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Vitamin D supplementation in obesity and during weight loss: A review of randomized controlled trials

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ABSTRACT

Vitamin D deficiency is common in obese individuals and during weight loss. The recommended vitamin D doses in this specific population are higher than for healthy adults. We reviewed vitamin D supplementation trials in obesity, and during medical or surgical weight loss, and report the effects on 25-hydroxyvitamin D [25(OH)D] concentrations and other relevant outcomes.

We conducted a systematic search in PubMed, Medline, Embase and the Cochrane library for relevant randomized controlled trials (RCTs) of oral vitamin D supplementation for at least 3 months in obese individuals without weight loss (OB), and those on medical weight loss (MWL) (2010–2018), and following bariatric surgery (Bar S) (without time restriction). Two reviewers screened the identified citations in duplicate and independently and performed full text screening. One reviewer completed data extraction.

We identified 13 RCTs in OB, 6 in MWL and 7 in Bar S. Mean baseline 25(OH)D concentrations ranged between 7 and 27 ng/ml in OB, 15–29 ng/ml in MWL and 15–24 ng/ml in Bar S. In OB (Total N 2036 participants), vitamin D doses of 1600–4000 IU/d increased mean 25(OH)D concentrations to ≥30 ng/ml. Based on three trials during MWL (Total N 359 participants), vitamin D doses of 1200–4600 IU/d for 12 months increased 25(OH)D concentration to ≥30 ng/ml. In Bar S (Total N 615 participants), doses ≥2000 IU/d were needed to reach 30 ng/ml. The change in 25(OH)D concentration was inversely proportional to the administered dose, and to BMI and baseline level with doses of 600–3000 IU/day. With these doses, the change in 25(OH)D concentration [Δ25(OH)D] per 100 IU/d was 0.5–1.2 ng/ml.

Three trials assessed bone mineral density as a primary outcome, but only one of them showed a protective effect of vitamin D against bone loss at all sites post-Bar S. There was no effect of vitamin D on weight loss. Data on extra-skeletal parameters, namely glycemic and vascular indices were mostly identified in OB, and findings were inconsistent.

In conclusion, Vitamin D doses ≥1600–2000 IU/d may be needed to reach a 25(OH)D concentration of 30 ng/ml in obese individuals and following bariatric surgery. The optimal concentration in this population is unknown, and whether the above doses protect against weight loss induced bone loss and fractures still needs to be confirmed. There is no clear evidence for a beneficial effect of vitamin D supplementation on cardio-metabolic parameters in obese individuals, and data on such parameters with weight loss are very scarce. Well-designed long term RCTs assessing the effect of vitamin D supplementation during weight loss on patient important outcomes are needed.

Contents

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1. Background

Since 1957, the burden of obesity has increased by at least 3-folds worldwide [1]. In 2016, 39% of adults were overweight and 13% were obese [1]. Such rates vary by country, and are as high as 36–38% in the US and some countries from North Africa [2]. Obesity is associated with several co-morbidities, in addition to increased mortality [3]. Indeed, modest weight loss, of 3–5%, results in an improvement in various health outcomes [4–6]. Several treatment options are currently available for weight management, including surgical and non-surgical approaches [7]. Weight loss varies widely across interventions, and is highest following bariatric surgery (Bar S) [8].

BMI, and specifically fat mass, is a known determinant of vitamin D status [9], and vitamin D deficiency is common in individuals with obesity [10,11]. Such deficiency is multifactorial [10,12]. Low intake of vitamins and supplements, poor dietary habits and low sun exposure are important risk factors [10]. In addition, changes in the activity and expression of enzymatic pathways involved with vitamin D metabolism have been suggested, including a decrease in the expression of hydroxylating enzymes in adipose tissue, namely 25-hydroxylase and 1α-hydroxylase, a decrease in hepatic 25-hydroxylation secondary to fatty liver, and an increase in 25-hydroxyvitamin D [25(OH)D] degradation through enhanced 24-hydroxylase activity [10,13]. The hepatic 25-hydroxylase is known to be regulated by 1,25-dihydroxyvitamin D level and vitamin D 3 [14], and drugs, such as phenobarbital and efavirenz [15]. Finally, dilution in a large body volume and sequestration in adipose tissue were also proposed [10,13,16]. Cross-sectional studies did not show any significant difference in vitamin D binding globulins levels, when comparing obese to normal weight individuals [17,18].

Scientific societies recognized the increased risk of hypovitaminosis D in individuals with obesity, and recommended screening in this specific population [19–21]. The recommended vitamin D doses in patients with obesity were also higher than those for the general healthy adult population (Table 1A) [19,22–26]. These recommendations were based on the achieved 25(OH)D concentration, rather than skeletal or extra-skeletal outcomes. For instance, the Endocrine Society suggested a dose of 6000–10,000 IU/d, to maintain a desirable 25(OH)D concentration at 30 ng/ml [19]. The American Geriatrics Society recommended to add a vitamin D dose of 500–800 IU/d in individuals with BMI ≥ 30 kg/m^2, while the recommended dose in the healthy non obese population was 3000 IU/d [25]. The Central Europe guidelines recommend a dose of 1600–4000 IU/d, in obese adults and elderly, that is double the dose in the general population [24]. The International Osteoporosis Foundation (IOF) recommends 2000 IU/d for obese individuals, same as in patients with osteoporosis, while the dose in healthy adults is 800–1000 IU/d [22]. The target 25(OH)D level in the general healthy population is a matter of debate, and a range of 20–40 ng/ml was proposed in a recent review by experts [27]. The target level in individuals with obesity has not been defined. Data from the non-obese individuals showed that a 25(OH)D level < 30 ng/ml may be associated with secondary hyperparathyroidism, and therefore secondary bone resorption [19,28].

While no specific guidance on vitamin D supplementation during medical weight loss, several guidelines on the peri-operative care of patients following bariatric surgery have recommended vitamin D doses, varying between 3000 IU/d and 50,000 IU 1–3 times per week (Table 1B) [29–32]. These recommendations were mostly based on expert opinion [13].

Table 1A
Summary of vitamin D replacement guidelines in individuals with obesity[a].

Society	Recommendation	Level of evidence
International Osteoporosis Foundation 2010 [22]	Intake may need to be adjusted upward to as much as 2000 IU/d in individuals who are obese	No grading
Endocrine Society 2011 [19]	We suggest a higher dose (two to three times higher; at least 6000–10,000 IU/d) of vitamin D to treat vitamin D deficiency to maintain a 25(OH)D level above 30 ng/ml, followed by maintenance therapy of 3000–6000 IU/d	Suggestion based on high quality
Health Council of the Netherlands 2012 [23]	Overweight or obese people often have lower serum 25-hydroxyvitamin D concentrations. Because it is unclear whether this is associated with an elevated risk of health complaints in this population, the Committee has not defined separate dietary reference values for this group	No grading
Central Europe Guidelines 2013 [24]	Obese adults and elderly: supplementation of 1600–4000 IU/day, depending on severity of obesity, is recommended throughout the whole year	No grading
Geriatric Society 2014 [25]	Add 500–800 IU/d on top of the dose recommended for the general population	No grading
Scientific Advisory of Nutrition Committee 2016 [26]	Evidence suggests that obese people are also at risk of low serum 25(OH)D concentrations. However, there are currently insufficient data to make a different recommendation from that proposed for the general population	No grading

Table 1B
Summary of vitamin D replacement guidelines in individuals undergoing bariatric surgery[a].

Society	Recommendation	Level of evidence
Endocrine Society 2010 [29]	Bariatric surgery (type of surgery unspecified) First phase (weeks 1–2, liquids): oral vitamin D 50,000 IU/d Second phase (weeks 3–6, soft food): Calcitriol D 1000 IU/d Vitamin D can be provided with Ergocalciferol, 50,000 IU one to three times per week	No grading
	Case of severe malabsorption: 50,000 IU vitamin D 1–3 times daily Malabsorptive surgical procedures "Vitamin D supplementation is recommended postoperatively for malabsorptive obesity surgical procedures and the doses be adjusted by a qualified medical professional based on serum markers and measures of bone density"	Strong recommendation with moderate quality of evidence
American Society for Metabolic and Bariatric Surgery 2016 [30]	Vitamin D 3000 IU daily, until 25(OH)D ≥30 ng/ml	Grade D, BEL4
	A 70–90% lower vitamin D3 bolus dose is needed (compared to vitamin D2) to achieve the same effects as those produced in healthy non-bariatric surgical patients	Grade A, BEL1
British Obesity and Metabolic Surgery Society 2014 [31]	Gastric bypass and sleeve gastrectomy: Usual practice is in the region of a minimum of 800–1200 mg calcium and 800 IU/d vitamin D. Additional vitamin D supplementation will also be needed following the BPD/DS Preparations may be given as: • 50,000 IU capsules, one given weekly for 6 wk (300,000 IU) • 20,000 IU capsules, two given weekly for 7 wk (280,000 IU) • 800 IU capsules, five a day given for 10 wk (280,000 IU) This may then be followed by maintenance regimens 1 month after loading with doses equivalent to 800 to 2000 IU/d (occasionally up to 4000 IU/d), given either daily or intermittently at a higher equivalent dose	No grading
Interdisciplinary European Guidelines on Surgery of Severe Obesity 2014 [32]	Adjustable gastric banding, Roux-en-Y gastric bypass: Vitamin and micronutrient supplements (oral) should routinely be prescribed to compensate for their possible reduced intake and absorption Bilio-pancreatic diversion: Lifelong daily vitamin and micronutrient supplementation (vitamins should be administered in a water-soluble form): Vitamins A, D, E and K	No grading

BEL: Best evidence level; BEL 1: meta-analysis and RCTs; BEL 4: No evidence; Grade A: ≥1 conclusive level 1 publications demonstrating benefit ≫ risk; Grade D: Grade D: No conclusive level 1, 2, or 3 publication demonstrating benefit ≫ risk.
[a] Information was taken verbatim from the guidelines.

This manuscript reviews randomized controlled trials (RCTs) investigating the effect of vitamin D replacement, in individuals with obesity and no weight loss (OB), those with medical weight loss (MWL), or surgical weight loss (Bar S), on serum 25(OH)D concentrations, mineral, skeletal and extra-skeletal parameters and outcomes.

2. Methodology

We conducted a systematic search in PubMed, Medline, Embase and the Cochrane Library, targeting the period 2010–2018. We used Mesh terms and keywords relevant to obesity, weight loss, vitamin D and RCT. We included any RCT of at least 3 months duration, in adults with obesity (mean BMI of participants ≥30 kg/m^2 in at least one arm) without weight loss, or those on a MWL intervention (lifestyle and/or drug therapy), receiving different doses of oral vitamin D supplementation, placebo or control. For OB, we included only trials with at least 50 participants per arm. For MWL, we included all trials regardless of their sample size, since we expected to identify a limited number of trials. We also updated a previous search strategy conducted in 2015, without time restriction, for a currently ongoing Cochrane systematic review and meta-analysis of vitamin D supplementation in patients with obesity undergoing Bar S [13,33]. The search strategy used Mesh terms and keywords relevant to obesity, weight loss, bariatric surgery and RCT. We included any RCT on oral vitamin D supplementation, given for at least 3 months, in patient's pre and/or post Bar S. We did not restrict to any specific sample size. For further details on the search strategy and eligibility criteria (see Appendix 1A and 1B–1C).

Two reviewers (AB, RS) screened the title, abstract and the full text of the potentially eligible citations, using a priori prepared screening forms. One reviewer (AB) completed abstraction on the following variables: participants' baseline characteristics, BMI, weight changes, vitamin D dose and co-intervention, 25(OH)D concentrations, vitamin D assay, and other mineral and skeletal parameters and outcomes. For other variables, data abstraction included only results on primary and secondary outcomes, based on checking of trial respective protocol in trials registries. When the achieved 25(OH)D concentration was not provided, we estimated it by adding the mean baseline concentration and the mean change, if available. We estimated the increase in the 25(OH)D concentration per 100 IU/d (Δ25(OH)D per 100 IU/d) by dividing the change in 25(OH)D concentration (ng/ml) by the dose (IU/d), multiplied by 100. This method for estimation of the change in 25(OH)D concentration per IU/d was previously reported [34]. If the change in 25(OH)D concentration was not provided, we estimated it by subtracting the mean achieved concentration from the mean baseline concentration.

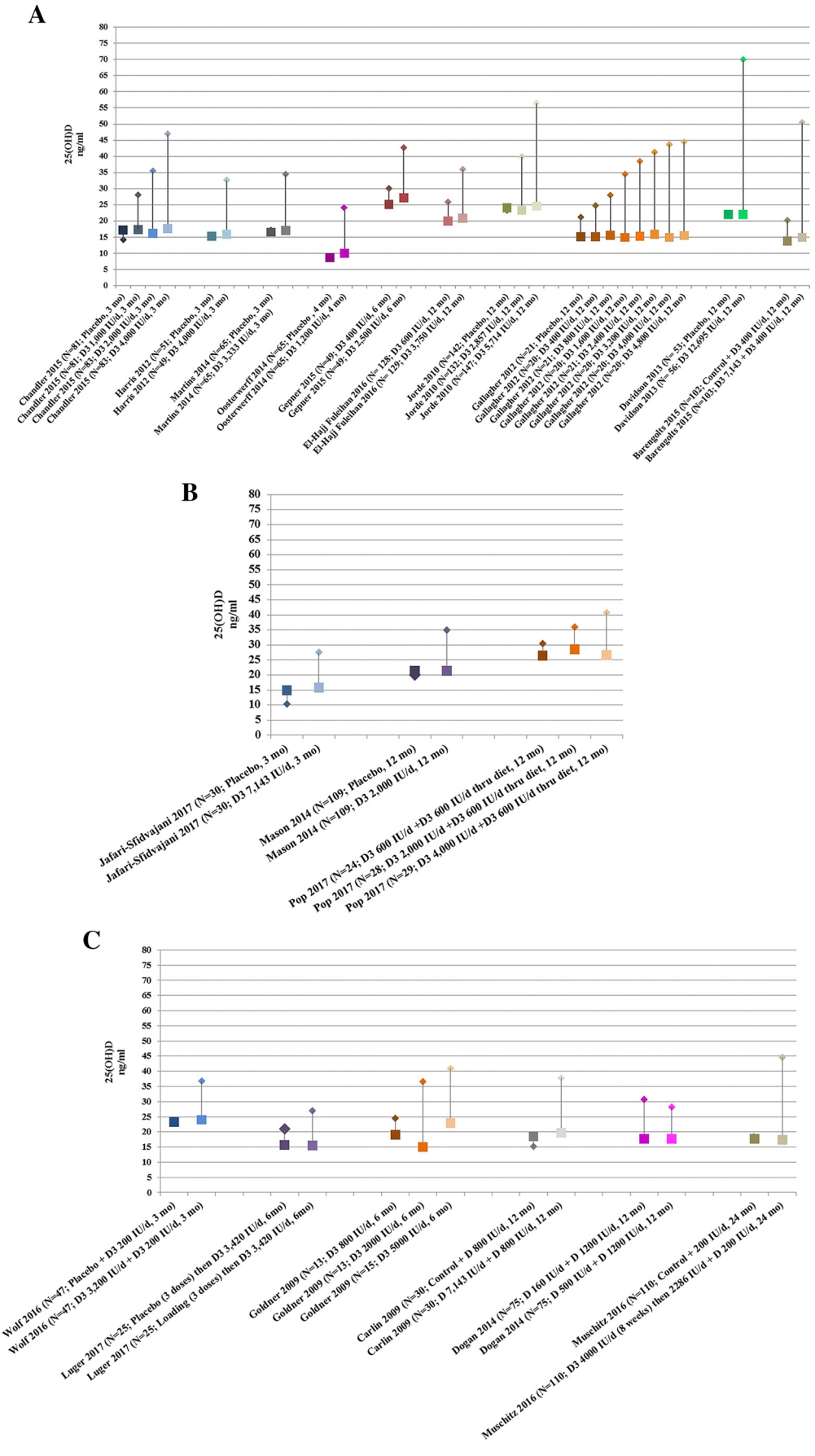
When at least 6 study arms were available, we assessed the correlation between the Δ25(OH)D per 100 IU/d and each of baseline 25(OH)D and baseline BMI, using Spearman correlation. We used SPSS version 25.0 (IBM). We considered a $p < 0.05$ as statistically significant.

3. Results

The search on obesity and medical weight loss yielded 5151 citations, and the search update in bariatric surgery recovered 563 citations. We identified 13 RCTs in OB, and 6 RCTs in individuals undergoing MWL with a hypocaloric diet and/or exercise. We did not identify any trial conducted in individuals on pharmacologic weight loss. In the Bar S search update, we identified one RCT in addition to the six trials previously identified [16]. For full details on the flow diagram, please refer to (Appendix 2A and 2B).

3.1. Vitamin D Supplementation in Obese Individuals

Thirteen trials compared the effect of different vitamin D doses between each other's or to control/placebo. One 5-year study reported a dropout rate of >30% [35], and was excluded from our discussion, in view of the high attrition rate. Ten studies were conducted in the USA and Europe, and two were from the Arab region, Lebanon and Iran [36,37]. Three trials were conducted exclusively in postmenopausal women [38–40], one trial targeted only men [41], while all the others


A
25(OH)D ng/ml
Chandler 2015 (N=81; Placebo, 3 mo)
Chandler 2015 (N=81; D3 1,000 IU/d, 3 mo)
Chandler 2015 (N=83; D3 2,000 IU/d, 3 mo)
Chandler 2015 (N=83; D3 4,000 IU/d, 3 mo)
Harris 2012 (N=51; Placebo, 3 mo)
Harris 2012 (N=49; D3 4,000 IU/d, 3 mo)
Martins 2014 (N=65; Placebo, 3 mo)
Martins 2014 (N=65; D3 3,333 IU/d, 3 mo)
Oosterwerff 2014 (N=65; Placebo , 4 mo)
Oosterwerff 2014 (N=65; D3 1,200 IU/d, 4 mo)
Gepner 2015 (N=49; D3 400 IU/d, 6 mo)
Gepner 2015 (N=49; D3 2,500 IU/d, 6 mo)
El-Hajj Fuleihan 2016 (N= 128; D3 600 IU/d, 12 mo)
El-Hajj Fuleihan 2016 (N= 129; D3 3,750 IU/d, 12 mo)
Jorde 2010 (N=142; Placebo, 12 mo)
Jorde 2010 (N=132; D3 2,857 IU/d, 12 mo)
Jorde 2010 (N=147; D3 5,714 IU/d, 12 mo)
Gallagher 2012 (N=21; Placebo, 12 mo)
Gallagher 2012 (N=20; D3 400 IU/d, 12 mo)
Gallagher 2012 (N=21; D3 800 IU/d, 12 mo)
Gallagher 2012 (N=20; D3 1,600 IU/d, 12 mo)
Gallagher 2012 (N=21; D3 2,400 IU/d, 12 mo)
Gallagher 2012 (N=20; D3 3,200 IU/d, 12 mo)
Gallagher 2012 (N=20; D3 4,000 IU/d, 12 mo)
Gallagher 2012 (N=20; D3 4,800 IU/d, 12 mo)
Davidson 2013 (N= 53; Placebo, 12 mo)
Davidson 2013 (N=56; D3 12,695 IU/d, 12 mo)
Barengolts 2015 (N=102; Control + D3 400 IU/d, 12 mo)
Barengolts 2015 (N=103; D3 7,145 + D3 400 IU/d, 12 mo)
B
25(OH)D ng/ml
Jafari-Sfidvajani 2017 (N=30; Placebo, 3 mo)
Jafari-Sfidvajani 2017 (N=30; D3 7,143 IU/d, 3 mo)
Mason 2014 (N=109; Placebo, 12 mo)
Mason 2014 (N=109; D3 2,000 IU/d, 12 mo)
Pop 2017 (N=24; D3 600 IU/d +D3 600 IU/d thru diet, 12 mo)
Pop 2017 (N=28; D3 2,000 IU/d +D3 600 IU/d thru diet, 12 mo)
Pop 2017 (N=29; D3 4,000 IU/d +D3 600 IU/d thru diet, 12 mo)
C
25(OH)D ng/ml
Wolf 2016 (N=47; Placebo + D3 200 IU/d, 3 mo)
Wolf 2016 (N=47; D3 3,200 IU/d + D3 200 IU/d, 3 mo)
Luger 2017 (N=25; Placebo (3 doses) then D3 3,420 IU/d, 6mo)
Luger 2017 (N=25; Loading (3 doses) then D3 3,420 IU/d, 6mo)
Goldner 2009 (N=13; D3 800 IU/d, 6 mo)
Goldner 2009 (N=13; D3 2000 IU/d, 6 mo)
Goldner 2009 (N=15; D3 5000 IU/d, 6 mo)
Carlin 2009 (N=30; Control + D 800 IU/d, 12 mo)
Carlin 2009 (N=30; D 7,143 IU/d + D 800 IU/d, 12 mo)
Dogan 2014 (N=75; D 160 IU/d + D 1200 IU/d, 12 mo)
Dogan 2014 (N=75; D 500 IU/d + D 1200 IU/d, 12 mo)
Muschitz 2016 (N=110; Control + 200 IU/d, 24 mo)
Muschitz 2016 (N=110; D3 4000 IU/d (8 weeks) then 2286 IU/d + D 200 IU/d, 24 mo)

included both genders [42–47]. The mean age of participants ranged between 35 and 71 years, and the mean BMI ranged between 28.2 and 35.2 kg/m^2 (Appendix 3A) [36–47]. Five studies extended over 12 months [36,38,41–43] and seven lasted 3–6 months [37,39,40,44–47]. The vitamin D doses ranged between 400 and 12,700 IU/d, and were administered as daily, weekly or monthly supplements. Vitamin D was given as Ergocalciferol in one study only [41], while it was Cholecalciferol in the remaining 11 studies. Six studies included concomitant calcium supplementation, with doses ranging from 200 to 1000 mg/d [36,38,43–46]. Compliance to supplements reported in five studies was >90% [36,37,39,43,44]; for further details see Appendix 3A [36–47].

3.1.1. Effect of Vitamin D Supplementation on 25(OH)D Concentration

The mean baseline 25(OH)D concentration ranged between 7.4 and 27.2 ng/ml. It was <20 ng/ml in six studies and ≤10 ng/ml in one. All studies, except one, reported on the achieved and/or the change in 25(OH)D concentration post-intervention. 25(OH)D concentration was the primary outcome in two studies [38,44]. Four studies used the gold standard 25(OH)D assays, high pressure liquid chromatography (HPLC) or liquid chromatography mass spectrometry (LCMS) [36,39,42,46].

Six studies extended over 3 to 6 months (Total N randomized 871 participants). In one RCT, 4000 IU/d vitamin D for 3 months increased 25(OH)D concentration by 16.7 ng/ml, while it remained stable in the control arm [45]. Another one used the same dose, or placebo, in a population with a lower baseline 25(OH)D of 7.4–12.5 ng/ml, and compared the response in metabolically healthy obese (MHO) to metabolically unhealthy obese (MUHO) [37]. The increments were not statistically different between MHO and MUHO, of 22.5 ng/ml and 25.3 ng/ml, respectively [37]. A lower dose of 100,000 IU/d per month, with a similar baseline, increased 25(OH)D concentration by 17.5 ng/ml [47]. One 3-month trial compared multiple doses of vitamin D to each other and to control [44,48]. The increase in 25(OH)D was of 10.8, 19.4 and 29.4 ng/ml, for doses of 1000, 2000 and 4000 IU/d, respectively [44]. The effect on 25(OH)D concentration weaned off 3 months post-discontinuation, with a significant decrease by 5.9–15.6 ng/mL, depending on the initial dose [44]. A dose of 1200 IU/d for 4 months increased the concentration by 14 ng/ml, when the mean baseline 25(OH)D was 10 ng/ml [46,49]. Supplementation with either 400 IU/d or 2500 IU/d resulted in increments in 25(OH)D concentrations, by 5 ng/ml and 15.5 ng/ml, respectively, 6 months later [40]. In short term studies, doses ≥2000 IU/d achieved mean 25(OH)D concentration ≥ 30 ng/ml, regardless of the baseline level (Fig. 1A and Appendix 3A) [36,38,40–47].

Five studies extended over 12 months (Total N randomized 1165 participants). Vitamin D doses of 600 IU/d to 3750 IU/d, increased 25(OH)D concentration by 5.9 and 15.1 ng/ml, respectively, in elderly with a mean baseline 25(OH)D of 20 ng/ml [36]. A high dose of 50,000 IU weekly was compared to placebo, with 400 IU/d administered to both study arms, starting at a mean baseline of 14–15 ng/ml, resulted in an estimated increment in mean 25(OH)D concentration of 35.6 ng/ml in the high dose group, and 7.5 ng/ml in the low dose [41]. In a study of seven incremental doses of vitamin D, compared to placebo, the increment in serum 25(OH)D was parallel to the doses, and tended to plateau at 44.8 ng/ml with doses of 3200–4800 IU/d [50]. Serum 25(OH)D concentration increased by 16.7 ng/dl and 32 ng/ml at vitamin D doses of 2857 IU/d and 5714 IU/d, respectively [43]. Finally, a trial that compared a very high dose of 12,700 IU/d to placebo, reported a 25(OH)D concentration increase of 70 ng/ml at 3 months, levels that were sustained until trial completion [42]. In long term studies, doses of 400–800 IU/d failed to achieve a mean concentration of 30 ng/ml, even when the mean baseline was 20 ng/ml. With doses ≥1600 IU/d, the mean achieved 25(OH)D concentration was ≥30 ng/ml. The mean achieved 25(OH)D concentration was ≥50 ng/ml in three studies administering doses 5700–12,700 IU/d (See Fig. 1A and Appendix 3A) [36,38,40–47].

For the moderate dose range, there was a negative association between baseline 25(OH)D and the Δ25(OH)D per 100 IU/d (−0.747, p-value: 0.013), and a trend for a negative association between baseline BMI and the Δ25(OH)D per 100 IU/d (R: −0.633, p-value: 0.067), in obese subjects see Appendix 4, Figure 1A and 1B. Conversely, for the high dose, there was no significant association between these variables and the Δ25(OH)D per 100 IU/d (Appendix 4, Figures 2A and 2B).

In summary, although a dose response is illustrated in most studies, be it short or longer term, the proportional increments in mean 25(OH)D concentrations per 100 IU/d of vitamin D are lower at higher doses, averaging 1–1.2 ng/ml at doses <600 IU/d, 0.5–1.2 ng/ml with doses 600–3500 IU/d and 0.4–0.7 ng/ml at doses exceeding 3500 IU/d (Table 2) [36–38,40–47].

3.1.2. Effect of Vitamin D Supplementation on Other Mineral and Skeletal Parameters and Outcomes

Bone mineral density (BMD) was the primary outcome in one trial only [51]. It demonstrated an increase in total hip and lumbar spine BMD for both treatment arms receiving vitamin D 600 IU/d or 3750 IU/d [51]. Conversely, there was no difference between the two arms in BMD or any other mineral parameter, with the exception of percent change in total body bone mineral content that was higher at the higher dose [51]. Another study reported on BMD as a secondary outcome, that was however not pre-specified in the trial protocol, and showed no significant changes between nor within treatment arms [43] (Appendix 5A) [36–47,49–55].

Six studies described the change in PTH level [43,45–47,49–51]. While two did not detect any significant difference between high and low doses [50,51]. There was a significant decrease in the PTH levels in the treatment groups compared to control in the other four [43,45–47,49]. Four studies had enrolled vitamin D deficient participants (25(OH)D concentration 10–17 ng/ml) [45–47,49,50] and the other two included participants with vitamin D insufficiency (25(OH)D concentration 20–25 ng/ml) [43,51]. Calcium level was a primary outcome in one study [43] and was assessed as secondary/exploratory outcome in three other studies [45,47,51]. None of the trials showed any significant change in calcium level between or within the arms [43,45,47,51]. Two studies reported on bone turnover markers, OPG, RANKL, osteocalcin and crosslaps [43,51]. There was a significant drop in markers within, but not between treatment arms [43,51] (Appendix 5A) [36–47,49–55].

3.1.3. Effect of Vitamin D Supplementation on Extra-skeletal Parameters

Nine trials assessed the effect of vitamin D supplementation in individuals with obesity on extra-skeletal parameters, as primary trial outcome (Appendix 5A) [36–47,49,52–55]. Insulin secretion or sensitivity, such as HOMA, McAuley, and Matsuda indices, and oral glucose insulin sensitivity, were evaluated in 6 studies [36,41–45]. Despite being adequately powered, three trials showed no effect of vitamin D, compared to placebo, or comparing high to low dose, on glycemic parameters [36,41,45]. Two other studies administered a high vitamin D dose or placebo, and reported a significant improvement in oral glucose sensitivity, or an increase in the insulin secretion rate [41,45]. One trial was completed a couple of years ago, but its results on HOMA indices have not been published yet [39]. Two trials assessed the progression rate to diabetes or pre-diabetes, while on vitamin D or placebo, also showed non-

Fig. 1. A: Mean serum 25(OH)D concentration in RCTs in obese individuals not undergoing weight loss, by intervention duration (<12 months and ≥12 months). Each color represents one study; dark colors represent low dose or controls, and light colors represent high dose (Data from [36,38,40–47]). B: Mean serum 25(OH)D concentration in RCTs in obese on medical weight loss, by intervention duration (<12 months and ≥12 months). Each color represents one study; dark colors represent low dose or controls, and light colors represent high dose (Data from [60,62,63]). C: Mean serum 25(OH)D concentration in RCTs in bariatric surgery, by intervention duration (<12 months and ≥12 months). Each color represents one study; dark colors represent low dose or controls, and light colors represent high dose (Data from [66–71]).

Table 2
Results on 25(OH)D levels in randomized controlled trials of vitamin D supplementation in obese individuals without weight loss, grouped by intervention duration and vitamin D dose.

	Study duration < 12 months					Study duration ≥ 12 months					
Author, year	Farzadfar 2018 [37]	Chandler 2015 [44]	Gepner 2013 [40]	Martins 2014 [47]	Oosterwerff 2014 [46]	Harris 2012 [45]	El-Hajj Fuleihan 2016 [36]	Barengolts 2015 [41]	Davidson 2013 [42]	Gallagher 2012 [38]	Jorde 2010 [43]
N Randomized	MHO: 110 MUHO: 105	328	98[b]	130	130	100	257	205	117	163	421
Low dose vitamin D (<600 IU/d)											
Intervention[a] (IU/d)	–	–	I1: D3 400 IU/d	–	–	–	I1: D3 600	C: Placebo + D2 400	–	I1: D3 400	–
Baseline 25(OH)D (ng/ml)			25.1 (10.1)				20 (7)	13.8 (5.9)		15.1 (4.3)	
Post intervention 25(OH)D (ng/ml)			30.1 (7.5)				25.9 (6.9)	20.2 (9.6)		24.8 (18–37)	
Calculated Δ25(OH) per 100 IU/d (ng/ml)			1.3				1	1.6		2.4	
Moderate dose vitamin D (600–3500 IU/d)											
Intervention (IU/d)	–	I1: D3 1000 I2: D3 2000	I2: D3 2500	D3 3333	I: D3 1200	–	–	–	–	I2: D3 800 I3: D3 1600 I4: D3 2400 I5: D3 3200	I1: D3 2857
Baseline 25(OH)D (ng/ml)		I1: 17.3 (9) I2: 16.1 (9.1)	27.2 (9.3)	17 (5.2)	10 (4.2)					I2: 15.6 (3.8) I3: 14.9 (4) I4: 15.3 (4) I5: 15.9 (3.3)	23.4 (9.4)
Post intervention 25(OH)D (ng/ml)		I1: 28.1 (9.9) I2: 35.5 (10.9)	42.7 (11.6)	34.5 (7.1)	24 (6.4)					I2: 28 (22–38) I3: 34.5 (28.4–44.5) I4: 38.5 (32.9–46.9) I5: 41.3 (29.6–48)	39.9 (8.1)
Calculated Δ25(OH) per 100 IU/d (ng/ml)		I1: 1 I2: 1	0.6	0.5	1.2					I2: 1.6 I3: 1.2 I4: 1 I5: 0.8	0.6
High dose vitamin D (>3500 IU/d)											
Intervention (IU/d)	I: D3 4000	I3: D3 4000	–	–	–	I: D3 4000 IU/d	I2: D3 3750	I: D2 7143 + 400	I: D3 12,695	I6: D3 4000 I7: D3 4800	I2: D3 5714
Baseline 25(OH)D (ng/ml)	MHO: 12.5 (6–22) MUHO: 8 (5–15.4)	17.6 (9.1)				15.9 (5.2)	20.9 (8.2)	14.9 (5.9)	22 (4.5)	I6: 14.9 (3.7) I7: 15.5 (3.6)	24.6 (8.3)
Post intervention 25(OH)D (ng/ml)	Change: MHO: 22.5 (18–29.5) MUHO: 25.3 (20.3–29.3)	47 (10.9)				Change: 16.7 (1.2)	36 (9.7)	50.5 (24.1)	70	I6: 43.7 (34–54.9) I7: 44.5 (34.56.9)	56.5 (13.9)
Calculated Δ25(OH) per 100 IU/d (ng/ml)	MHO: 0.6 MUHO: 0.6	0.7				0.4	0.4	0.5	0.4	I6: 0.7 I7: 0.6	0.6

Abbreviations: Δ: change, 25(OH)D: 25-hydroxyvitamin D, C: control, D2: Ergocalciferol, D3: Cholecalciferol, I: intervention, MHO: metabolically healthy obese, MHO; metabolically unhealthy obese, N/A: not available.
[a] Intervention expressed as equivalent daily dose of vitamin D.
[b] Total number of participants who completed the trial, number randomized not provided.

significant results [42,46,49]. One of them, reported a statistical decrease in HbA1C of 0.2% [42]. No effect of vitamin D supplementation on weight was detected in any trial. Whether this lack of effect is due to low power cannot be excluded, since BMI was assessed as a primary outcome only in one study [43].

Arterial stiffness, including aortic augmentation, aortic systolic pressure and aortic pulse pressure was the primary outcome in one study comparing vitamin D doses of 400 IU/d and of 2500 IU/d [40]. The augmentation index was lower in the higher dose group, while other parameters did not differ significantly across treatment arms [40]. One trial, stratifying the analysis according to the metabolic phenotype, metabolically healthy versus unhealthy, found that a high vitamin D dose of 4000 IU/d, results in a significant change in the level of specific metabolites compared to placebo. These metabolites are acyl-lysophosphatidylcholines (C16:0, C18:0, and C18:1), diacyl-phosphatidylcholines (C32:0, C34:1, C38:3, and C38:4), and sphingomyelin (C40:4), and are considered as mediators of the link between obesity and cardio-metabolic parameters [37].

3.2. Vitamin D Supplementation in Obese Individuals Undergoing Non-surgical Weight Loss

We identified 6 trials on weight loss following a caloric restriction diet and/or exercise. Two studies had a high dropout rate of 30–50% and were therefore excluded from our discussion [56,57]. Two trials were from the USA [58–60], one from Netherlands [61], and one from Iran [62]. One trial was conducted in younger women, mean age 28 (6) years [62], two were exclusively conducted in post-menopausal women [60,63], while another included both genders, with a mean

Table 3
Results on 25(OH)D levels in randomized controlled trials of vitamin D supplementation in obese individuals undergoing medical weight loss, grouped by intervention duration and vitamin D dose.

	Study duration < 12 months	Study duration ≥ 12 months	
Author, year	Jafari-Sfidvajani 2017 [62]	Pop 2017 [60]	Mason 2014 [63]
N randomized	60	81	218
Moderate dose vitamin D (600–3500 IU/d)			
Intervention[a] (IU/d)	–	I1: D3 600 + 600 I2: D3 2000 + 600	I: D3 2000
Baseline 25(OH)D (ng/ml)		I1: 26.5 (4.5) I2: 28.6 (4.7)	21.4 (6.1)
Post intervention 25(OH)D (ng/ml)		I1: 30.5 (5) I2: 36 (4.2)	35 (9.4)
Calculated Δ25(OH) per 100 IU/d (ng/ml)		I1: 0.3 I2: 0.3	0.7
High dose vitamin D (>3500 IU/d)			
Intervention (IU/d)	I: D3 7143	I3: D3 4000 + 600	–
Baseline 25(OH)D (ng/ml)	15.8 (4.9)	26.7 (3.7)	
Post intervention 25(OH)D (ng/ml)	27.6 (13.2)	40.8 (7.4)	
Calculated Δ25(OH) per 100 IU/d (ng/ml)	0.2	0.3	

Abbreviations: Δ: change, 25(OH)D: 25-hydroxyvitamin D, C: control, D2; Ergocalciferol, D3: cholecalciferol, I: intervention.
[a] Intervention expressed as equivalent daily dose of vitamin D.

age of 63 (3) years [61]. The range of mean baseline BMI was 29.4–32.5 kg/m^2. Two RCTs compared vitamin D at daily equivalent doses of 1100–7100 IU/day, to placebo, over 3 months [61,62] and 1 year [58,59]. Only one RCT compared 3 doses of 600, 2000 and 4000 IU/d of vitamin D and extended over 12 months [60] (Appendix 3B) [60,62,63]. With the exception of one study [58,59], the sample size was small (n = 24–40/arm), and if reported, the compliance rate was 83–97% [60,61,63].

3.2.1. Effect of Vitamin D Supplementation on 25(OH)D Concentration

Three studies reported on the achieved 25(OH)D concentration (Total N randomized 359 participants) [60,62,63]. None of the them used a gold standard assay (HPLC, LCMS) to measure 25(OH)D. The mean baseline 25(OH)D concentration ranged between 21.4 and 26.7 ng/ml in 2 studies [58,60], and was 15 ng/ml in the third [62]. There was a significant drop in 25(OH)D concentration of 1–4 ng/ml in the placebo arms [59,62], while the increment in 25(OH)D concentration varied widely post-intervention. Starting at a baseline of 15.8 ng/ml, the increment in mean 25(OH)D was 12 ng/ml at 3 months, in response to 50,000 IU/week [62]. A vitamin D dose of 2000 IU/d increased 25(OH)D concentration by 13.6 ng/ml at 12 months [58]. In another study, the estimated increments in mean concentrations for each of the 600, 2000 and 4000 IU/d doses, combined with an additional 600 IU/d, were 4, 7.4 and 14.1 ng/ml, respectively [60] (see Fig. 1B, Appendix 3B) [60,62,63].

In summary, the change in mean 25(OH)D per 100 IU/d of vitamin D was 0.3–0.7 ng/ml with doses of 600–3500 IU/d, while it was 0.2–0.3 ng/ml with doses exceeding 3500 IU/d (Table 3) [60,62,63].

Table 4
Results on 25(OH)D levels in randomized controlled trials of vitamin D supplementation in obese individuals undergoing bariatric surgery, grouped by intervention duration and vitamin D dose.

	Study duration < 12 months		Study duration ≥ 12 months			
Author, year	Wolf 2015 [70]	Luger 2015 [67]	Muschitz 2015 [71]	Dogan 2013 [69]	Carlin 2009 [66]	Goldner 2009 [68]
N randomized	94	50	220	150	60	41
Low dose vitamin D (< 600 IU/d)						
Intervention[a] (IU/d)	C: Placebo + D 200	–	C: Control + D 200	–	–	–
Baseline 25(OH)D (ng/ml)	23.2 (10.3)		17.7 (13–21.9)			
Post intervention 25(OH)D (ng/ml)	23.2 (11)		18 (15–22.1)			
Calculated Δ25(OH) per 100 IU/d (ng/ml)	0		0.1			
Moderate dose vitamin D (600–3500 IU/d)						
Intervention (IU/d)	I: D3 3200 + 200	I1: D3 2565	I: D3 2612	I1: D 160 + 1200 I2: D 500 + 1200	C: Control + D 800	I1: D3 800 I2: D3 2000
Baseline 25(OH)D (ng/ml)	24 (7.4)	15.7 (5.9)	17.4 (13.4–22.6)	I1: 17 (7.2) I2: 17.7 (8.2)	18.5 (9.4)	I1: 19.1 (9.9) I2: 15 (9.3)
Post intervention 25(OH)D (ng/ml)	36.9 (16.5)	21	44.6 (34.9–52.8)	I1: 30.7 (9.8) I2: 28.2 (10.2)	15.2 (7.5)	I1: Change: 5.4 (12.5) I2: Change: 21.6 (11)
Calculated Δ25(OH) per 100 IU/d (ng/ml)	0.4	0.2	1	I1: 1 I2: 0.6	N/A	I1: 0.7 I2: 1.1
High dose vitamin D (>3500 IU/d)						
Intervention (IU/d)	–	I2: D3 4350	–	–	I: D 7143 + 800	I3: D3 5000
Baseline 25(OH)D (ng/ml)		15.5 (5.7)			19.7 (8.5)	22.9 (10.3)
Post intervention 25(OH)D (ng/ml)		27			37.8 (15.6)	Change: 18 (16.5)
Calculated Δ25(OH) per 100 IU/d (ng/ml)		0.3			0.2	0.4

Abbreviations: Δ: change, 25(OH)D: 25-hydroxyvitamin D, C: control, D2; Ergocalciferol, D3: cholecalciferol, I: intervention, N/A: not available.
[a] Intervention expressed as equivalent daily dose of vitamin D.

3.2.2. Effect of Vitamin D Supplementation on Other Mineral and Skeletal Parameters and Outcomes

One study only assessed the effect of different vitamin D doses on the changes in the primary outcome of volumetric BMD in post-menopausal women, and showed no significant difference in any of the skeletal parameters between treatment arms [60]. However, there was a trend for less trabecular bone loss within each arm with increasing vitamin D doses, and doses of 2000–4000 IU/d prevented cortical bone loss, despite a concurrent 3% weight reduction [60]. The same trial also reported a drop in PTH and a significant increase in bone turnover markers, P1NP and CTX, over time, within each arm, while no difference was detected between arms [60].

Findings on the effect of vitamin D on muscle mass in obese individuals, undergoing weight loss with caloric restriction and exercise, were inconsistent. Vitamin D, at a dose of 8000 IU/week, co-administered with whey protein, yielded a significant increment in appendicular muscle mass, assessed as a primary outcome [61]; the increment was of 0.4(1.2) (kg) in the supplemented group, while there was a drop in the control group [61]. Conversely, another study showed a significant decrease in lean mass strength in the lower limbs in subjects receiving 2000 IU/d of vitamin D, and no change on the placebo [58]. The same study assessed lean mass and femoral neck and spine BMD as secondary outcomes, and detected no difference between arms [58] (Appendix 5B) [58–64].

3.2.3. Effect of Vitamin D Supplementation on Extra-skeletal Parameters and Outcomes

Vitamin D supplementation, at doses of 2000 IU/d, did not affect weight loss, a primary outcome, nor any other parameter including inflammatory markers, satiety and sex hormones, as compared to placebo [64]. However, these findings may be related to low power, given that the loss to follow up in this study was larger than what was expected [58,64]. Similarly, none of the other trials showed any effect of vitamin D supplementation on weight changes. Vitamin D supplementation had no effect on androgenic profile in obese young women following a hypocaloric diet [62].

3.3. Vitamin D Supplementation Following Bariatric Surgery

We identified 7 RCTs in Bar S. One study had a high dropout rate of >30%, and was therefore excluded [65]. Four studies were conducted in patients undergoing gastric bypass [66–69], one in sleeve gastrectomy [70], and another one combined both gastric bypass and sleeve gastrectomy patients [71]. The majority of the population consisted of women in their forties. BMI at randomization ranged between 42.9 and 50 kg/m^2 in 4 studies [67,69–71], and it was ≥50 kg/m^2 in 2 studies [66,68]. One trial extended over 24 months but we will only discuss the 6 months data, given the dropout rate of >30% thereafter [68]. Four trials administered vitamin D3, while the other two did not specify the type of supplement. The vitamin D daily equivalent dose ranged between 800 and 7142 IU per day, administered as daily [68–70], weekly [66,71] or biweekly [67], and was started in the peri-operative period in all trials. Calcium was given as a co-intervention, to all study arms in 3 studies [66,68,69]. The co-intervention differed between treatment arms in 2 studies where vitamin D supplementation was given as part of multivitamins preparation, with different content in other minerals and vitamins [69], or as part of lifestyle modifications, dietary and exercise intervention [71]. The sample size was relatively small, with <50 patients per arm with the exception of 2 studies [69,71] (Appendix 3C) [66–71].

3.3.1. Effect of Vitamin D Supplementation on 25(OH)D Concentration

The mean 25(OH)D concentration at baseline ranged between 10 and 20 ng/ml in 5 studies, and between 20 and 30 ng/ml in the remaining one (Total N randomized 615 participants). None of the trials used a gold standard assay (HPLC, LCMS) to measure 25(OH)D.

The achieved 25(OH)D concentration was the primary outcome in 2 trials [67,70]. One of them compared a loading dose of 300,000 IU, administered as 100,000 IU bolus at 0, 2 and 4 weeks post Omega Loop gastric bypass, followed by a maintenance dose of 3420 IU/d, compared to placebo loading and the same maintenance dose [67]. Both arms received an additional 252.3 (675.2) IU/d of vitamin D from multivitamins, throughout the study [67]. The increment in mean 25(OH)D concentration, starting at a baseline of 15 ng/ml, was 6 and 12 ng/ml at 6 months, in the control and intervention arm, respectively [67]. However, these finding are to be taken cautiously as 30% of the participants had liver fibrosis, thus affecting 25-hydroxylation of vitamin D [67]. A three-arm pilot study compared vitamin D 800, 2000 and 5000 IU/d in gastric bypass [68]. The baseline concentration differed significantly between arms, and ranged between 15 and 22.9 ng/ml [68]. At 6 months, the change in 25(OH)D concentration was 5.4, 21.6 and 18 ng/ml, in the low, intermediate and high dose, respectively [68]. The only study conducted in sleeve gastrectomy, compared a vitamin D dose of 3200 IU/d to placebo, in subjects receiving 200 IU as maintenance [70]. While the baseline 25(OH)D was 23–24 ng/ml, the estimated increase in the concentration was 13 ng/ml in the intervention, while no change was detected in the control arm [70].

Three studies lasted over ≥12 months [66,69,71]. Subjects randomized to 50,000 IU of vitamin D weekly increased their mean 25(OH)D concentration by 16.3(15.7) ng/ml, compared to a 4.4(11.4) ng/ml decrease in the control group [66]. With moderate doses of vitamin D, 1360 IU/d and 1700 IU/d, given as part of multi-vitamins, the estimated increase in mean 25(OH)D concentrations, from a baseline of 17 ng/ml, was 10.5–17.7 ng/ml [69]. A loading dose of 28,000 IU/week of vitamin D for 8 weeks, followed by 16,000 IU/week, for a total of 24 months, resulted in an increment in 25(OH)D of 27 ng/ml [71]. Two studies showed results at different time points, and suggested that 25(OH)D concentration reaches a plateau at 5–9 months post-surgery [67,71].

For the moderate dose of vitamin D, there was no association between the change in 25(OH)D level in response to supplementation in patients undergoing Bar S, and the baseline 25(OH)D concentration or BMI, each assessed separately (Appendix 4, Figures 3A and 3B).

In summary, in Bar S, vitamin D doses ≥2000 IU/d allowed to reach a mean 25(OH)D concentration > 30 ng/ml (Fig. 1C, Appendix 3C) [66–71]. The average increment in 25(OH)D concentration per 100 IU/d of vitamin D in this population ranged between 0.4 and 1.1 ng/ml with doses of 600–3500 IU/d, and 0.2–0.4 ng/ml at doses exceeding 3500 IU/d (Table 4) [66–71].

3.3.2. Effect of Vitamin D Supplementation on Other Mineral and Skeletal Parameters and Outcomes

All studies assessed one or more mineral parameter, including calcium, phosphate, PTH, and bone markers. No significant effect of vitamin D supplementation on serum calcium or phosphate levels was ever detected, with the exception of one year study that showed a lower phosphate level in the intervention, with a vitamin D dose of 28,000 IU of D3 weekly for 8 weeks then 16,000 IU/week, compared to control, co-administered with exercise and proteins, in subjects post-RYGB and SG [71]. The same study showed a lower drop in BMD at various skeletal sites, and lower increments in bone turnover markers, in the intervention arm, compared to control [71]. Five other studies did not demonstrate any significant difference in PTH levels between treatment arms [66–70]. However, Luger et al. showed that the rate of secondary hyperparathyroidism was significantly lower, by 70% [OR 0.3 (95% CI = 0.1, 0.9; p = 0.038)], starting at week 2 post-surgery, with a loading vitamin D3 dose of 100,000 IU weekly for 3 weeks, then 3420 IU/d, compared to placebo for 3 doses, followed by 3420 IU/d, over 6 months [67]. Vitamin D was also protective against hip bone loss in subjects receiving 50,000 IU/week, following RYGB, compared to control [66] (Appendix 5C) [66–71].

3.3.3. Effect of Vitamin D Supplementation on Extra-skeletal Parameters and Outcomes

Vitamin D supplementation did not affect weight loss in any of the included studies. However, none of them may have been powered to

show such effect. None of the studies evaluated other extra-skeletal parameters either as a primary or secondary outcomes.

4. Discussion

Our review of vitamin D trials revealed that moderate doses of vitamin D (≥1600–2000 IU/d), increased mean 25(OH)D concentrations to ≥30 ng/ml, in subjects in OB and MWL categories. The change in mean 25(OH)D concentrations per 100 IU/d of vitamin D was 0.5–1.6 ng/ml at moderate doses and 0.4–0.7 ng/ml at higher doses in OB group, and in general lower during weight loss. Slightly higher doses may be needed in Bar S, where the average increment in 25(OH)D concentration per 100 IU/d of vitamin D ranged between 0.4 and 1.1 ng/ml with moderate doses and 0.2–0.4 ng/ml with high doses. Few small studies were identified in obese individuals on diet and/or exercise. Several studies reported on the effect of vitamin D on BMD, PTH, glycemic indices and other extra-skeletal outcomes, but the results were inconsistent.

Individuals with obesity have a lower response to vitamin D supplementation, when compared to subjects with normal weight. An experimental study from the US, compared the response to UVB with whole body radiation, in obese and non-obese individuals, and showed a 57% lower response in the former group, most likely secondary to vitamin D sequestration, rather than decreased synthesis [72]. Similarly, the increments in 25(OH)D concentrations with oral vitamin D supplements were 20–30% lower in obese individuals, compared to those with a normal weight [50,73]. Such difference became clinically significant at doses ≥800 IU/d [50]. Furthermore, in a previous meta-analysis of 94 trials, body weight (kg) was a significant predictor of the response to vitamin D supplementation [74]. In our review, in individuals with obesity, starting at a mean baseline 25(OH)D concentration of 10–20 ng/ml, a vitamin D dose of 1600–4000 IU/d increased mean 25(OH)D to 30–40 ng/ml, thus allowing >50% of the population to reach the desired concentration of 20 ng/ml, by the end of the intervention. Such doses are higher than the recommended dose of 1500–2000 IU/d, by the Endocrine Society for the general population [19]. In obese individuals, the increment in 25(OH)D level with a moderate vitamin D dose was 0.5–1.2 ng/ml per 100 IU/d. Such response is lower than increments recently reported in a review of vitamin D supplementation trials in normal weight post-menopausal women, of 1–3 ng/ml per 100 IU/d vitamin D [34]. Noteworthy that in the latter studies, the range of baseline 25(OH)D concentrations was 12–16 ng/ml, lower than the levels in the majority of our included studies, findings that may in part explain the difference in the response obtained. With moderate doses in obese individuals, there was a negative association between the Δ25(OH)D per 100 IU/d and baseline 25(OH)D concentration and BMI. However, such correlation was not consistent in other dose categories, most likely secondary to the low number of studies available.

Vitamin D doses >5000 IU/d increased the mean 25(OH)D concentration to ≥50 ng/ml, a high level that is not recommended given the data on the possibility of a U-shaped relationship between 25(OH)D concentration and various major health outcomes [74–80]. In the included trials in obese individuals, the increase in 25(OH)D concentration per 100 IU/d was inversely proportional to the administered dose, with large variability across studies, most likely reflecting the impact of various confounders, including baseline 25(OH)D, vitamin D assay, baseline BMI, age and gender. One study administered vitamin D supplementation for 3 months and reported a drop in concentration at 6 months follow up, suggesting that, after replacement, a maintenance dose is needed [44]. Our findings may suggest a lower response in individuals with obesity, and therefore, higher vitamin D doses in order to reach a desirable level, as established in the general population. However, given that we included exclusively studies with mean BMI ≥ 30 kg/m^2, we could not compare the dose response between normal weight and obese individuals.

Weight loss decreases fat mass, and may result in a spontaneous increase in 25(OH)D concentration, secondary to the release of vitamin D sequestered in adipose tissue [81,82]. Previous systematic reviews of randomized and non-randomized weight loss studies showed an improvement in vitamin D status, with linear increments in parallel to weight loss; a clinically significant increase in concentration of >3 ng/ml was shown at weight loss ≥10% [81,83]. Therefore, some experts discussed the theory of "*reversed causation*" and that the efforts should be focused at weight loss interventions, which yield a spontaneous improvement in vitamin D status, rather than supplementing vitamin D to improve weight loss and other outcomes [81,82]. However, such spontaneous increments may not allow achieving the target level, and supplementation would still be needed. Our review did not detect a spontaneous increase in 25(OH)D concentration in the placebo arms of trials on individuals losing weight with lifestyle modification. This could be possibly explained by the small amount of weight loss (3–8%) in the included studies. In the intervention arms, the increase in 25(OH)D was parallel to increments in the vitamin D dose. However, the small number of studies identified does not allow definite conclusions regarding the vitamin D dose response. We did not identify any study on pharmacologic weight loss, whereby weight loss is expected to be more pronounced.

While we expect an improvement in 25(OH)D concentration with medical weight loss, it drops significantly following bariatric surgery. A previous systematic review of observational studies, assessing vitamin D status before and after bariatric surgery, showed that, despite various doses of supplementation, 25(OH)D concentration remained <30 ng/ml in the majority of the studies [13]. Bar S results in a drastic weight loss of 15–35%, depending on the surgical procedure, that persists at 5 and 10 years [5,84]. However, in addition to weight loss, there are several surgery-specific changes in the gastro-intestinal tract, including anatomy and physiology, and thus impaired digestion, changes in incretins secretion, and malabsorption, that all contribute to vitamin D deficiency [12,16]. Accordingly, vitamin D replacement following bariatric surgery is needed. In our review, all but one study were conducted in gastric bypass patients and the results suggest the need for doses ≥2000 IU/d to reach a 25(OH)D concentration of 30 ng/ml. Post-intervention, the achieved concentration varied widely, indeed driven by the limb length, and the % weight loss, in addition to the traditional confounders affecting the 25(OH)D concentration. Scarce data on the supplementation doses following SG, an increasingly popular surgery, where malabsorption is not a major component, and the role of rapid gastric emptying on the absorption of vitamin D still needs to be confirmed. One study in SG suggested that supplementation may be needed only in the first 3 months, as patients food intake is expected to improve thereafter [85]. Intra-muscular vitamin D preparations may constitute an attractive regimen for patients with malabsorption secondary to bariatric surgery. However, the efficacy, the frequency and the safety of such dosing in bariatric surgery needs further evaluation. Two trials administered a single high dose of 600,000 IU once at 4 years post gastric bypass [86], or BPD/DS [87], and reported a significant improvement in 25(OH)D concentration. In the general adult population, a systematic review on single loading doses of vitamin D showed that, in response to such doses, 25(OH)D concentration reaches a peak at 1 month after dosing, and drops thereafter [88]. Accordingly, such regimen is suboptimal in maintaining a sufficient 25(OH)D concentration beyond 3 months [88]. Furthermore, there are concerns regarding the safety of vitamin D status, in light of the reported increased falls and fractures with such regimens in the elderly population [89,90].

Our review summarizes the available literature related to vitamin D supplementation in the obese population and sheds light on knowledge gaps for future research. The Institute Of Medicine and the Endocrine Society have established the desirable 25(OH)D concentration, 20 and 30 ng/ml, respectively, based on data on musculo-skeletal outcomes in non-obese individuals [27,91]. Most studies did not exceed the upper tolerable level set by the IOM for the adult and elderly population of 4000 IU/day [91], but the data reviewed does not justify some of the high doses recommended by guidelines for obese individuals, reviewed

above. The effect on secondary hyperparathyroidism was inconsistent, most likely related to variability in baseline 25(OH)D and PTH levels. Few adverse events were reported in the included trials, even with doses as high as >12,000 IU per day, but such reporting was sketchy, and the long term safety of high doses of vitamin D in these populations remains unknown. Given the scarcity of data in obese individuals and those undergoing weight loss, the optimal level that may improve musculo-skeletal health remains unknown today. This is particularly relevant considering the increased fracture risk post-surgical [92] and non-surgical weight loss [93]. Three studies assessed BMD as a primary outcome. One in obese elderly without weight loss [51], another in menopausal women undergoing weight loss [60], and the third one was in patients undergoing RYGB or SG [71]. The latter study only showed a protective effect of vitamin D supplementation against bone loss, when it was co-administered with a high protein diet and regular exercise [71]. While supplementation may protect against weight loss induced bone loss, data on fracture risk reduction are lacking.

None of the studies revealed any effect of vitamin D on weight loss. However, this outcome was pre-defined as primary in only 2 studies. Such results, although possibly explained by low power, are in line with previous systematic reviews [94,95]. Several trials were powered to assess the effect of vitamin D on glycemic indices, but the results were inconsistent, and negative for an impact on the development of diabetes. Similar negative results were also previously reported in meta-analyses of RCTs on vitamin D supplementation and glycemic control in diabetic overweight and obese individuals [96,97]. However, sub-group analyses suggested a potential beneficial effect in individuals who were vitamin D deficient, defined as a baseline 25(OH)D concentration < 20 ng/ml upon enrollment [96]. Data on other extra-skeletal parameters, namely vascular and inflammatory, were scarce. Therefore, our conclusion is similar to that of the 2017 scientific statement of the European Society for Clinical and Economic aspects of Osteoporosis and Osteoarthritis (ESCEO) on vitamin D supplementation and the prevention and treatment of chronic disease: "*no evidence exists, so far, that administering vitamin D could reduce type 2 diabetes or obesity in the general*" [98]. Results of sub-group analyses from the "Vitamin D and Omega-3 Trial" (VITAL), comparing the effect of Cholecalciferol 2000 IU/d administered concomitantly with Omega-3 1 g/d, to placebo, on cancer or cardiovascular diseases, suggested a differential effect of vitamin D across BMI categories, specifically a cancer risk reduction for subjects with a BMI below the median of 27 kg/m^2 [99].

4.1. Strength and Limitations

Our review followed a systematic approach in the literature search and data abstraction, and allowed to map the available evidence on vitamin D supplementation in obese individuals. However, it has several limitations, in large part due to inherent limitations of the data available to-date. The included studies were quite heterogeneous, in terms of baseline 25(OH)D concentrations, vitamin D dose regimens, assays used, and many had a small sample size and unspecified power. Intra- and inter-assay CV for 25(OH) D measurements was only reported in 10/21 studies. No specific details were provided (N of duplicates for each, and whether manufacturer versus laboratory derived), except for one [38]. The numbers varied widely from 2.1 to 15.5%. The large disparity in the design of the identified studies and the variability in the parameters assessed do not allow the implementation of a proper meta-analysis. We included trials with participants with a mean baseline BMI ≥30 kg/m^2, and therefore, for some studies a substantial proportion of overweight individuals may have been included. This could have resulted in more modest effect size estimates in mean changes in 25 (OH) concentrations, and/or biased the results towards the null for health outcomes. The studies did not allow any clear conclusions regarding desirable vitamin D dose in obese subjects due to the lack of data on skeletal and other outcomes. The majority of the studies were conducted in Western countries, with poor representation from Asia and the Middle East, the latter regions being notorious for prevalent vitamin D deficiency and for registering some of the highest increments in obesity rates worldwide [1,100,101].

In conclusion, in individuals with obesity and following bariatric surgery, and specifically gastric bypass, vitamin D doses of 1600–4000 IU/d in general achieve a mean 25(OH)D concentration ≥ 30 ng/ml. Data on vitamin D replacement during medical weight loss are limited to few small studies. None of the studies demonstrated any effect of vitamin D on weight loss, and findings on glycemic indices and the risk of developing diabetes were inconsistent. Data on cardio-metabolic parameters in obese individuals undergoing medical or surgical weight loss is lacking.

5. Areas of Controversies and Future Directions

The beneficial effect of vitamin D supplementation on bone density and fractures in the general population has become currently a matter of debate, with the most recent meta-analysis showing no effect on fracture risk [102]. The results were unchanged in subgroup analysis based on BMI category [102]. However, this paper was criticized for methodologic limitations, namely vitamin D status of the participants enrolled in the included trials, the vitamin D regimen used, the exclusion of RCTs using calcium and vitamin D combined, assay variability and others [103]. More uncertainties dominate the practice of vitamin D supplementation in obese individuals with or without weight loss. The optimal 25(OH)D concentration in this specific population is unknown, and the traditional predictors of the response to vitamin D supplementation, such as baseline 25(OH)D concentration and BMI, need to be evaluated in large well-powered studies. Scarce data are currently available on the role of vitamin D supplementation in preserving bone health and protecting against weight loss induced bone loss and fractures. Furthermore, the beneficial effect on cardio-metabolic parameters in obese individuals is controversial, and data on such parameters with weight loss are scarce and limited by the wide heterogeneity of endpoint definition. Well-designed long term RCTs and individual patient meta-analyses assessing the effect of vitamin D supplementation in individuals with obesity and during weight loss on patient important outcomes are needed.

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Authors' Contribution

GEHF and MC designed the review outline and search strategy; RS conducted the search strategy; AB and RS screened titles and abstracts, and full texts; AB abstracted data; AB and MC wrote the paper, GEHF provided major input on the paper; AB, MC and GEHF had the primary responsibility of the final content of the manuscript.

Declaration of Interest

The authors declare no conflict of interest.

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