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ORIGINAL ARTICLE

The effect of bariatric surgery on serum 25-OH vitamin D levels: a systematic review and meta-analysis

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Summary

Background

Concerns have emerged about post-operative decreases in calcium and vitamin D following bariatric surgery. This review explores changes in metabolic bone health in persons with obesity undergoing gastric bypass surgery compared to non-surgical controls, providing an updated and comprehensive perspective on the literature.

Methods

An electronic search was conducted in MEDLINE, Pubmed, EMBASE and Cochrane databases to 8 November 2016. Eligible trials included randomized controlled trials or controlled observational studies of patients who have undergone laparoscopic gastric bypass surgery. Statistical analysis was carried out using the Cochrane Collaboration Review Manager (RevMan 5.0), and a random effects model was implemented. Outcomes were expressed as weighted mean difference (WMD). The primary outcome examined was change in 25-OH-D levels at 12 months post surgery, and secondary outcomes included change in bone mineral density (BMD) measurements at 12 months post surgery at the lumbar spine (LS) and total hip (TH).

Results

At 12 months, there was no significant difference in 25-OH vitamin D in the surgical group compared to controls (WMD = 6.79%; 95% CI: −9.01, 22.59; $p = 0.40$; $I^2 = 68\%$). There was no statistically significant difference between fracture risk in the surgical population compared to controls (RR = 1.24; 95% CI: 0.99, 1.56; $p = 0.06$; $I^2 = 0\%$). A significant BMD reduction was however shown at the TH (WMD, −7.33%, 95% CI = −8.70 to −5.97, $p < .001$, $I^2 = 0\%$), and a trend towards decline was observed at the LS (WMD, −1.73%, 95% CI = −3.56 to 0.11, $p = 0.06$, $I^2 = 0\%$). Changes at 24 months for applicable outcomes were similar to the results at 12 months.

Conclusions

Bariatric surgery may compromise metabolic bone health, but the paucity of high-quality literature limits conclusions.

Keywords: Bariatric surgery, metabolic bone disease, osteoporosis, vitamin d.

Introduction

The goal of bariatric surgery is to enhance weight-loss through either differential changes in gut hormones, restriction or a combination of the two. One particular complication of bariatric surgery, especially the malabsorptive surgeries, is 25-hydroxyvitamin D [25(OH) D] deficiency. (1) Persons with obesity often have predisposing metabolic bone disease because of physiological and lifestyle-related issues (2,3). Even before surgery, persons with obesity may have low levels of serum 25-hydroxyvitamin D because of nutritional deficiencies (4). This is worsened by the decreased bioavailability of 25-hydroxyvitamin D because of its sequestration in the additional adipose tissue. (3) Lifestyle factors also play a role. Because of a more sedentary

lifestyle and a tendency to wear clothes that cover more skin, these patients have lower sun exposure (2). After bariatric surgery, the decreased amount of skin and malabsorptive changes further can exacerbate this hypovitaminosis. (3) As a result of decreased 25-hydroxyvitamin D levels, subsequent hypocalcemia and secondary hyperparathyroidism can further compromise bone health. In one study with solely post-operative calcium and 25-hydroxyvitamin D supplementation, 25% of patients develop calcium deficiency after 2 years and 48% after 4 years despite replacement. As well, 25-hydroxyvitamin D deficiency was present 52 and 63% of patients, respectively (5,6).

The most recently published systematic review assessing changes in 25-hydroxyvitamin D levels in bariatric surgery patients was in 2014 (7). A range of new research in the form of observational studies and randomized controlled trials has been published since then, thus the rationale for this updated review (8). Additionally, this systematic review aims to encompass a range of secondary outcomes including changing PTH levels, BMD and incidence of fractures post-bariatric surgery. Overall, our review addresses more recent literature and a more expansive range of outcome measures. This should provide a more complete and more clinically useful assessment of metabolic bone health in these patients, guiding a multidisciplinary framework for their pre-operative and post-operative medical care. In particular, healthcare practitioners can use this information when providing dietary recommendations and nutrient supplementation.

In this review, the following clinical question is posed: In persons with obesity undergoing gastric bypass surgery for weight loss, is there a significant decline in serum 25-OH vitamin D levels measured at 3, 6 and 12 months post-operatively compared to patients who were referred for bariatric surgery, but were not surgical candidates, or chose to not proceed with the procedure?

Methods

Search strategy

This systematic review adhered to the recommendations by the Cochrane collaboration. A comprehensive literature search for relevant randomized controlled trials and controlled observational trials was conducted of three primary electronic databases: PubMed, EMBASE and MedLine. A broad search strategy (Tables 1 and 2) was used to capture all eligible patients with terms such as obesity, weight loss, weight reduction and body weight. Furthermore, a variety of search terms were used to include all weight-loss interventions such as bariatric surgery, gastric bypass, gastrectomy, Roux-en-Y, gastric sleeve and bariatric medicine. Finally, the examined outcomes included 25-hydroxyvitamin D, osteoporosis, parathyroid hormone, bone mineral density (BMD), frailty and bone fractures.

As part of the Gray Literature search, the Cochrane Central Register of Controlled trials and www.clinicaltrials.gov were searched to capture recent and ongoing clinical trials not included in the three primary electronic databases. In addition, the abstracts from the annual meetings of the American College of Rheumatology between 2010 and 2014 were manually searched to include studies that have not yet been published.

Inclusion and exclusion criteria

Studies were eligible for inclusion if they were randomized controlled trials or controlled observational trials published in English of patients who have undergone any form of bariatric surgery. Studies must have included patients over the age of 18 treated with bariatric surgery for weight loss compared to non-surgical controls with obesity. The intervention of interest is bariatric and/or metabolic surgery, including Roux-en-Y gastric bypass, and duodenal switch with or without biliopancreatic diversion. The primary outcome examined was change in serum 25-hydroxy (25-OH) vitamin D levels at 12 months follow-up period compared to baseline levels. Additionally, secondary outcomes included change in serum 25-hydroxy (25-OH) vitamin D levels at 24 months follow-up, incident self-reported fractures (any site) per patient year at 24 months follow up, change in total hip (TH) BMD at 12 and 24 months follow-up and change in lumbar spine (LS) BMD at 12 and 24 months follow-up. Authors were contacted when necessary for additional information on study methodology and insufficient or missing data.

Data screening and extraction

Two independent reviewers (AK and HB) assessed a total of 29,870 titles and abstracts retrieved from the search strategy to determine eligibility for full-text extraction. Disagreements were resolved by discussion at any stage of the review process or in the case where a consensus was not reached, a third independent rater (AL) determined eligibility. Ultimately, seven studies were chosen for full-text screening. Using a piloted standardized tested data collection form, data were extracted from the selected studies including study characteristics (authors, journal, year of publication, country or origin), study design, participants, demographic information, types of intervention, types of comparison, types of outcome measures (both primary and secondary) and results.

Table 1 Embase search strategy

# ▲	Searches	Results	Search type	Actions
	1	body weight/	197720	Advanced Display More »
	2	exp bariatric surgery/ or Bariatric surg*.mp.	21910	Advanced Display More »
	3	(bariatric adj3 surgery).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	18272	Advanced Display More »
	4	bariatric medicine.mp.	22	Advanced Display More »
	5	exp bariatrics/	137	Advanced Display More »
	6	exp stomach bypass/	11402	Advanced Display More »
	7	exp gastrectomy/	39482	Advanced Display More »
	8	gastric bypass.mp.	10723	Advanced Display More »
	9	(gastric adj3 bypass).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	10844	Advanced Display More »
	10	exp Roux Y anastomosis/ or roux-en-y.mp.	12355	Advanced Display More »
	11	(gastric adj3 sleeve).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	994	Advanced Display More »
	12	(weight adj2 loss adj2 surgery).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1392	Advanced Display More »
	13	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	65605	Advanced Display More »
	14	exp obesity/	309678	Advanced Display More »
	15	exp morbid obesity/	12854	Advanced Display More »
	16	weight reduction.mp. or exp weight reduction/	107233	Advanced Display More »
	17	weight loss.mp.	81146	Advanced Display More »
	18	exp body weight/	427097	Advanced Display

Continues

Table 1. *Continued*

# ▲	Searches	Results	Search type	Actions
	19	14 or 15 or 16 or 17 or 18	672957 Advanced	More » Display
	20	exp surgery/	3475571 Advanced	More » Display
	21	exp surgical technique/	1073365 Advanced	More » Display
	22	exp bariatrics/	137 Advanced	More » Display
	23	su.fs.	1715829 Advanced	More » Display
	24	20 or 21 or 22 or 23	3919154 Advanced	More » Display
	25	19 and 24	107828 Advanced	More » Display
	26	13 or 25	149526 Advanced	More » Display
	27	exp osteoporosis/ or osteopor*.mp.	114132 Advanced	More » Display
	28	exp osteopenia/	12939 Advanced	More » Display
	29	exp bone disease/	819316 Advanced	More » Display
	30	exp metabolic bone disease/	119632 Advanced	More » Display
	31	("25" adj3 hydroxy adj3 vitamin adj3 d).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	1681 Advanced	More » Display Delete
	32	exp vitamin D/ or vitamin d.mp.	108209 Advanced	More » Display
	33	exp hyperparathyroidism/ or hyperparathyroid*.mp.	32123 Advanced	More » Display
	34	parathyroid hormone.mp. or exp parathyroid hormone/	55548 Advanced	More » Display
	35	pth.mp.	24902 Advanced	More » Display
	36	(parathyroid adj3 hormone).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]	55597 Advanced	More » Display More »

Continues

Table 1. *Continued*

# ▲	Searches	Results	Search type	Actions
	37	bone fractures.mp.	5408	Advanced Display More »
	38	exp fracture/	207700	Advanced Display More »
	39	frailty.mp.	6303	Advanced Display More »
	40	27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39	947519	Advanced Display More »
	41	26 and 40	10221	Advanced Display More

Additionally, data extraction from published graphs was conducted using GraphClick (version 3.0.3) (9).

Data analysis

Statistical analyses were carried out in SPSS and the Cochrane Collaboration Review Manager (RevMan version 5.3.5). After the initial screening process, the Cochrane Collaboration's tool for assessing risk of bias and the Newcastle Ottawa Scale were applied to the randomized control trials and controlled observational studies, respectively (10,11). In order to measure any heterogeneity in the outcomes between studies, the chi-squared statistic was calculated. The level of agreement between the two reviewers, with regards to study selection, was measured using a Cohen's (unweighted) kappa statistic. For categorical outcome data, risk ratios (RR) were reported. For continuous outcome data, the weighted mean difference (WMD) was reported with 95% confidence intervals. Studies that reported continuous outcomes as median with an interquartile range (IQR) were transformed to mean and standard deviation (SD) using the method discussed in Wan *et al.* (12) A random effects model was implemented to conduct this meta-analysis, pooling the results from comparable studies.

Results

Study selection

Of the 12,246 articles retrieved from the initial search, as well as 17,676 records from the gray literature, and a thorough screen of the reference lists, seven studies were included in the review (Figure 1); five controlled observational and two randomized control studies. Studies were excluded at each stage for various reasons; 29,809 studies excluded after the title and abstract screen and 48 studies after the full-text screen. Reasons for exclusion at the full-text level are shown in Figure 1. Inter-rater agreement was 0.783 and 0.878 for the title and abstract, and full-text screen, respectively. Disagreements at the abstract and full-text screen stages were resolved by consensus, and the majority of studies were included to undergo screening at the following stage.

Study characteristics

A detailed description of study characteristics is presented in Table 3. A total of 4,282 bariatric surgical recipients were included in this study, the majority of whom were women (n = 3,153), and 15,630 controls. Age of the individuals included in these studies varied with the mean or median age above 40 in six of the seven studies. All patients were obese with baseline BMI $>$ 30, of which the cohorts from four of seven studies met criteria for extreme obesity with baseline BMI $>$ 40. Study publication years varied from 2004 to 2015 with six of seven studies having been published in the past 5 years.

Overall, the risk of bias in the seven included studies was low with neither the RCTs nor the included observational studies being assigned a high risk of bias (Tables 4 and 5).

Results of the meta-analysis

Effect of bariatric surgery on 25-hydroxyvitamin D *levels*

We were able to utilize data from three studies in total to compare differences in 25(OH)D levels,

Table 2 Medline search strategy

# ▲	Searches	Results	Search type	Actions
	1	exp Bariatric Surgery/ or Bariatric surg*.mp.	18677	Advanced Display More »
	2	exp Bariatrics/	16485	Advanced Display More »
	3	(bariatric adj3 surgery).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	9015	Advanced Display Delete More »
	4	Gastric Bypass/	5703	Advanced Display More »
	5	(gastric adj3 bypass).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	7934	Advanced Display Delete More »
	6	exp Gastrectomy/	26982	Advanced Display More »
	7	Bariatric medicine.mp. or exp Bariatric Medicine/	45	Advanced Display More »
	8	roux-en-y.mp. or exp Anastomosis, Roux-en-Y/	7541	Advanced Display More »
	9	(gastric adj3 sleeve).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	326	Advanced Display Delete More »
	10	(weight adj2 loss adj2 surgery).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	921	Advanced Display Delete More »
	11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	48954	Advanced Display More »
	12	exp Obesity/	154629	Advanced Display More »
	13	exp Obesity, Morbid/	12244	Advanced Display More »
	14	exp Weight Loss/	31057	Advanced Display More »
	15	weight reduction.mp. or Weight Loss/	31873	Advanced Display More »
	16	exp Body Weight/	369750	Advanced Display More »
	17	12 or 13 or 14 or 15 or 16	374657	Advanced Display

Continues

Table 2. *Continued*

# ▲	Searches	Results	Search type	Actions
	18	surgery.mp.	955244	Advanced More » Display
	19	exp Surgical Procedures, Operative/	2498235	Advanced More » Display
	20	exp Bariatrics/	16485	Advanced More » Display
	21	su.fs.	1650057	Advanced More » Display
	22	18 or 19 or 20 or 21	3352128	Advanced More » Display
	23	17 and 22	47318	Advanced More » Display
	24	11 or 23	83117	Advanced More » Display
	25	Osteoporosis/ or osteopor*.mp.	69200	Advanced More » Display
	26	exp Osteoporosis/	46554	Advanced More » Display
	27	osteopenia.mp. or exp Bone Diseases, Metabolic/	67671	Advanced More » Display
	28	("25" adj3 hydroxy adj3 vitamin adj3 d).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	1054	Advanced More » Display Delete
	29	exp Vitamin D/ or Vitamin D.mp.	63507	Advanced More » Display
	30	parathyroid hormone.mp. or exp Parathyroid Hormone/	36772	Advanced More » Display
	31	exp Hyperparathyroidism/ or hyperparathyroid*.mp.	27173	Advanced More » Display
	32	pth.mp.	18973	Advanced More » Display
	33	(parathyroid adj3 hormone).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]	36296	Advanced More » Display Delete
	34	bone fractures.mp. or exp Fractures, Bone/	147020	Advanced More » Display
	35	frailty.mp.	4567	Advanced More » Display

Continues

Table 2. *Continued*

# ▲	Searches	Results	Search type	Actions
	36	25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	306038	Advanced	More » Display
	37	**36 and 24**	**1636**	**Advanced**	More » Display
					More

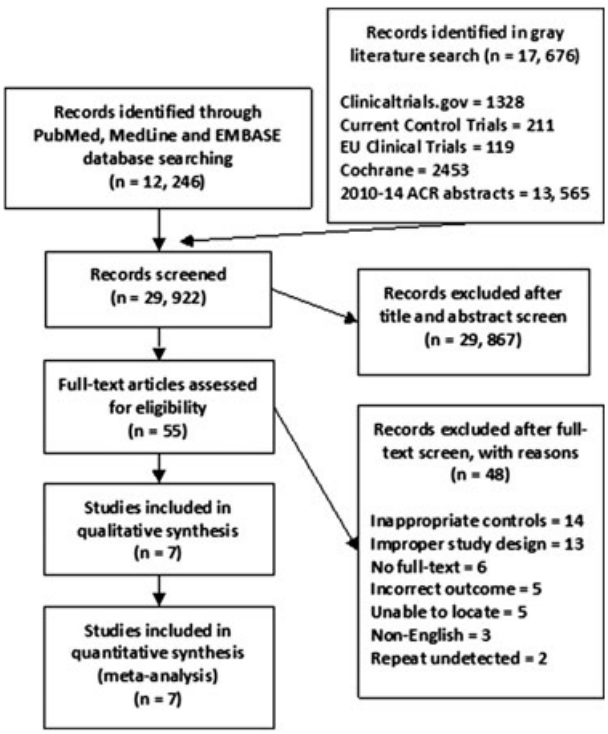

Figure 1 Flow diagram of study selection with number of studies included after each stage of screening process.

assessed by percent change from baseline, between bariatric surgery recipients and controls at 12 and 24 months (Aasheim *et al.*, 2012; Maghrabi *et al.*, 2015; Yu *et al.*, 2015) (13–15). At 12 months, no significant difference was found in 25(OH)D in the surgical group (n = 74) compared to controls (n = 58) (WMD = 6.79%; 95% CI: −9.01, 22.59; p = 0.40; I^2 = 68%) (Table 6, Figure 2). At 24 months, a similar finding of no significant difference between the surgical group (n = 40) and the control group (n = 28) was found (WMD = 51.60%; 95% CI: −36.18, 139.39; p = 0.25; I^2 = 88%) (Table 6, Figure 2).

Effect of bariatric surgery on self-reported fractures at 24 months post-surgery

Four studies (Ikramuddin *et al.*, 2015; Lalmohamed *et al.*, 2012; Lu *et al.*, 2015; Maghrabi *et al.*, 2015) were included that assessed incident self-reported fractures (any site) with the fracture outcome were measured by incident per patient year (16–18,14). Our data indicated a trend towards an increased fracture risk in the surgical population (n = 6,811) compared to controls (n = 25,285) (RR = 1.24; 95% CI: 0.99, 1.56; p = 0.06; I^2 = 0%) (Table 6, Figure 3).

Effect of bariatric surgery on total hip bone mineral density measurements

We were able to combine the results of two studies (Maghrabi *et al.*, 2015; Yu *et al.*, 2014) measuring total hip bone mineral density, as assessed by dual x-ray absorptiometry, at 12 and 24 months post-surgery compared to baseline measurements (14,15). At 12 months, the studies found a significant and negative difference in percent change in TH BMD in bariatric surgical recipients (n = 47) compared to controls (n = 35) (WMD = −7.33%; 95% CI: −8.70, −5.97; $p < .001$; I^2 = 0%) (Table 6, Figure 4). Similarly, at 24 months, a significant difference in percentage changes was found between the surgical group (n = 40) and the control population (n = 28) (WMD = −9.69%; 95% CI: −11.60, −7.78; $p < .001$; I^2 = 0%) (Table 6, Figure 4).

Effect of bariatric surgery on lumbar spine bone mineral density measurements

The results of three studies in total (Maghrabi *et al.*, 2015; von Mach *et al.*, 2004; Yu *et al.*, 2014) were included for the outcome of lumbar spine bone mineral density, as assessed by dual x-ray absorptiometry, at 12 and 24 months post-surgery (14,19,15). The studies examined percent change at 12 months in LS BMD in bariatric

Table 3 Study characteristics

Author (year)	Study design	Participants (*n*)	Gender composition (% female)	Age (years); median (IQR) or mean (SD)	Baseline BMI (kg m^{-2}); median (IQR) or mean (SD)	Type of surgery	Baseline vitamin D levels (ng ml^{-1}); median (IQR) or mean (SD)
Aasheim *et al.* (2012)	Prospective cohort	GB (27)	67	44 (36, 50)	46 (42, 50)	Laparoscopic RYGB	16.5 (11.9, 21.1)
		Control (23)	61	45 (35, 59)	40 (39, 44)		17.6 (13.6, 24.0)
Ikramuddin *et al.* (2015)	Randomized control	GB (60)	63	49 (9)	34.9 (3.0)	RYGB	—
		Control (59)	57	49 (8)	34.3 (3.1)		—
Lalmohammed *et al.* (2012)	Retrospective cohort	BS (2,079)	83.9	44.6 (11.1)	43.2 (7.2)	Gastric band, RYGB, other	—
		Control (10,442)	85.3	44.9 (11.2)	40.8 (6.4)		—
Lu *et al.* (2015)	Retrospective cohort	BS (2,064)	63.7	31.8 (9.2)	—	Sleeve gastrectomy, gastric bypass, other	—
		Control (5,027)	64.4	31.9 (9.9)	—		—
Maghrabi *et al.* (2015)	Randomized control	GB (18)	44.4	47.9 (9.7)	36.1 (2.6)	Laparoscopic RYGB	21.1 (18.9, 26.3)
		Control (17)	47.1	50.0 (8.4)	35.8 (3.0)		19.5 (16, 24.5)
Von Mach *et al.* (2004)	Prospective cohort	RYGB (4)	100	44.5 (4.8)	42.7 (2.2)	RYGB	—
		Control (6)	66.67	49.0 (2.9)	41.2 (1.2)		—
Yu *et al.* (2015)	Prospective cohort	RYGB (30)	87	47 (14)	45 (6)	RYGB	28 (11)
		Control (20)	89	46 (16)	45 (6)		24 (10)

Note: BS, bariatric surgery; GB, gastric bypass; RYGB, roux-en-Y gastric bypass.

Table 4 Risk-of-bias table for the randomized control trials*

Study	Random sequence generation	Allocation concealment	Blinding of participants, personnel and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other bias	Overall risk of bias
Ikramuddin *et al.* (2015)	Low	Low	Low	Low	Unclear	Unclear	Low
Maghrabi *et al.* (2015)	Low	Low	Low	Low	Unclear	Unclear	Low

*Risk of bias assessed using Cochrane risk-of-bias tool

surgical recipients (n = 47) compared to controls (n = 35) finding a trend towards a greater BMD reduction in the former group (WMD = −1.73%; 95% CI: −3.56, 0.11; p = 0.07; I^2 = 0%) (Table 6, Figure 5). A comparable trend was shown at 24 months between bariatric surgical recipients (n = 44) and controls (n = 35) (WMD = −5.18%; 95% CI: −10.84, 0.48; p = 0.07; I^2 = 86%) (Table 6, Figure 5).

Discussion

There are multiple mechanisms underlying the changes in bone health following bariatric surgery. Compared to nonsurgical weight loss, there are additional factors at play including decreased mechanical loading, nutritional deficiencies from differential changes in gut hormones, as well as accelerated bone turnover and elevated bone remodelling (20). These factors all lead to a decrease in bone mineral density, with a subsequent increased risk for fracturing. This meta-analysis is one of the first attempts at comprehensively analysing all these parameters. Here, there was no change in 25-hydroxyvitamin D levels, a trend towards increased fracture rates, and decreased BMD at the TH with a trend towards decreased BMD at the LS in bariatric surgery patients.

The lack of difference in 25-hydroxyvitamin D is not fully consistent with what has been previously observed in the literature, which may be due to the heterogeneity between studies. While Yu and Aasheim's studies both implemented the immunochemiluminometric assay, DiaSorin, measurement of 25-hydroxyvitamin D in Maghrabi's study and the parent STAMPEDE trial is unclear. Furthermore, the patient populations differ with

Table 5 Risk-of-bias assessment for cohort studies*

Study	Representativeness		Ascertainment of exposure	Demonstration that outcomes was not present at start of study	Comparability of cohorts on basis of design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Overall risk of bias
	Exposed cohort	Unexposed cohort							
Aasheim *et al.* (2012)	Truly representative†	Same community†	Secure record†	Not reported	Controlled for surgical eligibility	Independent assessment†	Yes (>1 year)†	<5% lost or description provided†	7
Lalmohammed *et al.* (2012)	Truly representative†	Same community†	Secure record†	Not reported	Controlled for baseline BMI	Independent assessment†	Yes (>1 year)†	>5% lost and no description given	6
Lu *et al.* (2015)	Truly representative†	Same community†	Secure record†	Yes†	Controlled for eligibility and baseline BMI	Independent assessment†	Yes (>1 year)†	>5% lost and no description given	8
von Mach *et al.* (2004)	No description given	No description given	Secure record†	Not reported	Controlled for baseline BMI	Independent assessment†	Yes (>1 year)†	Complete follow-up†	5
Yu *et al.* (2015)	Somewhat representative†	Same community†	Secure record†	Not reported	Controlled for baseline BMI	Independent assessment†	Yes (>1 year)†	<5% lost or description provided†	7

*Risk of bias assessed using a modified version of the Newcastle–Ottawa Scale. A higher overall score corresponds to a lower risk of bias.
†Item met assessment criteria.

respect to their geographic latitude. Higher latitudes are correlated with decreased sun exposure and consequently less UVB-mediated conversion of 7-dehydrocholesterol to 25-hydroxyvitamin D (21). Of the seven studies included in this review, study populations were from the United Kingdom, Rochester (USA), New York (USA), Minnesota (USA), Ohio (USA), Boston (USA), Taiwan and Basel (Switzerland). Although seasonal variations likely also play a role, they were not mentioned in these studies. Another important factor to consider is the differences in the aggressiveness of 25-hydroxyvitamin D supplementation post-bariatric surgery. One study in this review enforced 1,400 IU day^{-1} of 25-hydroxyvitamin D supplementation pre-operatively (14). Another study demonstrated different post-operative 25-hydroxyvitamin D supplementation between and within patient groups, revealing challenges with compliance to supplementation regimes (14). Finally, the last study excluded patients on bone-active medications – the specifics of which were not specified (15). Nevertheless, joint recommendations from the American Association of Clinical Endocrinologists (AACE), The Obesity Society (TOS) and the American Society for Metabolic and Bariatric Surgery (ASBMS) stress early supplementation with 25-hydroxyvitamin D – at least 3,000 IU per day – in persons with obese after bariatric surgery (22). They also recommend titrating 25-hydroxyvitamin D levels to therapeutic serum levels, with some patients needing dosages of at least 6,000 IU daily. The use of these supplementation strategies may have also contributed to our study's seeming incongruence with the anticipated deleterious changes in bone health in this patient population.

Similarly, while the data presented suggest an increase in fracture incidence in post-surgical bariatric patients, the literature is inconclusive. In general, the patients undergoing bariatric surgery are at relatively low risk for incurring osteoporotic fractures, largely based on their only modest declines in BMD and relatively young age. Therefore, in a low risk population, a very large sample size, very long follow-up duration or both are required to show a statistically significant difference in fracture incidence. Changes in BMD can be used as a surrogate outcome however to demonstrate an increase in fracture risk. One retrospective cohort study demonstrated an increase in the risk of fracture following surgery (23). Certainly, this is in keeping with the theoretical worsening in bone health, primarily 25-hydroxyvitamin D levels and BMD *t*-scores, following bariatric surgery. However, the literature is limited by a relatively short follow-up length. For example, one study in patients with primary hyperparathyroidism demonstrated no change in fracture incidence in patients 10 years post-operatively (24). With

Table 6 Summary of meta-analysis results

Outcome	Time point measured	No. of studies	Subjects; *n*		Effect estimate (95% CI)	I^2 value	Summary of differences
			Surgical recipients	Controls			
n	12 months	3	74	58	6.79* (−9.01, 22.59) $p = 0.40$	68%	No significant difference in vitamin D levels in GB recipients compared to controls
	24 months	2	40	28	51.60* (−36.18, 139.39) $p = 0.25$	88%	
Incident fracture per patient year	24 months	4	6,811	25,285	1.24** (0.99, 1.56) $p = 0.06$	0%	Trend towards increased risk of fracture in GB recipients compared to controls
Change in TH BMD	12 months	2	47	35	−7.33* (−8.70, −5.97) $p < .001$	0%	Significant reduction in BMD at TH in GB recipients compared to controls
	24 months	2	40	28	−9.69* (−11.60, −7.78) $p < .001$	0%	
Change in LS BMD	12 months	2	47	35	−1.73* (−3.56, 0.11) $p = 0.07$	0%	Trend towards decline in BMD at LS in GB recipients compared to controls
	24 months	3	44	35	−5.18* (−10.84, 0.48) $p = 0.07$	86%	

Note: GB, gastric bypass; LS, lumbar spine; TH, total hip.
*Effect estimate described by weighted mean difference.
**Effect estimate described as risk ratio.

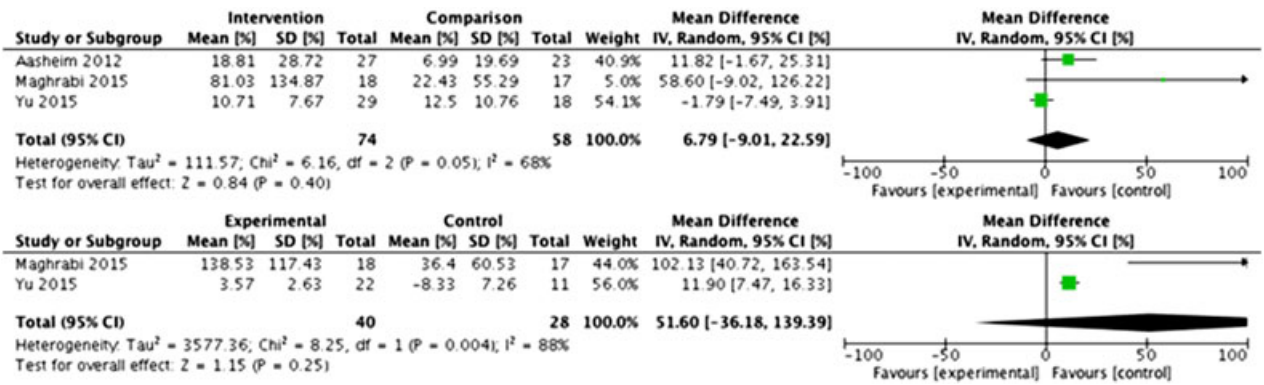

Figure 2 Effect of bariatric surgery on vitamin D levels at 12 (top) and 24 (bottom) months post surgery.

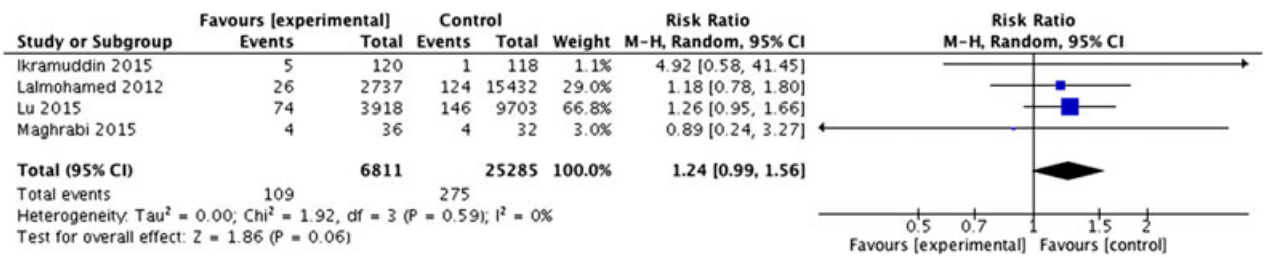

Figure 3 Effect of bariatric surgery on self-reported fractures at 24 months post surgery.

the theoretical secondary hyperparathyroidism in post-surgical bariatric patients, a follow-up period of this time may have produced more robust results. As well, some of the included studies measure self-reported fractures, while others required radiographic confirmation of fractures. This inconsistency in reporting makes it difficult

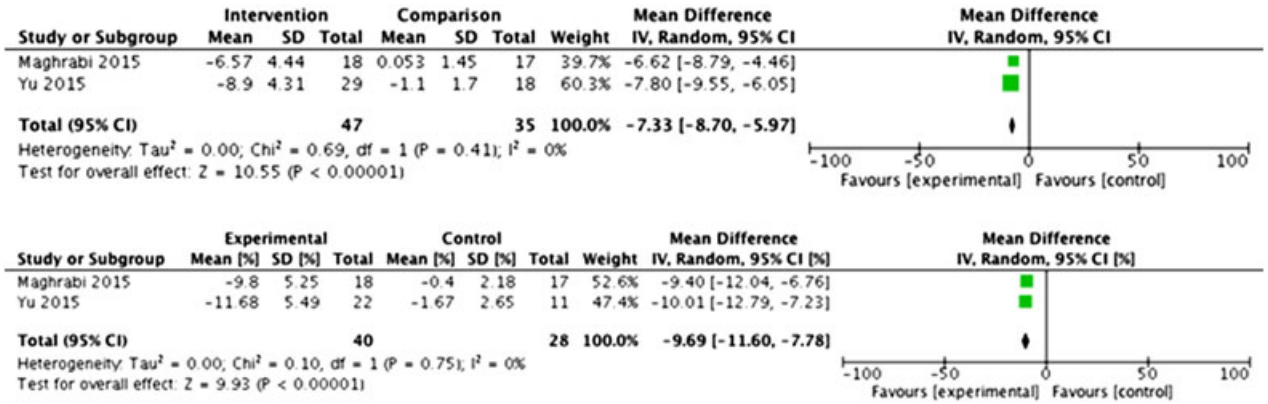

Figure 4 Effect of bariatric surgery on total hip (TH) BMD measurements at 12 (top) and 24 (bottom) months post surgery.

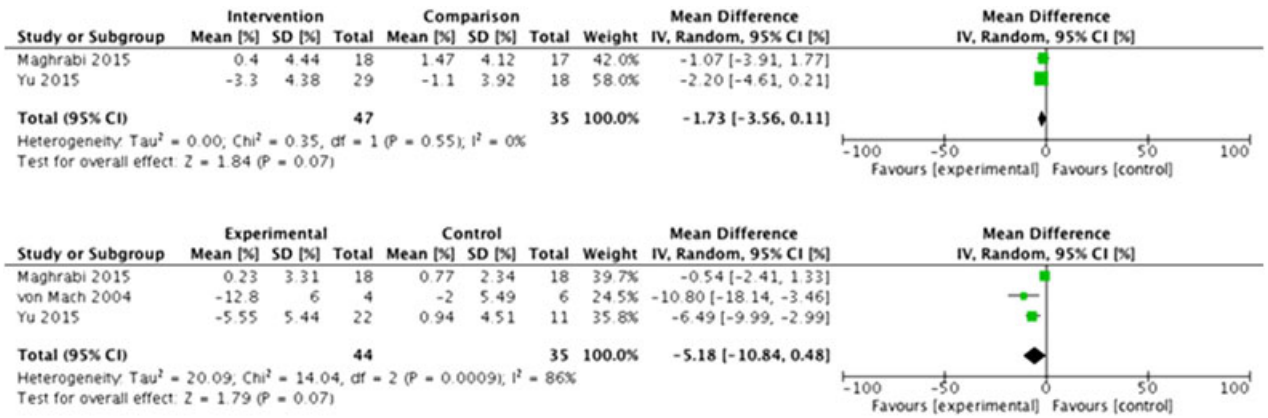

Figure 5 Effect of bariatric surgery on lumbar spine (LS) BMD measurements at 12 (top) and 24 (bottom) months post surgery.

to draw conclusions on fracture risk in bariatric surgery patients. This is also complicated by the fact that these patients are often still classified as still having obesity after surgery. While some studies suggest that low BMI may be protective for fracture risk, other studies suggest the opposite. (25) Interestingly, these relationships may vary based on the specific site of fracture. Osteoporotic fractures have predilections for certain sites as well so a comparison here is warranted (26). Importantly, the implications on fragility and frailty are not well documented in the literature.

Some of the data produced here – also reproduced elsewhere – suggests a trend towards a decrease in BMD after bariatric surgery. Currently, AACE/TOS/ASMBS state that patients for bariatric surgery should have BMD measurements at the lumbar spine and total hip before surgery and 2 years post-surgery (22). However, the Endocrine Society suggests that these patients need BMD measurements on an annual basis (27). This was reflected in the heterogeneity in the literature with follow-up ranging from 6 months post-operatively to 2 months with inconsistent measurements of pre-operative BMD. As mentioned previously, inconsistent standardization and reporting of usage of bone-active medications and pre-operative concentrations of 25-hydroxyvitamin D and calcium make it challenging to synthesize reported post-operative BMDs across studies. This is further limited by the small sample sizes. As a result, in order to develop a robust estimate, only the change in BMD 2 years post-operatively was presented. Some studies show that bone density continues to decrease after the first year post-operatively even after patients have lost their maximum weight (28). This stresses the importance of developing a consistent strategy to measuring BMD in these patients with comparison to non-surgical controls with obesity. Of course, optimizing 25-hydroxyvitamin D supplementation is intimately tied in here.

There are some limitations to this study worth noting. For one, there is clearly a paucity of high-quality evidence

in the area of metabolic bone disease in bariatric surgery patients. Although they were well performed, the studies included were mostly controlled observational studies with relatively small sample sizes. Despite a fairly robust literature search, there were a scarce amount of randomized controlled trials answering this important question. Perhaps, the challenge here lies in the growing popularity and proficiency in bariatric surgery techniques, making it more difficult to develop adequate populations of non-surgical controls with obesity. Although drawing conclusions here was restricted by the limited number of studies available, those selected have a low risk of bias. As a result, the strengths in the design and execution of this systematic review and meta-analysis implore further primary research and another look at this body of evidence in the near future.

Conclusion

With a large amount of bariatric procedures performed worldwide – now even expanding to patients with lower BMIs – it is imperative to better understand the potential negative effects of bariatric surgery on bone metabolism. Despite a very comprehensive search with good inter-rater reliabilities and sound methodology, only seven studies were deemed suitable for the final meta-analysis here. This paucity of high quality studies underscores a significant care and knowledge gap. There need to be appropriate screening protocols in place to detect 25-hydroxyvitamin D deficiency as well as ensure early and adequate supplementation. Recognizing some of these more vulnerable patients can help drive the implementation of pre-operative BMDs, especially given that a significant portion of these persons with obesity are already osteoporotic before surgery. (29) Follow-up BMDs post-operatively with standardized screening intervals and measurement protocols may also be helpful – currently, ASBMS only supports baseline DEXAs and post-operative scans in certain high-risk patients. (30) Implementation of a fracture prediction tool – such as Fracture Risk Assessment Tool (FRAX) and the Canadian Association of Radiologists and Osteoporosis Canada (CAROC) assessment tool – using clinical risk factors and BMD at the total hip can help identify the patients with an increased risk of fractures in the next 10 years; patients that additional pharmacologic and interdisciplinary resources can be focussed on. Ultimately, with the growing proportion of persons with obesity, osteoporosis and advanced age in our society, the medical and financial burden of these diseases independently and in tandem compel further research and better multidisciplinary care.

Disclosure

J.D.A. reports grants and personal fees from Amgen, grants and personal fees from Eli Lilly, grants and personal fees from Merck, grants from Actavis, personal fees from Agnovos, outside the submitted work. A.L. has previously had honorariums and has served as a speaker for Amgen and Eli Lilly. The rest of the authors have no conflicts to disclose.

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