83].

The first large study investigating long-term outcomes up to 10 years after bariatric surgery was developed at the Örebro University Hospital and Uppsala University Hospital, Sweden [75]. They recruited 293 patients who had surgery between 1993 and 2003. Serum concentrations of 25(OH)D, parathyroid hormone (PTH), alkaline phosphatase (ALP) and calcium were determined pre- and post-surgery. Sixty-five percent of all patients were classified as vitamin D deficient 10 years after surgery i.e., 25(OH)D < 50 nmol/l. The only pre-surgery predictor for vitamin D deficiency over this long-term follow-up was high BMI [BMI > 43 ($p = 0.0008$)] [75].

To date, only one RCT in this area was conducted at two Scandinavian hospitals that compared the effect of two different types of surgery procedures (RYGB; $n = 31$ or biliopancreatic diversion with duodenal switch ($n = 29$) on participants' vitamin D status [81]. Notably, the 25(OH)D concentrations increased among gastric bypass patients ($p < 0.001$), but tended to decrease among duodenal switch patients ($p = 0.059$) [81]. Biliopancreatic diversion in patients treated with duodenal switch induces fat malabsorption may be due to a deferred secretion of pancreatic enzymes and bile acids [84]. This could explain the lower concentrations of vitamins D that was observed after this procedure.

Pramyothin et al. investigated vitamin D in the abdominal fat and the circulation of obese patients up to 12 months after RYGB ($n = 17$). As expected, the authors observed a dramatic

loss of body fat [82]. However, there was no evidence that the vitamin D stored in the adipose tissue would significantly contribute to an increase of circulating vitamin D concentrations during the phase of losing body fat [82].

Overall, the major complications that have been described after bariatric surgery are vitamin D insufficiency, and lower bone mineral density with increased risk of fractures [85]. Based on the reviewed literature, the complication rate and type appears to be dependent on the type of surgical procedure, thus specific monitoring and supplementation regimens needs to be developed based on the type of surgical technique.

3.2. The effect of vitamin D supplementation after surgery-induced weight loss on vitamin D status

The potential use of pre- and post-surgery vitamin D supplementation after bariatric surgery has gained greater attention during the past years. Five studies (non-randomized studies (n=3), RCT (n=2)) have investigated the effect of vitamin D supplementation on vitamin D metabolism in patients after bariatric surgery (see Table 4) [66, 86–89].

Three non-randomized intervention studies have been performed recruiting both women and men undergoing gastric bypass surgery [86, 87, 89]. Flores et al enrolled n=228 individuals into two different sub-studies [86, 87]. Both studies used a supplementation of 1,000 mg calcium citrate and 800 IU vitamin D per day post-surgery. Study I (n=176) evaluated the effect of pre-surgery supplementation (different doses based on the individual's current 25(OH)D level) on post-surgery vitamin D concentration, while study 2 (n=52) advised an additional dose of 2,000 IU vitamin D per day [86]. Both schedules of daily vitamin D3 supplementation were effective, showing that 25(OH)D levels were significantly increased after 12 months ($p < 0.001$) and safe, as no serious adverse events were reported. [86]. The second study that advised an additional dose of 2,000 IU vitamin D per day demonstrated that 25(OH)D levels increased from a mean average of 32 nmol/L (+/- standard deviation [SD] 12) to 80 nmol/L (+/- 22 SD) after 4 months and to 75 nmol/L (+/- 15 SD) after 12 months ($p < 0.001$) [86].

The same authors published data on the effects of vitamin D and calcium supplementation after gastric bypass surgery [87]. Two-hundred twenty-two patients were evaluated pre- and post-surgery. One year post-surgery, 25(OH)D concentrations improved significantly with vitamin D supplementation, even though the majority of patients (71%) still had vitamin D concentrations below 75 nmol/L [87].

Another recent non-randomized intervention study investigated the effect of additional intake of vitamin D after bariatric surgery in n=164 morbidly obese patients. All patients received 400 IU of vitamin D per day. In the intervention group, vitamin D concentrations were measured every two weeks and an additional dose of 16,000 IU was applied every time vitamin D serum levels were below 30 ng/ml [89]. After 24 months, 68% of the patients in the intervention group reached normal levels of vitamin D compared to 48% in the non-intervention group [89].

Two RCTs have investigated the effects of different dosing regimens of vitamin D supplementation after bariatric surgery [66, 88]. After RYGB, n=60 patients were randomized into either (I) 50,000 IU vitamin D per day, or (II) no additional supplementation [66]. After 12 months a significant difference in the 25(OH)D levels between both groups was observed [66]. Average 25-hydroxyvitamin D levels had improved significantly in the supplementation group (14% and 37.8 ng/mL, respectively) compared to the control group (85% and 15.2 ng/mL, respectively; $p < .001$ for between-group comparison). No major adverse events of vitamin D supplementation have been reported for the intervention group. [66].

In the same year, Goldner et al randomized obese women and men into 3 groups receiving different vitamin D regimens (800/2,000/5,000 IU/day) [88] and reported that at the 12 month follow-up, the 800-, 2,000-, and 5,000-IU groups showed a proportional increases in 25(OH)D levels [of 27.5 $\pm$ 40.0 (mean $\pm$ SD), 60.2 $\pm$ 37.4, and 66.1 $\pm$ 42.2 nmol/L, respectively ($p = 0.09$)]. A total of 44%, 78%, and 70% in the three intervention groups achieved 25(OH)D levels ≥ 75 nmol/L (p for between group comparison = 0.38). The authors concluded that vitamin D replacement as high as 5,000 IU/day is safe to treat vitamin D deficiency in patients following RYGB surgery [88].

The 2010 DRI for Calcium and Vitamin D defines a tolerable upper intake level of 4,000 IU of dietary vitamin D for males and females from age 9 to age 70 [15]. However, vitamin D intake of 10,000 IU was not associated with vitamin D toxicities (e.g., hypercalcemia, poor appetite, nausea, vomiting) [15]. Based on the result from the reviewed studies, even a dose of 16,000 IU or 50,000 IU may be applied under continuous clinical monitoring, without the occurrence of classic toxicities.

In summary, vitamin D status needs continuous monitoring for long-term prevention in patients after bariatric surgery [90], and while significant improvement in vitamin D status has been achieved, there is still a subset of patients that would need higher doses as demonstrated in the present studies. Thus, doses and dosages, need to be individualized to minimize malabsorption and improve vitamin D status.

4. Future research

Studies on the effects of diet- and surgery-induced weight loss on vitamin D status are promising, yet not entirely consistent, and further studies are needed to fill several gaps in knowledge. While weight loss can successfully increase low vitamin D concentrations associated with overweight/obesity, it is unclear precisely how much weight loss is needed to achieve this effect and how permanent the effects are.

Given that only two out of six studies used combined dietary/exercise programs, further evidence is needed to evaluate whether exercise incrementally increases vitamin D status in individuals undergoing weight loss. Further, there may be a potential difference between outdoor vs. indoor exercise interventions, because vitamin D status is significantly correlated with sun exposure and this needs to be tested in more detail.

Animal and human studies have repeatedly shown that Vitamin D can be measured in adipose tissue, confirming that adipose tissue is not only an endogenous source of vitamin D but also a storage organ. After weight loss, the expression of vitamin D metabolizing enzymes (e.g., CYP24A1) can be increased, indicating that adipose tissue not only metabolizes vitamin D directly, but also dynamically alters its capacity for vitamin D activation and deactivation in obesity and during weight loss [91]. Hence, it appears plausible that weight loss leads to an increase of circulating vitamin D levels due to release from adipose tissue. Subsequently, less sequestration would occur that would also lead to improved bioavailability of vitamin D. It has been shown that this proposed mechanism exists in dietary-induced weight loss. Similar to diet-induced weight loss, bariatric surgery leads to a substantial loss of adipose tissue. Thus, a similar release of vitamin D from adipose tissue may be plausible. However, despite a temporal increase in vitamin D concentrations, the majority of patients remain vitamin D deficient after 12 months follow-up. The impact of diet-and surgery-induced weight loss on vitamin D status in subcutaneous and visceral adipose tissue needs to be investigated more thoroughly to identify more precise interventions, possibly targeted to the individual's adipose tissue quantity and composition.

Few studies on the effect of vitamin D supplementation after bariatric surgery have been identified. Only one study has used and investigated the effect of different supplemental dosages. While studies have shown that the recommended dosage is effective to stabilize vitamin D deficiency following bariatric surgery, there is still a subset of patients that would need higher doses and continuous monitoring as demonstrated in the present studies. Thus, more studies are needed to create the evidence base for appropriate and personalized dosing.

5. Conclusions

This paper reviewed the relationship between diet- and surgery-induced weight loss on vitamin D status in morbidly obese patients. There is strong evidence for a link between obesity and lower vitamin D status. Several biological mechanisms may underlie these associations. Prior research indicates that societal factors, a direct link via outdoor physical activity, or physiologic changes in the adipose tissue itself result in a sequestering of vitamin D metabolites [14, 36]. The randomized controlled trials and non-controlled intervention studies suggest that weight loss may improve 25(OH)D status, in a dose-dependent fashion. To date, these studies have been primarily performed in women. The reviewed RCTs have reported that vitamin D supplementation does not result in significantly increased weight loss. However, a reduction of fat mass with vitamin D supplementation has been reported in our here presented studies. We have restricted our review of studies of the strongest possible design in support of causality; specifically intervention studies and randomized controlled trials. Nevertheless, we cannot exclude that other factors may have played a role. Future research is needed to confirm these effects and identify potential mechanisms, particularly direct effects via adipose tissue.

Finally, while there is an established benefit of bariatric surgery in morbidly obese patients, it also induces a severe vitamin D deficiency for various reasons (e.g., dietary intolerance leading to reduced intake of dairy products, vomiting, non-adherence to supplement recommendations, malabsorption dilution) [40]. Despite the use of vitamin D

supplementation in large doses in the reviewed studies, there is still a subset of patients that suffer from vitamin D deficiency. More studies are needed to provide evidence-based guidelines for the clinical monitoring on vitamin D concentrations and supplementation of vitamin D after bariatric surgery.

In summary, diet-induced weight loss has been linked to an increase in vitamin D concentrations, while surgery-induced weight loss leads to a vitamin D deficiency. Thus, this review identifies novel research avenues that are needed to define appropriate recommendations for vitamin D supplementation.

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List of abbreviations

25(OH)D	25-hydroxy vitamin D
AACE	American Association of Clinical Endocrinologists
ALP	Alkaline Phosphatase
ASMBS	American Society for Metabolic and Bariatric Surgery
BMI	Body Mass Index
CRP	C-reactive Protein
DRI	Dietary Reference Intakes
IU	International Unit
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
PTH	parathyroid hormone
RCT	randomized controlled trial
RYGB	Roux-en-Y gastric bypass
RXR	retinoid-X-receptor
SD	standard deviation
TFCA	true fractional calcium absorption
VDR	vitamin D receptor

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Figure 1. Mechanisms underlying the effect of decreased vitamin D levels in obese individuals
Hypothesized alterations in vitamin D metabolism in obese Individuals including: a) altered metabolism in obese individuals that results in reduced synthesis and increased degradation (e.g. reduced 1-alpha-hydroxylase ($1\alpha\text{-OHase}$) activity, increased vitamin D catabolism in intestinal, malignant, immune, and bone cells), b) reduced sun exposure, c) reduced cutaneous synthetic capacity, d) sequestration in body pools (e.g. adipose tissue), and d) volumetric dilution [14].

Figure 2.
PRISMA Diagram for the search and selection process

Table 1

The effect of diet-induced weight loss on vitamin D status

Authors (year)	Study population	Intervention	Study design	Measurements			Average 25(OH)D change
				Weight	25(OH)D	PTH	
RCT							
Carter et al. (2016) [50]	n=64 overweight, premenopausal African American (n=33) and European American (n=31) women (20–45y)	4 week weight loss program <ul style="list-style-type: none">diet onlydiet + aerobic exercisediet + resistance exercise	RCT	✓	✓	✓	African American: +7.7 ± 1.1 (nmol/L) European American: + 11.2 ± 4.3 (nmol/L)
Rock et al.(2012) [49]	n=383 overweight or obese women (>18y)	24 months clinical trial weight loss program <ul style="list-style-type: none">reduced-fat (20–30% of energy)reduced-energy (typically 1,200–2,000 kcal/day)	RCT	✓	✓	✓	weight loss 5–10% of baseline: +2.7 (9.1) ng/ml weight loss >10%: +5.0 (9.2) ng/ml
Mason C. et al (2011) [46]	n=439 overweight or obese women (50–75y)	12 months weight loss program <ul style="list-style-type: none">diet modification (n=118)exercise (n=117)diet + exercise (n=117)control (n=87)	RCT	✓	✓	✓	no significant change between intervention and control groupsmean increase (ng/ml): weight loss of <5%: 2.1 weight loss of 5–9.9%: 2.7 weight loss of 10–14.9%: 3.3 weight loss of >15%: 7.7
Intervention study							
Pop et al. (2015) [51]	n=38 overweight and obese men (50–72y)	6 months <ul style="list-style-type: none">weight loss program (500–600 kcal deficit/day) (n=19)weight maintenance (n=19)	Intervention study	✓	✓	✓	weight loss: +10.5 ± 4.5 (nmol/L) Weight maintenance: +8.0 ± 0.1 (nmol/L)
Christensen et al. (2012) [47]	n=175 obese women (n=142) and men (n=33) (>50y) diagnosis of knee osteoarthritis	8 weeks formula weight-loss diet with <ul style="list-style-type: none">420–554 kcal/day810 kcal/day	Intervention study	✓	✓	✓	low calorie diet: +15.3 nmol/l (13.2–17.3; p<0.0001) high calorie diet: +43.7 nmol/l (32.1–55.4; p<0.0001)

Authors (year)	Study population	Intervention	Study design	Measurements			Average 25(OH)D change
				Weight	25(OH)D	PTH	
		followed by 8 weeks on a hypo-energetic 1200 kcal/day diet					
Tzotzas et al. (2010) [48]	n=69 obese women (n=44) (20–65y) healthy controls (n=25)	20 weeks <ul style="list-style-type: none">individual low calorie diet, based on an average calorie restriction of 1000 kcal/day	Intervention study	✓	✓	✓	obese group: +15.4 ± 6.0 ng/ml control group: +18.3 ± 5.1 ng/ml, p<0.05

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone; vitD, vitamin D; RCT, randomized controlled trial; y, year

Table 2

The effect of vitamin D supplementation on diet-induced weight loss

Authors (year)	Study population	Intervention	Study design	Measurements				Average weight change (kg)
				Weight	25(OH)D	BC	PTH	
Mason et al (2016) [64] Duggan et al (2015) [54] Mason et al (2014) [57]	n=218 overweight or obese women (50–75y) serum 25(OH)D >10ng/mL but <32 ng/mL	12 months intervention <ul style="list-style-type: none"> weight loss intervention + 2000 IU oral vitD/day weight loss + daily placebo 	RCT	✓	✓	✓		no significant difference between groups (p 0.05) intervention: -7.1 (-8.7, -5.7) control: -7.4 (-8.1, -5.4)
Shapses et al (2013) [60]	n= 82 obese postmenopausal women (>50y)	6 weeks <ul style="list-style-type: none"> 10µg vitD/day + 1.2g Ca/day + weekly 375 µg vitD 10µg vitD/day + 1.2g Ca/day + placebo 	RCT	✓	✓		✓	no significant difference between groups (p 0.05) supplement: -3.0 ± 1.2 placebo: -3.3 ± 1.2
Zhu et al (2013) [62]	n=43 overweight or obese women (n=40) and men (n=3) (18–25y)	12 weeks <ul style="list-style-type: none"> energy-restricted diet (- 500kcal/d) + 600 mg Ca + 125 IU vitD energy-restricted diet 	RCT	✓		✓		no significant difference between groups (p 0.05) supplement: -4.2 ± 0.4 no supplement: -3.5 ± 1.4
Salehpour et al (2012) [59]	n=77 overweight or obese women (mean age 38 ± 8.1y)	12 weeks <ul style="list-style-type: none"> vitD 25µg/day placebo (25 µg lactose/day) 	RCT	✓	✓		✓	no significant difference between groups (p 0.05) supplement: 0.3 ± 1.5 placebo: 0.1 ± 1.7
Rosenblum et al (2012) [58]	n=171 overweight or obese women (n=152) and men (n=19) (18–65y)	16 weeks <ul style="list-style-type: none"> 240 ml of regular orange juice 3x/day (RJ control) 240 ml of regular orange juice 3x/day + 350mg CA + 100 IU vitD (RJ caD) 240 ml or lite orange juice 3x/day (LJ control) 240 ml of regular orange juice 3x/day + 350mg CA + 100 IU vitD (LJ CaD) 240 ml of unfortified juice 3x/day (combined control) 	RCT	✓				no significant difference between groups (p 0.05) RJ control: -2.4 ± 3.5 RJ caD: -2.2 ± 3.0 LJ control: -2.3 ± 2.9 LJ caD: -2.9 ± 3.8 combined control: -2.4 ± 3.2 combined caD: -2.5 ± 3.3

Authors (year)	Study population	Intervention	Study design	Measurements				Average weight change (kg)
				Weight	25(OH)D	BC	PTH	
		<ul style="list-style-type: none"> 240 ml of unfortified juice 3x/day + 350mg CA + 100 IU vitD (combined caD) 						
Holecki et al (2008) [55]	n=44 obese women (45–55y)	3 months <ul style="list-style-type: none"> Ca carbonate + 25(OH)D weight reduction therapy 	RCT	✓	✓		✓	no significant difference between groups (p 0.05) supplement: -7.0 ± 2.6 no supplement: -8.4 ± 3.7
Zittermann et al (2009) [63]	n=200 overweight women (n=124) and men (n=76)(18–70y)	12 months weight reducing program <ul style="list-style-type: none"> + 83 µg vitD/day + placebo 	RCT	✓	✓		✓	no significant difference between groups (p 0.05) supplement: -5.7 ± 5.8 placebo: -6.4 ± 5.6
Sneve et al (2008) [61]	n=445 overweight or obese women (n=286) or men (n=159)(21–70y)	<ul style="list-style-type: none"> 20,000 IU vitD 2x/week (DD) 20,000 IU vitD/week + placebo (DP) placebo 2x/week (PP) 	RCT	✓	✓	✓	✓	no significant difference between groups (p 0.05) DD: 0.1 ± 3.8 DP: 0.3 ± 3.2 DP: 0.5 ± 3.9
Major et al (2007) [56]	n=63 overweight or obese women (mean age 43.6 ± 5.0 y)/daily calcium intake of <800 mg/d	15 weeks weight loss intervention <ul style="list-style-type: none"> + 600 mg Ca +200 IU vitD 2x/day + placebo 2x/day 	RCT	✓				no significant difference between groups (p 0.05) $-3.5 (-4.0, -3.0)$ supplement: -4 ± 0.7 placebo: -3.0 ± 0.6

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; PTH, Parathyroid hormone; vitD, vitamin D; Ca, calcium; IU vitD, international Unit vitamin D ($=0.025 \mu\text{g vitD}$); BC, body composition; RCT, randomized controlled trial; y, year;

Table 3

The effect of surgery-induced weight loss on vitamin D status

Authors (year)	Study population	Surgery type/Intervention	Study design	Measurements	Average 25(OH)D change	PTH	
RCT							
Aasheim et al (2009) [81]	n=60 obese women (n=42) or men (n=18) (20–50y)	<ul style="list-style-type: none"> Roux-en-Y gastric bypass (n=31) Biliopancreatic diversion with duodenal switch (n=29) 12 months follow-up	RCT	✓	✓	✓	25-hydroxyvitamin D concentrations increased among gastric bypass patients ($p < 0.001$), but tended to decrease among duodenal switch patients ($p = 0.059$)
Intervention study							
Raouf et al (2016) [83]	n= 32 obese women	<ul style="list-style-type: none"> Roux-en-Y gastric Bypass 5 year follow-up	Intervention study	✓	✓	✓	vitD deficiency ($< 50 \text{ nmol/L}$): Baseline: 47.7 ± 15.8 5-year follow-up: 47.1 ± 24.6
Costa et al (2015) [80]	n=83 obese women (n=67) or men (n=16) (25y)	<ul style="list-style-type: none"> bariatric surgery, Witingrove technique (n=56) nonsurgical control (n=27) 	Intervention study	✓	✓		vitD deficiency ($< 20 \text{ ng/mL}$): surgery: 60.4% non-surgery: 16.6%
Luger et al (2015) [70]	n=50 obese women (n=38) or men (n=12) (mean age 46y)	<ul style="list-style-type: none"> Omega-loop gastric bypass 12 months follow-up	Intervention study	✓	✓	✓	3 fold higher risk for vitD deficiency over 12 months OR=3.10, 95% CI (1.01–9.51) $p = 0.048$
Yu et al (2015) [69]	n=50 obese women (n=28) or men (n=22) (average age 47y)	<ul style="list-style-type: none"> Roux-en-Y gastric bypass (n=30) nonsurgical control (n=20) 24 months follow-up	Intervention study	✓	✓	✓	no significant difference between both groups. intervention: $29 \pm 10 \text{ ng/ml}$ control: $22 \pm 10 \text{ ng/ml}$
Carrasco et al (2014) [71]	n=40 obese women (19–50y)	<ul style="list-style-type: none"> Gastric bypass (n=23) Sleeve gastrectomy (n=20) 	Intervention study	✓	✓	✓	Gastric bypass: 20.5 ± 9.2 to $33.8 \pm 9.7 \text{ ng/ml}$ Sleeve gastrectomy: 26.2 ± 12.7 to $34.6 \pm 14.5 \text{ ng/ml}$

Authors (year)	Study population	Surgery type/Intervention	Study design	Measurements	Average 25(OH)D change		PTH	
					Weight	25(OH)D		
		12 months follow-up						
Karefylakis et al (2014) [75]	n=293 obese women (n=243) or men (n=50)(40 ± 9.9y)	<ul style="list-style-type: none"> Roux-en-Y gastric bypass 10 years follow-up 	Intervention study	✓	✓	✓	✓	65% vitD deficient (<50 nmol/L)
Biagiotti et al (2014) [73]	n=22 obese women (18–40y)	<ul style="list-style-type: none"> Roux-en-Y gastric bypass 6 months follow-up 	Intervention study	✓	✓	✓	✓	significantly increased
Beckman et al (2013) [72]	n=20 obese women (48 ± 2y)	<ul style="list-style-type: none"> Roux-en-Y gastric bypass 12 months follow-up 	Intervention study	✓	✓	✓	✓	increase of +10 ± 2 ng/ml after 12 months
Coupaye et al (2013) [74]	n=60 women (n=53) or men (n=7) (40.5 ± 10.3y)	<ul style="list-style-type: none"> Roux-en-Y gastric bypass (n=30) Sleeve gastrectomy (n=30) 	Intervention study	✓	✓	✓	✓	Roux-en-Y gastric bypass: 13.4 ± 9.1 to 22.8 ± 11.3 ng/ml (p.0.0001) Sleeve gastrectomy: 15.2 ± 9.5 to 24.1 ± 14.4 ng/ml
Casagrande et al (2012) [76]	n=22 obese women (27.2 ± 9.6y)	<ul style="list-style-type: none"> Roux-en-Y gastric bypass 12 months follow-up 	Intervention study	✓	✓	✓	✓	no significant increase pre-surgery: 11.7 (9.7–18.0) ng/ml 1-y follow-up: 15.7 (10.2–2.7) ng/ml
Sinha et al (2011) [79]	n=73 obese women (n=75) or men (n=39) (39.2 ± 10.8y)	<ul style="list-style-type: none"> Roux-en-Y gastric bypass (RYGB) (n=50) Gastric banding (GB) (n=18) Biliopancreatic diversion with duodenal switch (BPD/DS) (n=5) 	Intervention study	✓	✓	✓	✓	RYGB or BPD/DS: 22.1 to 31.0 ng/ml GB: 20.3 to 33.0 ng/ml
Pranyothin et al. (2011) [82]	n=17 obese women and men	<ul style="list-style-type: none"> Roux-en-Y gastric bypass 	Intervention study	✓	✓	✓		no significant increase in serum 25(OH)D were observed between baseline measurements (23.1 ng/ml)

Authors (year)	Study population	Surgery type/Intervention	Study design	Measurements	Average 25(OH)D change	PTH	
				Weight	25(OH)D		
		• post-surgery follow-up					and follow-up after 12 months (26.2 ng/ml)
Carlin et al (2006) [77]	n=108 obese women (n=100) or men (n=8) (46 ± 9y)	• Gastric bypass 12 months follow-up	Intervention study	✓	✓	✓	20 ng/ml pre-surgery to 24ng/ml 12 months post-surgery
Sanchez-Hernandez et al (2005) [78]	n=64 obese women or men (45 ± 10.9y)	• Roux-en-Y gastric bypass post-surgery follow-up	Intervention study	✓	✓	✓	normal (.50 nmol/L); 6.25 to 20.31% insufficient (25–50 nmol/L); 25.00 to 37.50% deficient (<25 nmol/L); 68.75 to 42.19%

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone; vitD, vitamin D; PYGB, Roux-en-Y gastric bypass; BPD/DS, Biliopancreatic diversion with duodenal switch; GB, gastric bypass; RCT, randomized controlled trial; y, year

Table 4

The effect of vitamin D supplementation after surgery-induced weight loss on vitamin D status

Authors (year)	Study population	Intervention	Study design	Measurements	Average 25(OH)D change	PTH	
RCT							
Carlin et al (2009) [66]	n=60 obese women with pre-surgery vitD depletion	12 months Roux-en-Y gastric bypass <ul style="list-style-type: none"> • 50,000 UI vitD/day • No additional vitD 	RCT	✓	✓	✓	Intervention: 16.32 ± 15.7 Control: -4.44 ± 11.4
Goldner et al (2009) [88]	n=45 obese women (n=36) or men (n=9) (>19y)	24 months Roux-en-Y gastric bypass <ul style="list-style-type: none"> • 800 UI vitD • 2,000 UI vitD • 5,000 UI vitD post-surgery supplementation/day	RCT	✓	✓	✓	800 IU: +27.7 ± 40.0 nmol/L 2,000 IU 60.2 ± 37.4 nmol/L 5,000 IU 66.1 ± 42.2 nmol/L
Intervention study							
Flores et al (2015) [86]	Study 1: n=176 obese women (n=140) or men (n=36) Study 2: n= 52 obese women (n=32) or men (n=20)	12 months bariatric surgery 1,000mg Ca citrate/day and 800 IU vitD/d Study1: pre-op vitD supplementation according to vitD level Study2: additional high dose of 2,000 IU vitD/day	Intervention Study	✓	✓	✓	Study 1: level increased from 40 to 77 nmol/L (p<0.001) no difference between different doses Study 2: level increased from 32 to 75 nmol/L (p. 0.001)
Lanzarini et al (2015) [89]	n=164 obese women (n=124) or men (n=40) (18–60y)	24 months bariatric surgery 400 IU vitD/day Intervention (n=106): additional supplementation with 16,000 IU vitD every 2 weeks if 25(OH)D serum levels were <30ng/ml	Intervention study	✓	✓	✓	Normal levels after 24 months: Intervention group: 68% of the patients Non-Intervention: 48.8% of the patients
Flores et al (2010) [87]	n=222 women (n=163) or men (n=59) (18–65y)	12 months gastric bypass patients with PTH >70 pg/ml received 1,200 mg/d Ca and 800 IU vitD/d	Intervention study	✓	✓	✓	with supplementation increase of only 11.5 nmol/L

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone; vitD, vitamin D; IU vitD, International Unit vitamin D (=0,025 µg vitD); RCT, randomized controlled trial; y, year