Hypovitaminosis D in bariatric surgery: A systematic review of observational studies

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ABSTRACT

Background. Obesity is a public health problem that carries global and substantial social and economic burden. Relative to non-surgical interventions, bariatric surgery has the most substantial and lasting impact on weight loss. However, it leads to a number of nutritional deficiencies requiring long term supplementation.

Objectives. The aims of this paper are to review 25-hydroxyvitamin D [25(OH)D] status pre and post bariatric surgery, describe the dose response of vitamin D supplementation, and assess the effect of the surgical procedure on 25(OH)D level following supplementation.

Methods. We searched Medline, PubMed, the Cochrane Library and EMBASE, for relevant observational studies published in English, from 2000 to April 2015. The identified references were reviewed, in duplicate and independently, by two reviewers.

Results. We identified 51 eligible observational studies assessing 25(OH)D status pre and/or post bariatric surgery. Mean pre-surgery 25(OH)D level was below 30 ng/ml in 29 studies, and 17 of these studies showed mean 25(OH)D levels ≤20 ng/ml. Mean 25(OH)D levels remained below 30 ng/ml following bariatric surgery, despite various vitamin D replacement regimens, with only few exceptions. The increase in post-operative 25(OH)D levels tended to parallel increments in vitamin D supplementation dose but varied widely across studies. An increase in 25(OH)D level by 9–13 ng/ml was achieved when vitamin D deficiency was corrected using vitamin D replacement doses of 1100–7100 IU/day, in addition to the usual maintenance equivalent daily dose of 400–2000 IU (total equivalent daily dose 1500–9100 IU). There was no difference in mean 25(OH)D level following supplementation between malabsorptive/combination procedures and restrictive procedures.

Conclusion. Hypovitaminosisis D persists in obese patients undergoing bariatric surgery, despite various vitamin D supplementation regimens. Further research is needed to determine the optimal vitamin D dose to reach desirable 25(OH)D levels in this population, and to demonstrate whether this dose varies according to the surgical procedure.

1.   Introduction

The obesity epidemic is a worldwide public health problem [1–3]. Its overall prevalence reached about 35% in 2009–2010 among US adults, with a mean body mass index (BMI) of 28.7 kg/m^2 (95% CI, 28.4–29.0) [4]. The prevalence of grades 2 and 3 obesity (BMI ≥ 35 and ≥40 kg/m^2, respectively) reached 15.4% during the same time period, according to NHANES data [5,6]. While in the US the percent change was greater in the earlier years, before 2000, compared to the most recent years [5,6], the prevalence of obesity is still increasing in developing countries [1]. Obesity is a risk factor for several non-communicable diseases, including cardiovascular, metabolic, pulmonary, gastrointestinal, orthopedic, neurologic and psychological complications [7]. Therefore, obesity carries a significant socio-economic burden [1,8], accounting for 0.7%–2.8% of healthcare expenditure of various countries [9]. Obesity is one the major global health targets set by the WHO in its 2013 World Health Assembly [8].

While medical therapy has limited effectiveness [10], ample evidence supports the efficacy of surgical intervention to treat this morbid condition [11,12]. Indeed, bariatric surgery results in a significant and sustained weight loss [13], a substantial reduction in cardiovascular risk factors [14], an improvement in diabetes control [15–17] and a decrease in mortality [18,19].

However, bariatric surgery leads to various nutritional and vitamin deficiencies, including vitamin D and others, requiring adequate follow up postoperatively [20,21]. Vitamin D deficiency in the bariatric surgery population is multifactorial, some factors being related to obesity, and might not resolve completely after surgery, and others may be related to the type of the surgical procedure and/or its consequences. The inverse relation between BMI and serum 25-hydroxyvitamin D [25(OH)D] level has been demonstrated in the large Framingham [22] and NHANES III [23] studies and confirmed in a meta-analysis of multiple cohorts, using Mendelian randomization [24]. In the latter analysis, an increasing BMI allele score (combining a battery of 12 BMI SNPs) was significantly associated with lower 25(OH)D level [24]. Decreased sun exposure, altered dietary habits, and lack of intake of adequate amounts of various minerals and vitamins in obese individuals are all contributing factors [25,26]. Furthermore, obese individuals have decreased bioavailability of vitamin D, secondary to its sequestration in subcutaneous and visceral fat, despite normal vitamin D cutaneous synthesis and gastrointestinal absorption, compared to lean control subjects [27]. Compared to lean subjects, obese individuals have decreased expression of the vitamin D metabolizing enzymes, 25-hydroxylase and 1α-hydroxylase in cutaneous and visceral adipose tissues [28]. A decrease in the activity of the hepatic 25-hydroxylase activity has been previously described, and may be secondary to non-alcoholic fatty liver disease [29]. Volumetric dilution, rather than sequestration, has been suggested to explain the low 25(OH)D level in obese. Therefore, it was proposed to adjust daily vitamin D supplementation according to body weight, in order to be able to reach desirable levels [30]. This would require supplementation of 70–80 IU/kg body weight to reach 30 ng/ml, or 30–40 IU/kg body weight to reach 20 ng/ml [30]. The role of obesity-associated inflammation on vitamin D level has been also suggested and needs to be further elucidated [31]. The surgical procedure per se affects 25(OH)D status. In malabsorptive procedures, fat malabsorption is a major contributor to deficiencies in liposoluble vitamins, secondary to bypass of primary absorption sites in the small intestine (duodenum, jejunum and ileum) and impaired digestion [32,33]. In fact, duodenal surgical bypass decreases cholecystokinin secretion, which results in a reduction in the secretion of the pancreatic lipolytic enzymes and alteration in biliary salts, leading to problems in fat digestion, and thus steatorrhea [34]. Following both, malabsorptive and restrictive procedures, dietary intolerance with reduced intake of dairy products, vomiting, and non-adherence to supplement recommendations worsen 25(OH)D status further [32,33]. Finally, secondary hyperparathyroidism may be a contributory factor resulting in increased 25(OH)D hydroxylation, therefore decreasing 25(OH)D level [35].

The recommended 25(OH)D desirable level in the general population has been a matter of intense debate [36]. While the Institute Of Medicine (IOM) recommends a target of 20 ng/ml [37], the Endocrine Society aims at a higher level of 30 ng/ml [38]. Both societies based their recommendations on evidence related to musculo-skeletal outcomes. Despite the controversy around the desirable 25(OH)D cutoffs, it has been demonstrated that low 25(OH)D levels in bariatric surgery patients result in skeletal complications, including bone loss [39,40]; the latter has been recently confirmed using quantitative computed tomography (QCT), which assesses volumetric bone mineral density (vBMD) [41,42]. Furthermore, in addition to the classically described secondary hyperparathyroidism [43,44], several cases of osteomalacia have been reported following malabsorptive weight loss surgeries [45–47].

The aims of this paper are to review 25(OH)D status pre and post bariatric surgery, describe the dose response of vitamin D supplementation in this specific population, and assess the effect of the surgical procedure on 25(OH)D level following supplementation.

2.   Materials and Methods

2.1.   Literature Search

We searched the following databases: Medline, PubMed, the Cochrane Library, and EMBASE. The search timeframe was 2000–April 2015, since the accuracy of vitamin D assays has improved in the last decade, following the introduction of the International Quality Assessment Scheme for Vitamin D

metabolites (DEQAS), in 1997 [48]. We used the following MeSH terms: vitamin D, vitamin D deficiency, bariatrics, bariatric surgery, gastric bypass, gastroplasty, biliopancreatic diversion, anastomosis, Roux-en-Y, gastroenterostomy, pancreaticojejunostomy, gastrectomy, jejunoileal bypass, obesity, overweight. Recently retrieved review articles on this topic and others available in the authors' libraries were also considered.

2.2. Study Selection

This review focuses on observational studies (prospective, retrospective and cross-sectional). We included studies conducted on obese adult patients undergoing bariatric surgery and assessing 25(OH)D status before and/or after any type of bariatric surgery, with or without vitamin D supplementation.

We excluded studies that:

- Were published as abstract only.
- Had a number of participants undergoing bariatric surgery of <50.
- Did not specify the bariatric surgery type.
- Did not report results for each bariatric surgery type (malabsorptive versus restrictive) separately.
- Did not provide 25(OH)D levels, or the proportion of participants reaching a certain 25(OH)D level, or 25(OH)D level unit.
- Did not define the cutoff for vitamin D deficiency, when the proportions of individuals with vitamin D deficiency were provided.
- Did not define the dose of vitamin D administered post operatively, whether maintenance or treatment dose, while presenting results on 25(OH)D status post operatively.

2.3. Data Abstraction

We (MC, and KS or NN) screened all the retrieved references. Similarly, we assessed all citations judged as potentially eligible by at least one of the reviewers for inclusion in the systematic review. We compared results and resolved disagreements by discussion with a third reviewer (GEHF).

We also performed data abstraction in duplicate and independently. Data collected include: author's name, year of publication, country, number of participants, type of surgical procedure, vitamin D supplementation dose, 25(OH)D levels, vitamin D assay (Appendix).

To assess vitamin D status before bariatric surgery, we compared 25(OH)D levels in different BMI categories: 40–45, 45–50 and >50 kg/m^2. In each category, we calculated the weighted mean and pooled standard deviation of 25(OH)D level (ng/ml). Weights were based on sample size. Calculations were done using the following formulas:

$$\text{Weighted mean} = (n1\,m1 + n2\,m2 + \ldots + ni\,mi)/n1 + n2 + \ldots + ni$$

[49]

Weighted pooled Standard Deviation (SD)

$$= \sqrt{\left[\left[(n1{-}1)(Sd1)^2 + (n2{-}1)(Sd2)^2 + \ldots + (ni{-}1)(Sdi)^2\right]\big/(n1{-}1)\right.}$$
$$\left. +(n2-2) + \ldots + (ni{-}1)\right]$$

(assuming equal variances, and by extrapolation from the pooled standard deviation calculation of 2 independent samples)

[50]. In the aforementioned formulas, "n" is the number of participants in each arm, "m" is the mean 25(OH)D level, "Sd" is the standard deviation of the level in each arm.

Assuming normality of the distribution of 25(OH)D levels, and using the mean 25(OH)D levels of the included studies, we estimated the proportion of individuals reaching the target level of 20 ng/ml, as recommended by the IOM [37], in each study.

25(OH)D levels were reported in ng/ml; for conversion into nmol/l multiply by 2.496.

3. Results

Fig. 1 represents the study selection process. The search strategy identified 1868 citations. Following duplicate removal, we were left with 1337 citations. After title and abstract screening, we judged 181 articles as potentially eligible. We excluded 130 articles for the presence of one or more exclusion criteria. Therefore, we used data from 51 observational studies, illustrating 25(OH)D status before and/or after various types of bariatric surgery (Appendix). All studies were conducted in Europe and the United States, except one study conducted in Israel (Appendix).

3.1. 25(OH)D Status Before Bariatric Surgery

Thirty six studies assessed 25(OH)D status before bariatric surgery (Appendix). Fig. 2 represents studies that have a number of participants of at least 50 per study group or subgroup, based on bariatric surgery type. It shows that mean 25(OH)D levels were ≤20 ng/ml in fifteen studies [51–65], and between 20 and 30 ng/ml in the others [66–77]. The weighted mean 25(OH)D levels (ng/ml) did not differ significantly between studies, classified according to the baseline participants' mean BMI (mean BMI ≥ 50 kg/m^2, mean BMI between 45 and 50 kg/m^2 and mean BMI ≤ 45 kg/m^2) (Fig. 2). Similarly, the weighted mean 25(OH)D levels of studies divided into 2 categories (mean BMI ≥ 50 kg/m^2 versus mean BMI <50 kg/m^2) also did not differ significantly (data not shown). Two other studies [78,79], in addition to the restrictive procedure arm of a third one [69] were not represented on Fig. 2, as the number of participants per surgical procedure group was <50. These studies also showed a mean 25(OH)D level of less than 20 ng/ml before bariatric surgery (Appendix). Mean 25(OH)D level was surprisingly high, reaching 39.4 ng/ml, in a group of obese individuals undergoing Roux-en-Y Gastric Bypass (RYGB) [80]. However, this study did not provide the mean BMI of participants, and therefore, it was not represented in Fig. 2. Finally, four studies did not report 25(OH)D levels, but they provided the pre-operative proportion of individuals with 25(OH)D level < 20 ng/ml, of 66% [81], or <30–32 ng/ml, varying from 23% to 98% [82–84].

3.2. Vitamin D Levels Following Bariatric Surgery With and Without Vitamin D Supplementation

Forty six studies assessed 25(OH)D status within 1 to 11 years following bariatric surgery (Appendix). These were divided into categories according to the type of the surgical procedure

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┌─────────────────────────────────┐
│ Number of articles identified   │
│ from Medline, PubMed, Embase    │
│ and the Cochrane Library:       │
│ 1,868                           │
└─────────────────────────────────┘
                │
                ▼
┌─────────────────────────────────┐
│ Number of articles screened by  │
│ Title and Abstract after        │
│ duplicate removal:              │
│ 1,337                           │
└─────────────────────────────────┘
                │              ┌─────────────────────────────┐
                ├─────────────▶│ Number of articles excluded:│
                │              │ 1,156                       │
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│ Number of full text articles    │
│ screened:                       │
│ 181                             │
└─────────────────────────────────┘
                │
                ├─────────────▶
                ▼
┌─────────────────────────────────┐
│ Number of articles included:    │
│ 51                              │
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Number of articles excluded for specific reasons: **130**
- Studies published as abstract only: 44
- Studies with a small sample size (<50 participants undergoing bariatric surgery): 46
- Studies that did not mention vitamin D dose (maintenance dose or dose administered in case of vitamin D deficiency or insufficiency): 19
- Studies that did not mention 25(OH)D level or the proportion of participants reaching a certain 25(OH)D level or results for each bariatric surgery type (malabsorptive versus restrictive) not presented separately: 10
- Studies that did not provide cutoffs to define vitamin D sufficiency/deficiency when the proportion of deficient individuals was reported: 3
- Studies that did not define the 25(OH)D level unit: 1
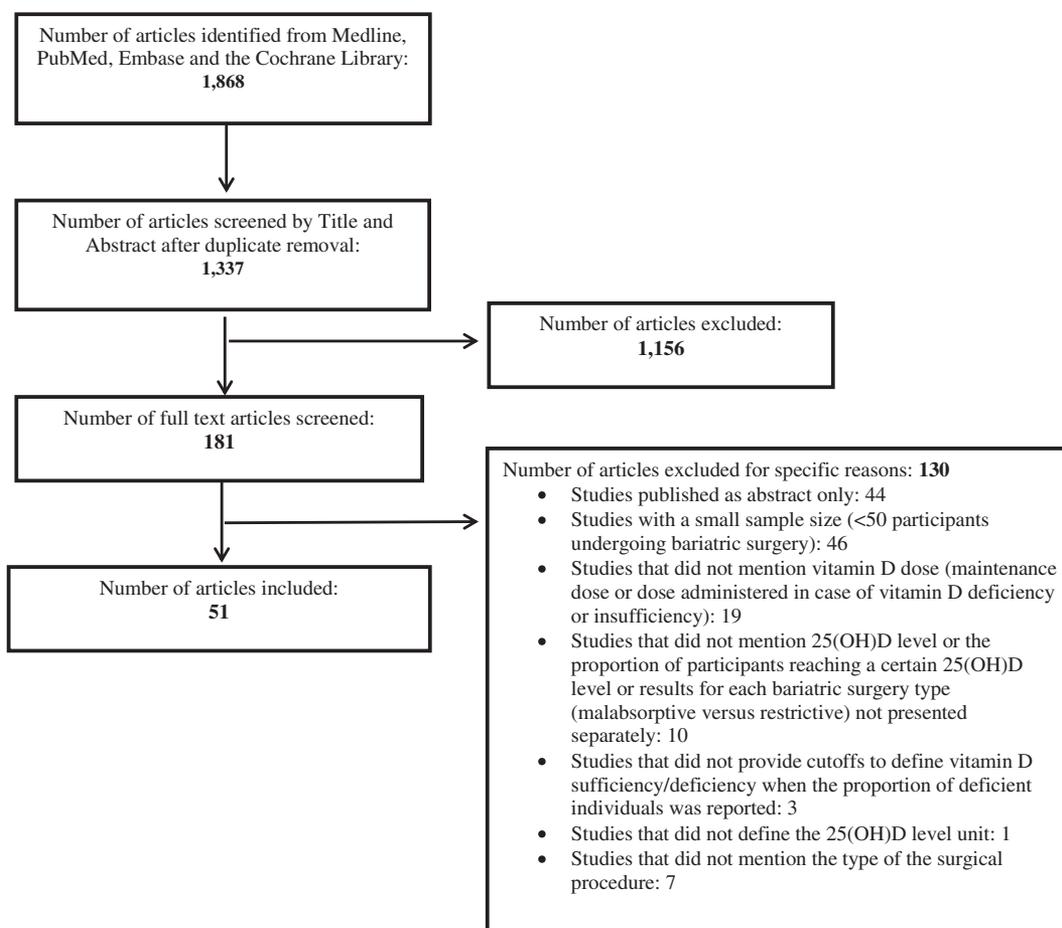- Studies that did not mention the type of the surgical procedure: 7

Fig. 1 – Flow diagram for study selection for the period 2000–2015. Following title and abstract and full text screening, 51 articles were included in the systematic review.

and the dose range of vitamin D supplementation. Only eight studies showed a mean 25(OH)D level > 30 ng/ml at 6 to 24 months post operatively [51,52,60,66,69,73,75,80]. Thirteen studies showed a mean 25(OH)D level < 20 ng/ml at 6 months to 11 years post operatively [51,54,55,64,78,85–92]. The remaining studies, almost half, reported a 25(OH)D level between 20 and 30 ng/ml [53,56–59,62,67–71,76,77,79,93–100].

3.3.   Vitamin D Supplementation Dose and Response in Bariatric Surgery

There was a high variability in vitamin D supplementation regimens administered post operatively, including enteral and parenteral preparations, daily and intermittent schedules (i.e. weekly, biweekly, monthly or every 3 months), and a wide range of equivalent daily doses, from 200 IU [57] to 28,500 IU [54]. Several studies used additional supplemental regimens in subjects who were deficient, as shown in Fig. 3 and detailed in the Appendix. The timing of 25(OH)D status assessment also varied, from as early as 3 months [58–68], to as late as 11 years post operatively [87].

3.3.1.   Dose Response Between the Administered Vitamin D Dose and the Increments in Serum 25(OH)D Levels
Thirty studies evaluated 25(OH)D level before and after bariatric surgery, at 3 months to 10 years post-operatively. Fig. 3 represents mean 25(OH)D level in studies that included at least 50 participants in each surgical procedure group, and that assessed 25(OH)D status pre and 1 year post operatively. There was a trend for larger increments in mean 25(OH)D levels with higher doses. However, these increments were not consistently in concordance with the dose administered, and the statistical significance of the change in 25(OH)D level was not assessed in all the studies (Fig. 3, see Appendix for studies not represented on Fig. 3).

Starting at a mean baseline 25(OH)D level of 13–25 ng/ml, the change in 25(OH)D level did not exceed 8 ng/ml at 6 to 12 months post operatively, even with daily dosing up to 2000 IU daily [51,56,58,63,70,71,79,94] (Fig. 3, Appendix), with only one exception [57] (Appendix). Furthermore, 25(OH)D level did not change [67,68,76] or even decreased [64,72,78] in several studies at one year follow up, despite supplementation (equivalent daily dose range 200–800 IU) (Fig. 3, Appendix). Avgerinos et al. showed an initial increase followed by a
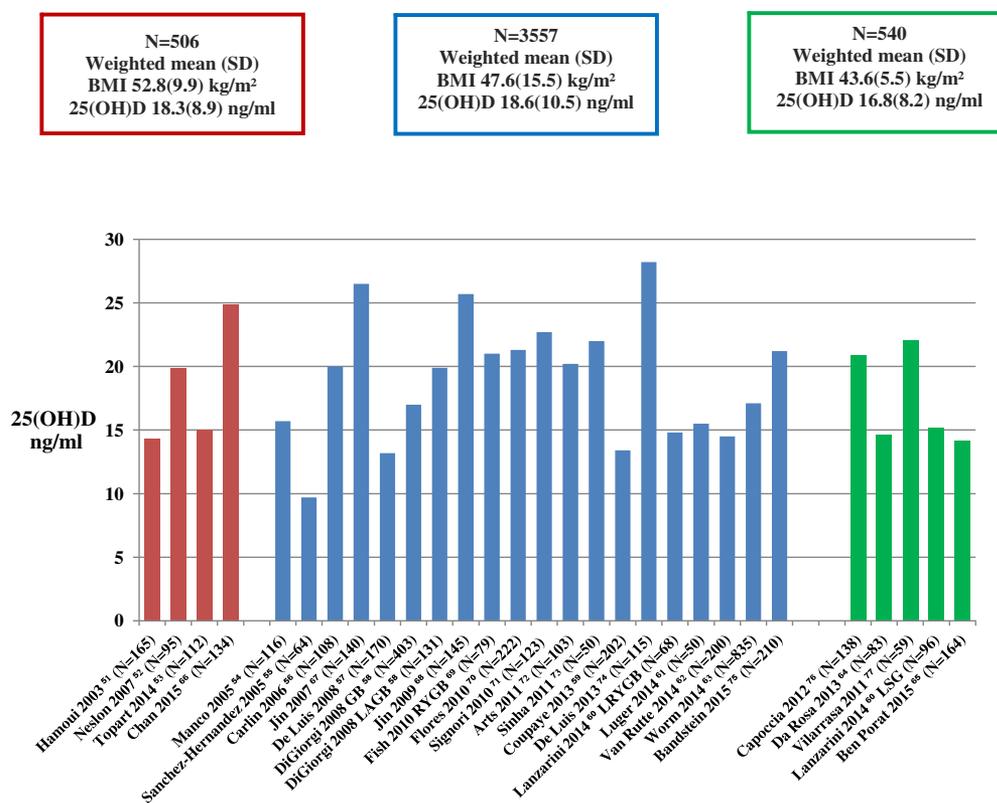
Fig. 2 – Mean 25(OH)D level (ng/ml), by BMI categories, before bariatric surgery in observational studies. Studies represented are those that have a number of participants of at least 50 per study sub-group. Surgical procedures include malabsorptive and combination procedures, except DiGiorgi 2008, Laparoscopic Adjustable Gastric Banding arm [58], Lanzarini 2014, Laparoscopic Sleeve Gastrectomy (LSG) arm [60], Capoccia 2012, LSG arm [76], Van Rutte 2014, LSG arm [62], Ben Porat 2015, LSG arm [65]. Red bars represent studies with mean BMI ≥50 kg/m^2; blue bars represent studies with mean BMI between 45 and 50 kg/m^2; green bars represent studies with mean BMI ≤ 45 kg/m^2. The difference between the weighted mean 25(OH)D levels in BMI categories was not clinically significant and did not show a decrease in 25(OH)D level with increasing BMI.

drastic decrease in 25(OH)D level at 1 year following RYGB, despite sustained vitamin D supplementation of 800 IU daily; findings that remain unexplained [80]. De Luis et al. showed an increase in mean 25(OH)D level of 15 ng/ml at 2 years after BPD, with administration of a small dose of vitamin D of 200 IU daily, followed by a decline and return to baseline level at 3 years [57]. Hamoui et al. assessed the effect of limb length in duodenal switch (DS) on 25(OH)D status, and demonstrated that a long common channel of 100 cm allowed a better improvement in 25(OH)D level at 18 months, compared to a short common channel of 75 cm (a difference in 25(OH)D level of 14.7 ng/ml between the 2 sub-groups at 18 months) [101].

Conversely, studies administering a maintenance vitamin D supplementation of 400–2000 IU daily, and additional doses to deficient and/or insufficient individuals (additional equivalent dose range 1100 IU–7100 IU, total daily dose received 1500–9100 IU), with the exception of Fish et al. [69], consistently demonstrated an increase in mean 25(OH)D level of 9–13 ng/ml at six months [59] (Appendix), and at one year post operatively (Fig. 3) [52,60,62,66,73,75]. The mean baseline 25(OH)D level in this group of studies was 13–25 ng/ml.

3.3.2. *Relationship of Vitamin D Dose, Type of Bariatric Surgery, and Achievement of a Desirable 25(OH)D Level*

In studies where no vitamin D supplement was administered, mostly following RYGB procedures, the mean 25(OH)D level achieved post-operatively was in low to mid-teens, in ng/ml, across the board [55,86,87,102,103].

Three studies conducted on patients undergoing laparoscopic sleeve gastrectomy (LSG) surgery suggest that a vitamin D dose less than 1000 IU/d may not be sufficient to raise mean levels to above the desirable value of 20 ng/ml, even in restrictive procedures [76,81,90].

Studies of malabsorptive or combination procedures, with supplementation up to 2000 IU of vitamin D daily, achieved mean 25(OH)D levels at or above 20 ng/ml, provided mean levels did not start below such cutoff pre-operatively [67,68,70,71,76,79,80,90,94,104]. When baseline 25(OH)D level was <20 ng/ml, three studies showed an increase in mean 25(OH)D level to above the target [57,58,63], while three others did not [51,64,78].

Conversely, two studies that involved biliopancreatic diversion (BPD) and that administered very high doses of
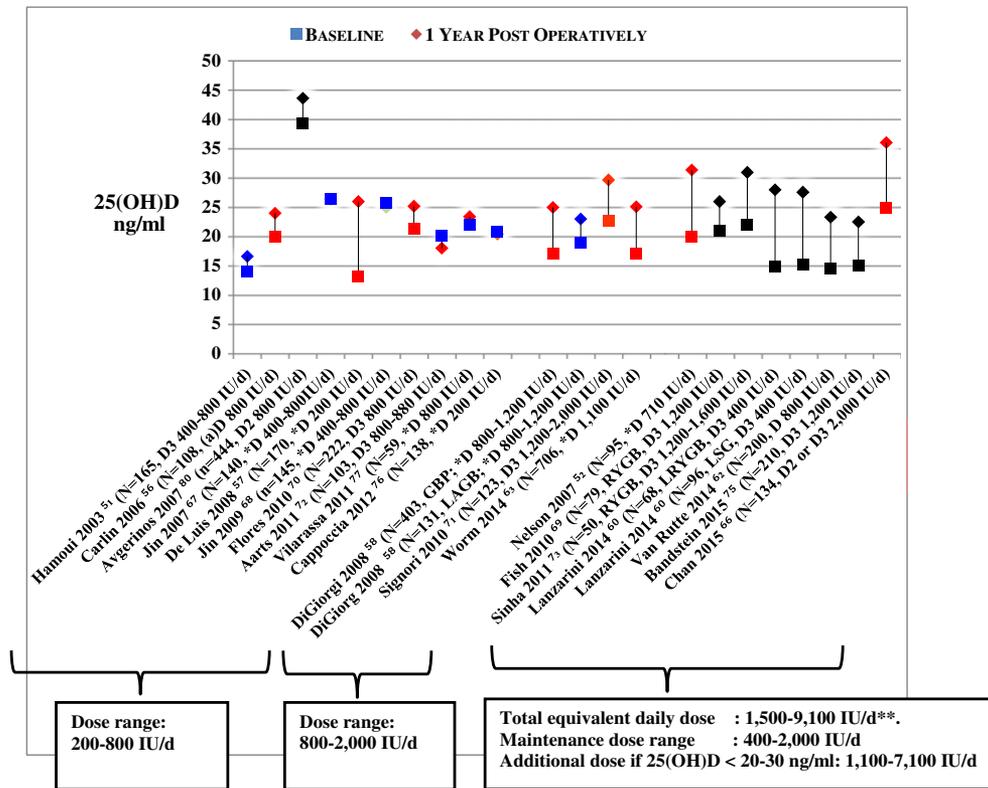
Fig. 3 – Mean 25(OH)D level before and 1 year after bariatric surgery in observational studies. Studies represented are those that have a number of participants of at least 50 per study subgroup. Surgical procedures include malabsorptive and combination procedures, except DiGiorgi 2008, Laparoscopic Adjustable Gastric Banding arm [58], and Capoccia 2012, Laparoscopic Sleeve Gastrectomy arm [76]. Studies were divided according to vitamin D supplementation dose range. All subjects were allocated vitamin D supplementation post operatively at various doses, as mentioned in the figure; for full details see Appendix. 25(OH)D status following supplementation showed a trend for a larger increase in 25 (OH)D level with higher vitamin D supplementation doses. The red color indicates a significant change in 25(OH)D level following bariatric surgery. The blue color indicates a non-significant change in 25(OH)D level. The black color indicates that statistical significance of the change in 25(OH)D status was not reported in the individual study.*Type of vitamin D not provided.**Excluding Fish et al.

vitamin D (6472 IU/d in one and the equivalent of 28,571 IU/d in another) showed mean 25(OH)D to remain in the low to mid-teens 5 years post-operatively [54,92].

Finally, studies that administered vitamin D, as a maintenance dose to all participants (≤2000 IU daily), and additional doses (range of equivalent daily doses: 1100–7100 IU, total daily dose received 1500–9100 IU) to vitamin D deficient/insufficient individuals, following malabsorptive and combination procedures, achieved a mean 25(OH)D level above 20 ng/ml in five studies, with mean baseline 25(OH)D level 13–21 ng/ml [53,59,62,69,100], and above 30 ng/ml in six studies, with mean baseline 25(OH)D level 15–25 ng/ml [52,60,66,69,73,75] (Fig. 3 and Appendix).

Assuming normality of the distribution of 25(OH)D levels, and considering studies of malabsorptive and combination procedures, we estimated that the proportion of participants achieving the target 25(OH)D level of 20 ng/ml, increased from 14% to 67% to 63%–76%, on vitamin D doses of up to 2000 IU daily [57,58,63,67,70,71,77,93,104]. These proportions increased from 25% to 55% at baseline, to 70%–93% at study completion, in studies administering replacement doses as

add-on to the vitamin D maintenance regimen in vitamin D deficient individuals [52,53,59,60,62,69,73,75].

3.4. Comparative Effect of Restrictive Versus Malabsorptive and Combination Procedures on 25(OH)D Status in Individuals Undergoing Bariatric Surgery

We identified only five studies comparing 25(OH)D status before and after vitamin D supplementation, in restrictive versus malabsorptive or combination procedures, within the same study, and we could not identify the emergence of a consistent trend in results (Table 1). DiGiorgi et al. compared 25(OH)D levels following RYGB versus Laparoscopic Adjustable Gastric Banding (LAGB) in subjects who received vitamin D 800–1200 IU daily and found no significant difference in mean levels both at 1 and 2 years post operatively, between the two groups [58]. Similarly, Lanzarini et al. compared prospectively LSG versus Laparoscopic Roux-en-Y gastric bypass (LRYGB) patients, when all participants received the same dose of vitamin D supplementation for a 6-month duration. A significantly higher 25(OH)D level in LSG

Table 1 – Mean 25(OH)D level following restrictive procedures compared to malabsorptive and combination procedures within the same study, with or without vitamin D supplementation, in observational studies (prospective, retrospective and cross sectional).

Author Year	Study design N*/surgery type	Vitamin D assay	Vitamin D Dose	25(OH)D at baseline (ng/ml)		25(OH)D following bariatric surgery (ng/ml)		Authors conclusion
				Mean (SD) or median (range)	Below cutoff %	Mean (SD) or median (range)	Below cutoff %	
DiGiorgi 2008 [58]	Prospective 403 GBP 131 LAGB	NA	All participants received vitamin D 800–1200 IU/d [a]	GBP: 17(8) LAGB: 19(9) [b]	< 20 GBP: 67% LAGB: 58%	At 12 mo: GBP: 25(12); LAGB: 23(9) At 24 mo: GBP: 24(12); LAGB: 25(10) → No difference between groups. [c]	< 20 At 12 mo: GBP: 37%; LAGB: 37% At 24 mo: GBP: 40%; LAGB: 33%	Same vitamin D requirements may be needed in both groups.
Coupaye 2009 [78]	Prospective 21 AGB 49 GBP	RIA	D3 500 IU/d in GBP only.	AGB: 13.4(8.6) GBP: 12.7(10.8) [c]	–	At 12 mo AGB: 11.9(4.2); GBP: 19.9(9.9) → Significantly higher mean 25(OH)D level in GBP compared to AGB. [c]	–	Results inconclusive.
Fish 2010 [69]	Retrospective 79 RYGB 48 LAGB	NA	All: Pre op: D3 50,000 IU 3 times/week for 1 month for deficient. Post op: D3 1200 IU/d [a,d]	LABG: 25(7–112) RYGB: 21(6–45) [b]	< 30 LABG: 75% RYGB: 88%	At 12 mo LABG: 32(12–53); RYGB: 26(5–49) → Significantly lower mean 25(OH)D level in RYGB compared to LABG. [b]	< 30 At 12 mo: LABG: 41%; RYGB: 63%	RYGB may require higher vitamin D supplementation dose.
Vilarrasa 2013 [79]	Prospective 33 RYGB 33 SG	ECLIA	D3 400 IU/d in SG and 400 + 800 IU/d in RYGB	RYGB: 20.1(8) SG: 17.6(8) [b]	–	At 12 mo RYGB 21.6(8.4); SG 20.1(7.2) → No significant difference between the 2 groups [b]	–	RYGB may require higher vitamin D supplementation dose.
Lanzarini 2015 [60]	Prospective 96 LSG 68 LRYGB	ECLIA	D3 400 IU/d Intervention group if 25(OH)D < 30 ng/ml at 3 or 6 mo follow up: D2 16,000 IU every 2 weeks; for a maximum of 6 mo	LSG: 15.2 (7.0) LRYGB: 14.8 (2.8) [c] Intervention group: LSG: 15.0(7.0); LRYGB: 12.8(6.7) [c] Non-intervention group: LSG: 15.7 (7.1); LRYGB: 18.4(9.9) [c]	–	At 12 mo LSG: 27.6 (16.6); LRYGB: 28.0 (14.2) Intervention group LSG: 28.0 (18.8); LRYGB: 28.8 (15.8) Non-intervention LSG: 26.8(11.4); LRYGB: 26.3 (10.6) At 24 mo LSG: 37.9 (18.4) LRYGB: 34.3 (19.0) Intervention group LSG: 41.0 (20.7); LRYGB: 39.0 (18.9) Non-intervention group LSG: 31.1 (9.1); LRYGB: 20.2 (11.0) → Significantly lower mean 25(OH)D in LRYGB only at 24 mo [c]	< 30 mg/ml At 12 mo Intervention group LSG: 67; LRYGB: 66 Non-intervention group LSG: 63; LRYGB: 62 At 24 mo Intervention group LSG: 27 LRYGB: 37 Non-intervention group LSG: 40; LRYGB: 78	RYGB may require vitamin D supplements for a longer duration.

Abbreviations: AGB: Adjustable Gastric Banding; ECLIA: Electrochemiluminescence based immune analysis; GBP: Gastric Bypass; LAGB: Laparoscopic Adjustable Gastric Banding; IU/d: International Unit per day; mo: months; NA: not available; RIA: Radioimmunoassay; RYGB: Roux-en-Y Gastric Bypass; SG: Sleeve Gastrectomy.

[a] Vitamin D type not specified.
[b] No significant difference in 25(OH)D level between the 2 groups, based on our own calculations using mean and standard deviation data provided in studies.
[c] No significant difference as provided in studies.
[d] Previously deficient individuals received additional vitamin D3 800–1600 IU daily.

compared to LRYGB was reported only at 2 years follow up [60]. A retrospective study showed lower 25(OH)D levels in RYGB compared to LAGB, when all participants received the same dose of vitamin D supplementation [69]. Coupaye et al. compared Adjustable Gastric Banding (AGB) to Gastric Bypass (GBP) procedures, and showed higher 25(OH)D levels in GBP patients [19.9 (9.9) ng/ml], compared to AGB patients [11.9 (4.2) ng/ml]; the GBP subgroup only received 500 IU of vitamin D3 daily [78]. Vilarrasa et al. showed no significant difference in 25(OH)D level between RYGB and Sleeve Gastrectomy (SG) groups when vitamin D supplementation doses were 800–1200 IU daily in the former group and 400 IU in the latter group [79]. Three other studies were not included in our discussion; the first one did not provide 25(OH)D levels [82], the second did not report the standard deviation of 25(OH)D level following intervention [73] and the third one did not administer vitamin D supplementation [86].

4.   Discussion

This systematic review underscores that all the literature describing 25(OH)D status pre and post-bariatric surgery comes from western populations, the United States and Europe. Data from non-western countries, which account for the fastest growing population worldwide, and for some of the fastest growing rates of obesity, are lacking.

Mean 25(OH)D levels in obese individuals before bariatric surgery were consistently below 30 ng/ml, and for almost half the studies at or below 20 ng/ml. Following bariatric surgery, mean 25(OH)D levels remained <30 ng/ml, despite various vitamin D supplementation regimens, with the exception of few studies where vitamin D deficiency was corrected using vitamin D replacement equivalent daily doses of 1100–7100 IU, as add-on to the maintenance dose of 400–2000 IU daily usually administered to all the study participants (total equivalent daily dose 1500–9100 IU). Studies using such regimens showed a substantial increase in mean 25(OH)D level, of 9–13 ng/ml, and allowed to the majority of the study population to reach the desirable 25(OH)D level of 20 ng/ml [52,60,62,66,73,75], as recommended by the Institute Of Medicine (IOM) [37].

Although the increments in mean 25(OH)D levels following supplementation tended to parallel the increase in the vitamin D dose (Fig. 3), they still remained below the expected range of increments, of 0.7–1 ng/ml for each 100 IU of vitamin D, depending on the baseline 25(OH)D level [105].

It is speculated that patients undergoing restrictive procedures would require less vitamin D supplementation, compared to malabsorptive and combination procedures, since the intestinal area responsible for vitamin D absorption is preserved in the former procedures [21]. However, the limited and inconsistent data available herein do not validate such expectations (Table 1). Two small randomized controlled trials administered the same vitamin D supplementation dose to SG and RYGB patients. They showed a significantly higher 25(OH)D level in SG groups, compared to RYGB groups, following 1 year of vitamin D supplementation [106,107]. Indeed, starting with a baseline 25(OH)D level of 20.1–

24.3 ng/ml and with a supplementation dose of 600 IU daily, the difference in 25(OH)D levels achieved was 13 ng/ml in one study [106]. Conversely, with a similar baseline 25(OH)D level of 21.1–21.7 ng/ml, and a larger supplementation of 3333 IU (daily equivalent dose), the difference was only of 1.5 ng/ml [107].

Our findings show that there is a high variability in the response to vitamin D supplementation in individuals undergoing bariatric surgery. In fact, in addition to the known predictors affecting the 25(OH)D level achieved in the general population, including baseline 25(OH)D levels and vitamin D dose, the effect of other predictors, specific to the bariatric surgery population, remains unknown. These predictors include: the amount of body fat in each patient, the type of surgery and the degree of malabsorption following surgery. Therefore, it may be difficult to recommend one vitamin D dose that would be optimal to all, and an individualized approach seems reasonable. Indeed, following malabsorptive and combination procedures, monitoring of 25(OH)D level to assess the response to therapy has been recommended by the Endocrine Society and the American Association of Clinical Endocrinologists (AACE)/The Obesity Society (TOS)/American Society for Metabolic and Bariatric Surgery (ASBMS) guidelines on the perioperative care of patients undergoing bariatric surgery [108,109]. While bi-annual monitoring was recommended by the ES guidelines [108], monitoring at 1, 3, 6 and 12 months was recommended by the AACE/TOS/ASBMS guidelines [109]. Noteworthy, vitamin D doses as high as 9000 IU daily have been used following bariatric surgery (Appendix), and similar to doses up to 10,000 IU daily used in the general population, such doses have been shown to be safe [110,111]. Vitamin D toxicity did not occur until 25(OH)D level exceeded 100 ng/ml [110,111]. Active vitamin D supplementation is not recommended to patients undergoing bariatric surgery, but it has been suggested, exceptionally, in refractory cases with symptomatic hypocalcemia [108,109].

4.1.   Strength and Limitations

This is the first extensive systematic review of four major medical literature databases, addressing 25(OH)D status in patients undergoing bariatric surgery. One previous systematic review by Compher et al., published in 2008, was limited to only one database, PubMed. It showed a high prevalence of hypovitaminosis D pre and postoperatively, with no specific information on vitamin D supplementation dose, response to therapy, or analysis by type of surgery [112]. Several other reviews summarize the available evidence on various nutrient deficiencies following bariatric surgery, but none of them focused specifically on vitamin D nutritional status [20,21,34,113].

Although randomized controlled trials (RCTs) represent the highest quality of evidence, these are difficult to implement and take a long time to complete. Furthermore, they are quite expensive and in this specific instance, considering that the drug to be used is regular vitamin D, they also do not provide interest for pharma sponsored trials. Thus observational studies provide the initial basis and the best readily available evidence to assess and to establish correlations between predictors and surrogate outcomes, as well as other important major outcomes [114]. Therefore, while awaiting

the results of a systematic review of RCTs, our paper presents a thorough and updated overview of the available literature relevant to this topic to-date.

Our review has several limitations. We did not systematically assess the quality of the included studies, but we have described, in detail, the current available evidence. Our results are derived from observational studies, with the known drawbacks of difficulty in sorting out confounding factors, and most noteworthy, assessing compliance issues. In fact, only 6 studies presented details on participants' compliance to vitamin D supplementation (Appendix). Furthermore, information related to vitamin D supplementation dose, type (D2 vs D3) and the exact duration of supplementation was lacking in many reports. Details on 25(OH)D assay were missing in some studies, and even when mentioned, the information obtained was limited by the wide variations in levels obtained with the various assays [115,116]. Seven studies used the more reliable high pressure liquid chromatography (HPLC) assay to measure 25(OH)D level (Appendix) [57,59,64,66,75,87,88] and only one study used the gold standard Liquid Chromatography Mass Spectrometry (LCMS) [52]. Finally, the timing of 25(OH)D level measurement differed between studies, which may affect the 25(OH)D level reached. In fact, a transient increase in 25(OH)D level by 2–4 ng/ml in the early post-operative phase (at 1 to 6 months) has been demonstrated, without vitamin D supplementation, an increase that was explained to occur due to the mobilization of 25(OH)D from adipose tissue [117]. However, others concluded that the contribution of fat mass to serum 25(OH)D level may not be significant, as the increase in 25(OH)D level falls within the coefficient of variation of the 25(OH)D assay [118]. Indeed, the higher compliance and the strict follow up in the immediate post-operative phase could explain, at least in part, such early transient improvement in vitamin D status.

Our findings shed light on the lack of high quality evidence, needed to define the optimal vitamin D dose needed in the bariatric surgery population. Furthermore, the role of vitamin D supplementation in improving patient important outcomes such as BMD, fracture prevention, cardiovascular benefits or others, in this population remains unknown.

5. Conclusion

Based on evidence derived from observational data, mean 25(OH)D level remains less than 30 ng/ml, before and after all types of bariatric surgery, and for several studies it is below 20 ng/ml, despite various vitamin D supplementation regimens. In addition to the maintenance dose, vitamin D replacement in insufficient and deficient individuals, using equivalent daily doses of 1100–7100 IU, is needed in order to allow for the majority of the population to reach a desirable 25(OH)D level of 20 ng/ml. The effect of the surgical procedure, restrictive versus malabsorptive, on the vitamin D dose response is inconsistent. Indeed, these findings have several limitations, related to the inherent drawbacks of observational studies, confounding factors and compliance problems.

Further research is needed to determine the optimal dose of vitamin D supplementation and replacement in individuals undergoing bariatric surgery, and whether this dose varies according to the surgical procedure.

Authors' roles

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Declaration of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.metabol.2015.12.004.

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