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Changes in volumetric bone mineral density and bone quality after Roux-en-Y gastric bypass: A meta-analysis with meta-regression

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Summary

This meta-analysis aimed to assess the effect of Roux-en-Y gastric bypass (RYGB) on three-dimensionally assessed volumetric bone mineral density (vBMD) with the effect of time on these changes, on bone quality, and the agreement of dual-energy X-ray absorptiometry (DXA) with quantitative computed tomography (QCT) or high-resolution peripheral QCT (HR-pQCT) estimates of bone loss. We searched PubMed, Web of Science, Cochrane, Scopus, and EBSCO. Longitudinal studies on adults undergoing RYGB in which vBMD was assessed by QCT or HR-pQCT with ≥6 months follow-up were included. Total hip (TH) changes were reported in four studies, lumbar spine (LS) in eight, radius in eight, and tibia in seven. Significant post-RYGB vBMD reductions occurred at all skeletal sites analyzed. Meta-regression revealed that time post-RYGB was significantly associated with vBMD deterioration in all skeletal sites except at the TH. RYGB also led to significant deterioration on bone quality. DXA underestimated LS and overestimated TH bone losses post-RYGB. In conclusion, RYGB was associated with significant vBMD loss, which makes screening of bone mass progression by three-dimensional technology a crucial clinical issue to prevent fracture risk and osteoporosis.

KEYWORDS
bariatric surgery, DXA, microarchitecture, QCT

1 | INTRODUCTION

Obesity is a major risk factor for non-communicable health problems,[1] such as type 2 diabetes, nonalcoholic fatty liver disease, coronary artery disease, obstructive sleep apnea, and osteoarthritis.[2] Its prevalence has tripled in the last four decades,[3] affecting approximately 2.1 billion adults worldwide[4] with serious health[5] and economic implications.[6] Severe obesity (body mass index [BMI] ≥ 35 kg m^{-2}), in particular, reduces median survival by 8–10 years.[7] Bariatric surgery (BS) is the most effective treatment for severe obesity,[8] improving quality of life,[9] mortality risk,[10] and associated comorbidities.[11] Nevertheless, despite its many cardiometabolic health benefits, epidemiological evidence suggests that malabsorptive BS procedures, such as the Roux-en-Y gastric bypass (RYGB), increase bone fracture risk.[12] A recent systematic review[13] estimates that at a mean post-operative follow-up of 2.2 years, the risk of any fracture was 45% higher in patients undergoing malabsorptive BS procedures compared to controls with obesity and 61% higher compared to those undergoing restrictive BS procedures. Several studies show that RYGB leads to an increase in bone resorption[14,15] and, consequently, to bone mass loss[16] at several skeletal sites[17] that tend to persist long after BS,[18] potentially compromising bone strength. Nevertheless, there is also evidence that patients with obesity tend to have a higher bone mass compared to normal weight counterparts[19] and that, despite bone mass losses, many post-BS patients maintain an areal bone mineral density (aBMD) T score within the normal range (T score > − 1).[20] This suggests that increases in fracture risk observed in these patients could result mostly from changes on other bone parameters besides bone mass.

Most studies investigating the effect of BS on bone mass have relied mostly on aBMD assessed by Dual-energy X-ray absorptiometry (DXA). This technique however can have substantial measurement errors in this population due both to a large amount of adipose tissue and the drastic changes in body size and composition occurring after BS.[21,22] Additionally, bone fracture depends not only on bone mass but also on bone quality[23] that represents the sum of all bone characteristics that influence its ability to resist a fracture,[24] most of which cannot be assessed with DXA. In opposition, imaging techniques based on the volumetric assessment [volumetric BMD (vBMD)] of bone mass and structure, such as quantitative computed tomography (QCT) and high-resolution peripheral QCT (HR-pQCT), overcome several of these limitations.[25] Since they are less affected by changes in body size and composition, they can provide a more accurate estimate of bone mass losses in post-BS patients.[21,22] Importantly, they can also provide relevant information on cortical and trabecular bone geometry and microarchitecture[26] that are paramount to understand the mechanisms whereby RYGB increases fracture risk.

Previous meta-analyses of the effect of RYGB on bone mass loss[17,27,28] have all relied exclusively on DXA-derived estimates of aBMD, which can lead to substantial measurement errors and are unable to provide information on bone quality. Most of these previous studies also have very short follow-ups, usually between 1 and 2 years. Consequently, and considering that a substantial portion of the fracture risk in post-BS patients could result from changes in bone quality parameters other than bone mass alone,[29] it is clinically relevant to accurately determine to what extent are bone mass, geometry, and microarchitecture affected by RYGB. This could improve post-BS patients' medical care and reduce fracture risk.

The aims of this systematic review and meta-analysis with meta-regression are to determine: (i) the effect of RYGB on vBMD, (ii) how RYGB affects bone geometry and trabecular microarchitecture, and (iii) the degree of agreement between estimates of aBMD and vBMD losses following RYGB.

2 | METHODS

This systematic review and meta-analysis with meta-regression of longitudinal studies is registered at PROSPERO (CRD42021260106) and was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[30] (PRISMA checklist presented as supporting information).

2.1 | Search strategy

To conduct the current systematic review, Pubmed®, Web of Science®, Cochrane, Scopus®, and EBSCO® were searched from inception to June 11, 2021. The supporting information Table S1 fully details the search strategy. Relevant studies from reference lists of included studies (snowball technique) were also screened. Two authors independently performed the search (A.H.M, F.D.S) and individually performed the eligibility criteria assessment through title and abstract screening, and the full text was inspected whenever detailed information was needed. Duplicate records were removed, and all records of potential interest were saved to an Endnote database (Endnote X9, Thomson Reuters, San Francisco, CA, USA). Disagreements were resolved by a third author (L.V). After the final pool, full texts were analyzed, and all relevant data were extracted. Disagreements and ambiguity were resolved by discussion and consensus among the authors.

2.2 | Eligibility criteria and studies selection

Studies were included using the following criteria: (i) Participants: adults (aged 18–65) with BMI ≥ 35 kg m^{-2}; (ii) Interventions: patients submitted to RYGB that followed the standard post-BS medical care; (iii) Comparators: same patients before BS; (iv) Outcomes: the primary outcome was vBMD assessed at least one clinically relevant skeletal site by either QCT (total hip [TH] or lumbar spine [LS]) or by HR-pQCT (radius or tibia). Secondary outcomes were cortical and trabecular bone microarchitecture variables from radius and tibia assessed by HR-pQCT, namely: cortical vBMD, cortical porosity (Ct. Po), cortical

thickness (Ct.Th), trabecular vBMD, trabecular number (Tb.N), trabecular separation (Tb.Sp), trabecular thickness (Tb.Th), and trabecular bone volume fraction (Tb.BV/TV), radius, and tibia failure load estimated by finite element analysis as well as aBMD at the TH, LS, and one-third radius assessed by DXA. The minimum follow-up between pre-post intervention was 6 months since this is considered the minimum length of time required to detect vBMD changes[31]; and (v) Study design: longitudinal studies (e.g., cohort, clinical trials, and quasi-experimental). In cases where the studies included more than one group, only the group exclusively involved in the standard medical care after RYGB was considered for the analyses. Whenever the same study sample and follow-up measurements were reported in different studies, only the outcome from the study with the larger sample size was used to avoid data overlap.

2.3 | Data extraction

Whenever available, the following data were extracted from each study: author, year, sample size, sex, post-menopausal status, pre-BS BMI, post-surgery nutritional and pharmacological interventions, bone mass evaluation technique, and skeletal regions assessed. Data regarding the outcomes of interest were collected at pre-BS and at all available follow-up visits. Outcome data that were only available from figures were extracted with WebPlotDigitizer (version 4.4; Pacifica, CA, USA).[15,20,22,29,32] Outcomes reported as the median and interquartile range (IQR) were converted into mean and standard deviation (SD) based on Wan and colleagues' formula.[33] Whenever standard error or confidence intervals (CI) were reported as dispersion measures, SD was calculated according to the Cochrane-recommended formulas.[34] When outcomes were reported as absolute values, these data were converted to percentage change by subtracting between pre-and post-BS mean data and dividing by pre-BS data. More information regarding data transformations to run this meta-analysis can be found elsewhere (https://bit.ly/3syo95N). Two authors (A.H.M and L.V) independently performed data extraction and discrepancies were resolved by discussion with a third author (G.B). No authors were contacted to obtain further information. The data file used to perform the statistical analysis is presented in supporting information Table S2.

2.4 | Studies quality assessment

The Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group[35] developed by the National Heart, Lung and Blood Institute (NHLBI) was used to evaluate the methodological quality of the included studies. This tool comprises 12 items that can be answered with either yes, no, cannot be determined, not applicable, or not reported. Overall quality may be rated as good, fair, or poor. Study quality was independently reviewed by two authors (A.H.M. and G.B), and disagreements were resolved through discussion with a third author (F.D.S).

2.5 | Statistical analysis

Statistical analyses were conducted using the metafor package (version 3.0–2)[36] in the R statistical software (version 4.1.0; R Foundation for Statistical Computing, Vienna, Austria). Three-level random-effects hierarchical meta-analysis models were used to estimate the pre-post mean percentage difference with 95% CI for all outcomes. As the model can deal with hierarchically structured data, more than one follow-up time point from the same study could be included.[37] The Z test was used to assess the overall effect with statistical significance set at $p < 0.05$.

Heterogeneity present in each analysis of the primary outcomes was initially assessed by the I^2 statistic,[38] which estimates the amount of heterogeneity relative to the total amount of variance in the observed effects excluding variance from sampling error. Heterogeneity, according to I^2, was qualitatively rated as 0–40% not important, 30–60% moderate, 50–90% substantial, and 75–100% considerable.[39] Furthermore, since the meta-analytic models applied to encompass three hierarchical levels, the total variance sources were decomposed into (i) random sampling error, (ii) variance within studies (due to time effect), and (iii) variance between studies.

Meta-regressions were also used to explore the potential effect of several relevant moderators on bone mass and microarchitecture change after RYGB. Due to their clinical significance, body composition variables, such as percentage of body mass loss, lean mass loss, and fat mass loss after RYGB, were initially explored in these analyses but were not included due to the low number of studies available for any of the primary outcomes. The only moderator with sufficient data to perform the meta-regression was the time after RYGB, and therefore, its influence was tested for all clinically relevant skeletal sites. The proportion of total variance explained by the predictor (time after RYGB) was reported as a pseudo-R^2 and computed as

$$R^2 = \frac{\tau^2_{RE} - \tau^2_{MR}}{\tau^2_{RE}}$$

where τ^2_{RE} is the heterogeneity based on the random-effects model and τ^2_{MR} is the amount of heterogeneity based on the meta-regression model.

Finally, to evaluate whether there were differences in the estimation of bone mass losses following RYGB assessed by 2D (aBMD; DXA) and 3D (vBMD; QCT or HR-pQCT) techniques, the mean percentage change differences were computed by subtracting the post-RYGB vBMD change assessed by 3D techniques from aBMD change obtained with DXA. To be included in this analysis, studies must have assessed BMD in at least one of three designated skeletal regions (TH, LS, or radius) by both 2D and 3D techniques. The same three-level random-effects hierarchical model structure was used to pool the effect sizes in this analysis.

The publication bias assessment was not conducted following the recommendations for analysis involving less than 10 studies.[40,41]

2.6 | Strength of the body of evidence assessment

The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was used for assessing the certainty of the evidence for the primary outcomes.[42,43] GRADE (rating from 1 to 4) evaluation started with the maximum rate, but as only longitudinal studies were considered in the analysis, all outcomes were downgraded into two levels by default. Other domains presenting serious limitations were also downgraded by one level. Certainty of the evidence was independently reviewed by two authors (A.H.M., and F.D.S.), and disagreements were resolved through discussion with a third author (G.B).

3 | RESULTS

3.1 | Study selection and characteristics

Table 1 provides the details of the included studies. A total of 151 articles were initially identified from the literature searches (149 from databases and 2 from citation searching). Of these, 54 remained after removing duplicates, of which 30 were excluded based on title and abstract, and 11 were excluded during a full-text assessment. The main reasons for exclusion were: (i) lack of longitudinal design ($n = 5$), (ii) reports derived from the same original study with substantial data reporting overlap ($n = 5$), and (iii) no assessment of any of the primary outcome measures ($n = 1$). Fourteen studies met the inclusion criteria and were included in the systematic review (Figure 1).

All pooled studies were published between 2014 and 2021. The sample size of the studies varied between 7 and 45 patients, and most studies included both women and men, except for 3 studies in which only women were included.[29,44,49] The participants' average age ranged between 41 and 58 years and pre-BS average BMI ranged between 37 and 48 $kg\,m^{-2}$. In most studies, usual post-BS medical care included multivitamin nutritional supplements. DXA and QCT were used in most of the studies, except for two studies[15,44] in which only QCT was used. Post-BS follow-up time ranged from 6 to 84 months. The weighted mean follow-up time calculated according to weight attributed to each study in the meta-analysis was 14.2, 11.9, 10.9, and 10.8 months at TH, LS, radius, and tibia, respectively.

3.2 | Methodological quality assessment

Using the NHLBI quality assessment tool, nine studies were rated as good,[14,15,22,29,32,44–46,50,51] four as fair,[20,47–49] and none as poor. The main limitations detected were related to the lack of a priori calculation of the sample size and low statistical power, lack of blinding during outcomes assessment, high dropouts, and limitations with statistical analyses. A detailed description of the risk of bias assessment is reported in supporting information Table S3.

3.3 | vBMD changes at TH, LS, radius, and tibia after RYGB

3.3.1 | Overall effect

Figure 2 shows the vBMD mean percentage change after RYGB on the several skeletal regions of interest. There was a significant vBMD reduction after RYGB at the TH (−3.4% [95% CI −5.9 to -0.8]; $p = 0.009$), LS (−6.3% [95% CI −9.8 to −2.8]; $p < 0.001$), radius (−6.6% [95% CI −11.3 to −2.0]; $p = 0.005$), and tibia (−7.5% [95% CI −11.6 to −3.3]; $p < 0.001$).

3.3.2 | Sensitivity analysis

The heterogeneity for the analyses of the overall effects (Figure 2) regarding TH, LS, radius, and tibia was 71%, 95%, 99%, and 98% respectively. The heterogeneity decomposition revealed that 91.3% of the variance in LS vBMD changes derived from the between-studies differences, while 70.8% of the variance in TH, 98.7% in radius, and 98.2% in tibia was explained by the time effect (supporting information Table S4). Since the variance derived from between-studies differences in LS was considerable, and it was observed that the results of one study[15] substantially diverged from the others, a sensitivity analysis excluding this study was conducted (supporting information Table S4). After removing this study, the difference between studies' heterogeneity decreased from 91.3% to 73% while the overall effect was not affected.

3.3.3 | Meta-regression

A meta-regression to evaluate the effect of the follow-up time on vBMD decreases after RYGB was performed (Figure 3). The time after RYGB was significantly associated with a vBMD reduction at the LS ($p = 0.009$; $R^2 = 0.18$), radius ($p < 0.001$; $R^2 = 0.84$), and tibia ($p < 0.001$; $R^2 = 0.97$) but not at the TH ($p = 0.698$; $R^2 = 0.00$).

3.3.4 | Certainty of evidence

The certainty of the evidence for each outcome using the GRADE approach is presented in Table 2. The certainty of post-RYGB vBMD estimated changes was graded as (i) low at the TH because no serious limitations were observed in any domain; (ii) very low certainty at the LS due to serious limitations detected in an inconsistency; (iii) moderate certainty at the radius and the tibia because no serious limitations were observed in any domain, and the strength of evidence was upgraded in one level based on "dose-response gradient" presence.

TABLE 1 Characteristics of the included studies

Author and year	Sample size (*n*%; %♀; %postm)	Sample characteristics [mean ± SD or median (IQR)]		Post-RYGB drugs and supplements	Outcomes	Follow-up (months)	Quality
		Age (years)	Pre-RYGB-BMI (kg m^{-2})				
Beekman et al. 2021[44]	14; 100%♀; 100%	58 ± 4	38 ± 4	Omeprazole and calcium carbonate/ cholecalciferol	QCT: LS	12	Good
Bredella et al. 2017[32]	11; 90%♀; NR	48.6 ± 8.9	44.1 ± 5.1	NR	QCT: TH, LS; DXA: TH, LS	12	Good
Brzozowska et al. 2021[45]	7; 71%♀; 60%	51.1 ± 7.6	42.3 ± 7.7	Vitamin D (25-OH > 75 nmol/L) and calcium (≥1000 mg/day)	QCT: LS; DXA: TH, LS, 1/3radius	12, 24	Good
Frederiksen et al. 2016[46]	24; 58%♀; 6.7%	41.2 ± 8.06	42.9 [38.7 to 47.0]	Daily intake of vitamin D (1920 IU) and calcium (800 mg)	HR-pQCT: 1/3radius, tibia; DXA: TH; LS	6, 12	Good
Hansen et al. 2020[47]	17; 59%♀; 5.9%	43 ± 9	42 ± 6	Daily intake of vitamin D3 (38 mg;), calcium carbonate (1000–1200 mg) and multivitamin tablet	HR-pQCT: 1/3radius, tibia; DXA: TH, LS	24, 84	Fair
Ivaska et al. 2017[15]	21; 91%♀; NR	47.1 ± 9.9	48.5	Daily intake of vitamin D3 (20 μg), calcium (1000 mg) and multivitamin tablet (including 10 μg vitamin D3)	QCT: LS	6	Good
Krez et al. 2021[29]	17; 100%♀; 41%	43 ± 10	44 ± 5	Vitamin D (50,000 IU/week)	HR-pQCT: 1/3radius, tibia; DXA: TH, LS, 1/3 radius	12, 24, 36,48	Good
Lindeman et al. 2018[48]	21; 81%♀; 44%	51.1 ± 14	45 ± 7	Daily intake of vitamin D (3000 IU) and calcium (1200–1500 mg)	QCT: LS; HR-pQCT: 1/3radius, tibia; DXA: TH, LS	24, 42, 60	Fair
Murai et al. 2019[49]	24; 100%♀; 19%	42.1 ± 8.2	48.5 ± 8.1	Daily intake of vitamin D3 (3000 IU), calcium (1200–1500 mg) and protein (≥60 g)	HR-pQCT: 1/3radius; DXA: TH, LS, 1/3radius	9	Fair
Schafer et al. 2018[14]	45; 79%♀; 23%	46 ± 12	44 ± 7	Intake of vitamin 25OHD to maintain ≥30 ng/ mL and daily intake of calcium (1200 mg)	QCT: LS; HR-pQCT: 1/3radius, tibia; DXA: TH, LS, 1/3radius	6, 12	Good
Shanbhogue et al. 2017[50]	23; 61%♀; 4%	42.6 ± 7.8	42 [38 to 47]*	NR	HR-pQCT: 1/3radius, tibia; DXA: TH, LS	12, 24	Good
Tan et al. 2015[51]	10; 50%♀; 0%	45.6 ± 9.1	36.7 ± 4.4	Daily intake of calcium (100 mg) and ergocalciferol (50,000 IU)	QCT: TH, LS; DXA: TH, LS	12	Good
Yu et al. 2014[22]	26; 87%♀; 33%	47 ± 14	45 ± 6	NR	QCT: TH, LS; DXA: TH, LS	12	Good
Yu et al. 2015[20]	22; 87%♀; 33%	47 ± 14	45 ± 6	Daily intake of vitamin D (3000 IU) and calcium (1200–1500 mg)	QCT: TH, LS; HR-pQCT: 1/3radius, tibia; DXA: TH, LS	12, 24	Fair

♀, women; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; HR-pQCT, high resolution peripheral QCT; LS, lumbar spine; NR = not reported; postm, postmenopausal; QCT, quantitative computed tomography; RYGB, Roux-en-Y-gastric bypass; TH, total hip.

[a]Range.

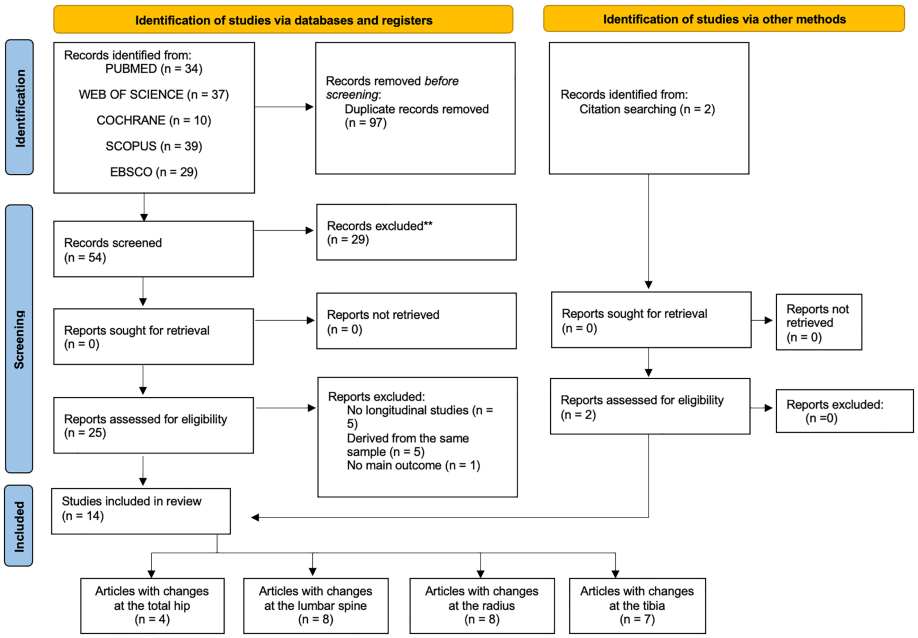

FIGURE 1 Flow diagram of study selection

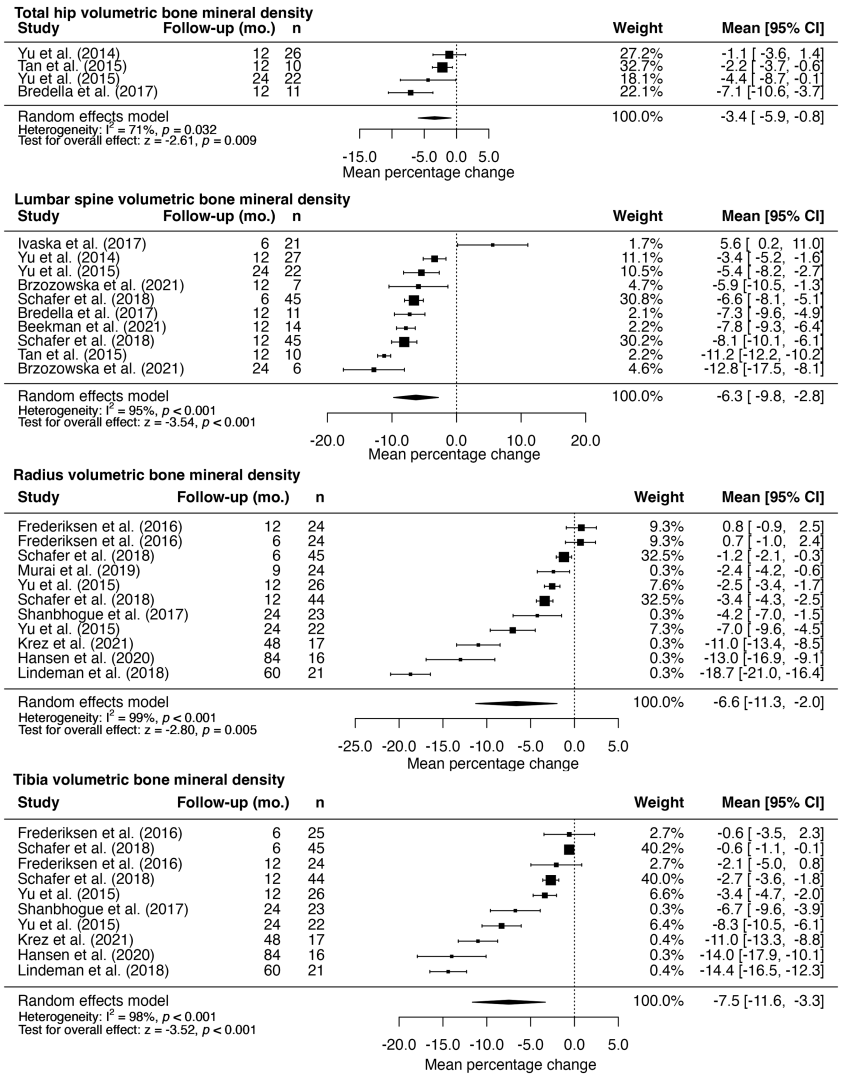

FIGURE 2 vBMD mean percentage change after RYGB at the TH, LS, radius, and tibia

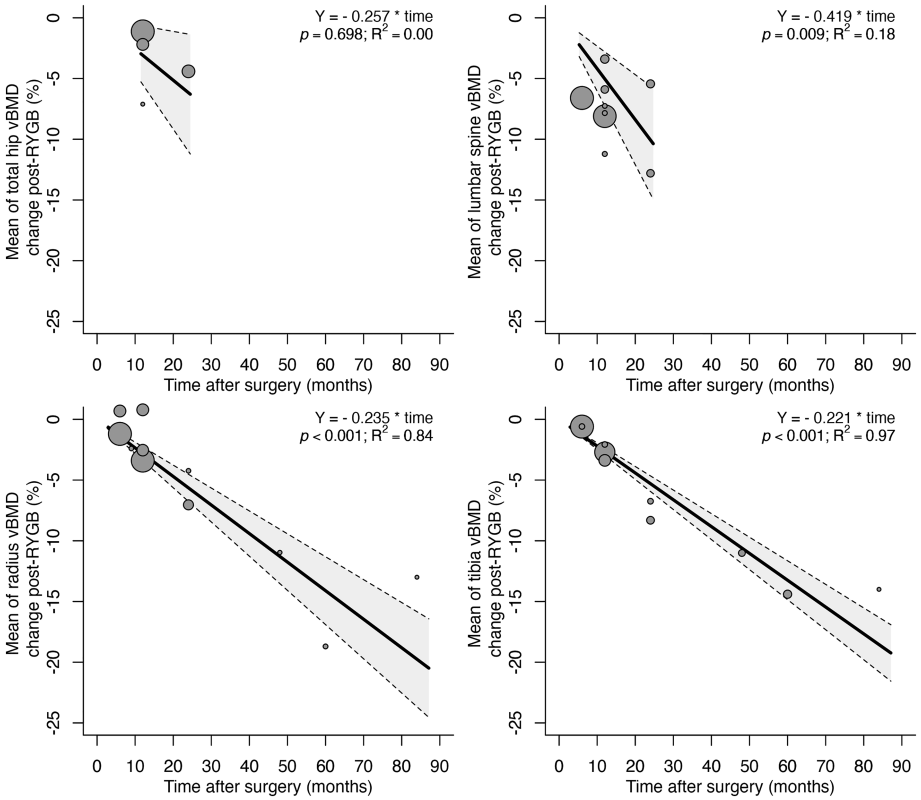

FIGURE 3 Meta-regression for assessing the effect of follow-up time on vBMD decreases

3.4 | Bone quality changes at the distal radius and tibia after RYGB

Cortical and trabecular bone microarchitecture changes after RYGB at the distal radius and tibia are depicted in Figures 4 and 5, respectively. The effect sizes of each outcome for both skeletal sites are summarized in supporting information Table S5. After RYGB, there was a significant reduction of the cortical ($p = 0.033$) and trabecular ($p = 0.020$) vBMD at the radius and a non-significant trend for a decrease in the cortical ($p = 0.060$) and a significant decrease in the trabecular vBMD ($p = 0.011$) at the tibia. Post-RYGB, Ct.Po increased significantly at the radius ($p = 0.001$) and tibia ($p = 0.023$), while Ct.Th significantly decreased at the radius ($p < 0.001$) and tibia ($p < 0.001$). Significant decreases in Tb.N were also found at the radius and tibia (in all $p < 0.01$), while Tb.Sp was also significantly increased at both radius and tibia (in all $p < 0.001$). No significant changes were observed on both Tb.Th and Tb.BV/TV either at the radius or tibia ($p > 0.05$). No significant changes in trabecular failure load after RYGB at any skeletal sites were also observed ($p > 0.05$).

3.5 | Comparison of BMD assessment techniques: 2D (DXA) versus 3D (QCT and HR-pQCT)

BMD measurement differences regarding 3D and 2D techniques at the TH, LS, and radius are presented in Figure 6. Four studies were used to compare both techniques at TH,[20,22,32,51] using data from 12 and 24 months of follow-up, three at the radius,[14,29,49] with data from 6, 9, 12, and 48 months of follow-up and six at the LS,[14,20,22,32,45,51] with data from 6, 12, and 24 months of follow-up. BMD reductions following RYGB at the TH assessed by DXA were significantly larger than those assessed by QCT (−5.5% [95% CI −7.7 to −3.2]; $p < 0.001$). In opposition, BMD reductions at the LS assessed by DXA were significantly lower than those identified by QCT (4.7% [95% CI 0.7 to 8.7]; $p < 0.001$). There were no differences between BMD changes assessed by DXA and QCT at the radius (2.7% [95% CI −2.7 to 8.1]; $p = 0.332$).

4 | DISCUSSION

This systematic review and meta-analysis with meta-regression aimed to assess the effect of RYGB on skeletal health by determining how vBMD assessed by QCT or HR-pQCT and bone quality parameters change following surgery. The main study findings indicate that, after RYGB, there are significant vBMD losses at the TH, LS, radius, and tibia. Importantly, higher vBMD losses at LS, radius, and tibia were identified with longer follow-ups. Bone quality was also negatively affected by RYGB as shown by the deterioration of almost all cortical and trabecular bone parameters assessed at the radius and tibia. Due to the caveats of DXA-derived aBMD measurements in post-BS patients,[21] we also sought to determine the differences in aBMD assessed by DXA and vBMD assessed by QCT or HR-pQCT in these patients. Having QCT and HR-pQCT as a reference, DXA was found to significantly underestimate LS and to overestimate TH post-RYGB BMD losses. This is clinically relevant since therapeutic decisions are largely based on aBMD estimates of bone mass.

TABLE 2 Summary of findings. Effect of Roux-en-Y gastric bypass on volumetric bone mineral density

Skeletal region[a]	Studies	No. of patients[b]	Certainty assessment					Absolute effect	
			Risk of bias	Inconsistency	Indirectness	Imprecision[c]	Other	percentage change (95% CI)	Certainty
Total hip	4	47	not serious[d]	not serious	not serious	not serious	none[e]	MD **-3.4% higher** (−5.9% to −0.8%)	⨁⨁◯◯ LOW
Lumbar spine	8	135	not serious[d]	serious[f]	not serious	not serious	none[e]	MD **-6.3% higher** (−9.8% to −2.8%)	⨁◯◯◯ VERY LOW
Radius	8	136	not serious[d]	not serious	not serious	not serious	dose response gradient[g]	MD **-6.6% higher** (−11.3% to −2.0%)	⨁⨁⨁◯ MODERATE
Tibia	7	113	not serious[d]	not serious	not serious	not serious	dose response gradient[g]	MD **-7.5% higher** (−11.6% to −3.3%)	⨁⨁⨁◯ MODERATE

GRADE Working Group grades of evidence.
High certainty: The current evidence provides a very good indication of the likely effect, and the likelihood that the actual effect will be substantially different is low.
Moderate certainty: The current evidence provides a good indication of the likely effect, and the likelihood that the actual effect of the treatment will not be substantially different is moderate.
Low certainty: The current evidence provides some indication of the likely effect, but the likelihood that the actual effect will be substantially different is high.
Very low certainty: The current evidence does not provide a reliable indication of the likely effect, and the likelihood that the actual effect will be substantially different is very high.
CI, confidence interval; MD, mean difference.
[a]Volumetric bone mineral density (vBMD) assessed by quantitative computed tomography (QCT) at total hip and lumbar spine and high-resolution peripheral QCT (HR-pQCT) at radius and tibia.
[b]Only considered the sample size from the first follow-up moment (unlike statistical analysis in which more than one follow-up time point from the same study were included).
[c]All the studies presented adequate sample size according to power calculation for meta-analysis.
[d]All the studies were rated as "good" or "fair" (none as poor) in the overall risk of bias according to the Quality Assessment Tool for Before-After Studies With No Control Group.
[e]Publication bias assessment was not performed due to the small number of studies included and no upgrade (rating up) was given based on "large effect," "plausible confounding," and "dose response gradient" domains.
[f]Presences of moderate between-study heterogeneity ($I^2 \geq 50\%$) observed in the meta-analysis.
[g]Publication bias assessment was not performed due to the small number of studies included, and no upgrade was given based on "large effect" and "plausible confounding" domains, but the certainty of evidence was upgraded based on "dose response gradient" domain considering the cumulative effect of time on bone loss after Roux-en-Y gastric bypass observed through the meta-regression.

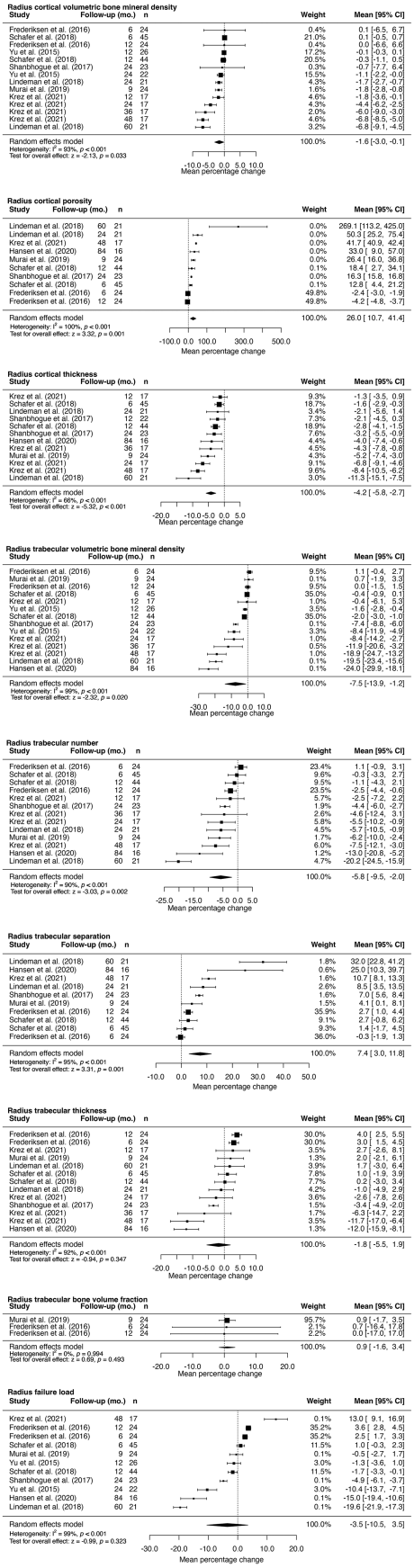

FIGURE 4 Bone quality mean percentage change after RYGB at the radius

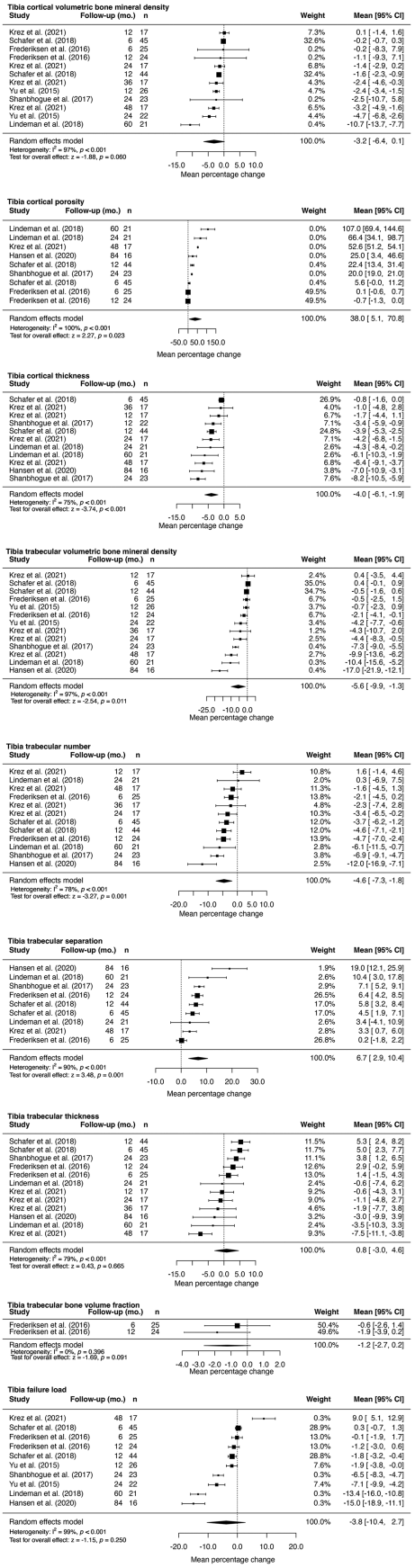

FIGURE 5 Bone quality mean percentage change after RYGB at the tibia

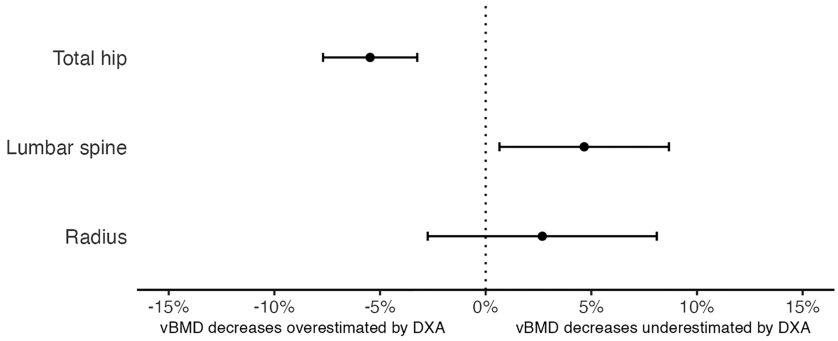

FIGURE 6 Differences between BMD assessment techniques (DXA versus QCT and HR-pQCT)

To the best of our knowledge, this is the first meta-analysis focusing on the effect of RYGB on vBMD. Our findings revealed that RYGB induces a significant vBMD reduction, which is in line with previous meta-analyses assessing bone mass after surgery through DXA. Rodríguez-Carmona and colleagues[27] reported that, at the end of the first year after surgery, patients submitted to mixed restrictive and malabsorptive procedures (e.g., biliopancreatic diversion and RYGB) displayed an aBMD reduction at central skeletal sites. Similar results were also reported when only studies involving RYGB were considered.[17] Yu[52] also reported DXA hip aBMD decreases ranging from 5 to 11% in the TH and 3 to 7% in the LS but an unclear effect at the radius at the first follow-up year after RYGB. Our results also showed that approximately 1 year after RYGB a rapid decline of vBMD tended to occur at the TH (0.8% to 5.9%) as well at the LS (2.8% to 9.8%). Nevertheless, our results also show substantial vBMD losses at the radius and tibia. These findings show that, not only central skeletal sites but also the appendicular skeleton is negatively affected by RYGB, including a non-weight-bearing skeletal site such as the radius. This is particularly interesting, since several authors have proposed that the decrease of mechanical loading resulting from the substantial weight loss might be the main factor for RYGB-induced bone loss, at least during the massive weight loss phase that typically occurs throughout the first year after surgery.[53–55] By contrast, our results support recent findings showing that gravitational loading changes to which RYGB patients are exposed during the first year after surgery do not fully explain the typically observed bone losses.[56] This suggests that the detrimental effect of RYGB on BMD is mostly systemic in nature. Although incompletely understood, factors such as nutritional malabsorption, energy deficits, and changes in adipose and gastrointestinal hormones could be the main contributors to RYGB-induced bone loss.[57–59]

A relevant finding of the present study indicates that vBMD reductions observed following RYGB seem to worsen for higher follow-up times, suggesting a cumulative deleterious effect throughout the years after surgery. Our meta-regression analysis estimated that, on average, the annual vBMD losses at the LS, radius, and tibia are 5.0%, 2.8%, and 2.7%, respectively. It is important to highlight that this average bone loss rate can only be assumed within the analyzed time frame, which is from 6 months to 2 years for LS, and from 6 months to 7 years for radius and tibia. This time effect was not observed at the TH, possibly due to the scarce number of available studies with sufficient follow-up data on this specific skeletal site. The time effect on vBMD was found to be more consistent at the radius and tibia, as these were the skeletal sites for which there were reports with longer follow-ups. Our meta-regression models allowed us to estimate, with some confidence, that vBMD at the radius and tibia may decrease up to values between 15 and 25% 7 years after RYGB, going well beyond what would be expected due to the effect of aging alone.[60] These findings are particularly worrisome considering that most patients undergo BS at their 40s[61] and provide a rationale for why RYGB not only increases the risk of major osteoporotic fractures but does so in a time-dependent manner, with a more pronounced fracture risk increase occurring since the third-to-fifth year after surgery.[12,62–64] Moreover, Ahlin and colleagues[12] recently published a non-randomized prospective controlled intervention with up to 26 years of follow-up and found a significant trend towards a higher cumulative incidence of major osteoporotic fractures over the years. These authors found a 3.77-fold increase in major osteoporotic fracture risk in patients undergoing RYGB compared with counterparts with severe obesity.[12]

The increase in bone fracture risk that occurs after BS may not only be due to substantial decreases on bone quantity (bone mass) but also due to a concomitant impairment of its quality.[23] We aggregated data from the studies that assessed bone microarchitecture through HR-pQCT. By pooling the effect size of these studies, it was possible to observe an expressive deterioration on cortical and trabecular parameters both at the radius and tibia after RYGB. Cortical porosity seems to be one of the most expressive RYGB side effects, which is particularly problematic since bone strength declines as a seventh power function of the increase in this parameter,[65] which may lead to a considerable increase in the risk of fracture.[66] Trabecular bone tissue was also affected as seen through the trabecular number reduction and trabecular separation increase, which are also important bone quality paraments for fracture risk prediction, even after adjustment for BMD.[67] Although an overall deterioration of bone microarchitecture was observed, this was not reflected on a failure load reduction, at both the radius and tibia. It must be considered that the estimation of bone failure load reduction through finite element analysis has a higher variability compared to the other bone quality variables, which may conceal the true effect of BS on this bone strength outcome. The analysis of the bone microarchitectural alterations following BS is important for understanding the bone fracture risk in these patients since,

despite bone mass losses, several studies report a relatively low incidence of *T* scores ≤ −2.5 according to DXA standards.[53,68] Therefore, the observed increase in bone fracture risk is not just due to bone mass loss but also due to impairments in bone quality, leading to a reduction in bone strength.

We explored potential discrepancies between 2D (i.e. DXA) versus 3D BMD assessment techniques. Despite the limited number of available studies, we observed that, compared to 3D techniques, DXA tends to overestimate bone losses at the TH and to underestimate losses at the LS, while no differences were observed for the radius. It is important to keep in mind that although the magnitude of the changes in aBMD and vBMD at TH and LS are different, these changes point in the same direction, that is, both skeletal sites presented an accentuated bone loss after RYGB. Interestingly, a study showed that the percent change in aBMD after adding fat layers decreases at LS and presents a trend for an increase at the TH.[21] The effect of fat mass on DXA accuracy may vary with the device manufacturer and model,[21,69–72] but the massive fat loss occurring after BS may progressively diminish the DXA assessment error. This may lead to the overestimation of actual BMD loss at the TH and to the underestimation at the LS found in the present meta-analysis. In contrast, more advanced imaging techniques[73,74] seem to be less affected by body composition changes, due to the sensitivity of the device.[21] The technical reasons that may explain the BMD magnitude discrepancies reported by DXA are not clear but might be related to changes on several parameters prompted by BS, namely the amount of fat,[21,75] inhomogeneity of soft tissue,[76] amount and bone marrow composition[77,78] and artifact magnification such as bone distance from the X-ray source and detector array.[79] QCT and HR-pQCT are more precise techniques for the detection of changes in bone mass[21,25] since they measure the real vBMD (in three dimensions) and differentiate soft tissue during bone density calculation, making them less susceptible to changes in body composition.[21]

These findings have relevant clinical implications, underlying the importance of screening bone mass and bone quality progression and highlighting the essential role of preventive strategies to preclude the premature development of bone fragility and consequent increase in fracture risk in post-RYGB patients. The therapeutic options that have been proposed are based on nutritional, physical exercise, and pharmacological interventions.[80] Although current findings seem to suggest that these options may mitigate RYGB-induced bone deterioration, due to the very low strength of evidence, no final conclusion can be drawn about the best treatment strategy that should be followed, emphasizing the urgency of further investigation on this research field.[81–83] It should also be mentioned that RYGB is no longer the most frequently performed BS procedure worldwide since 2014, being surpassed by the sleeve gastrectomy,[84] which is mainly based on a restrictive component. Although most of the evidence indicates that restrictive procedures have a lower impact on fracture risk compared to RYGB,[62,85] recent findings showed that an increased fracture rate may be observed on the long term.[12] Therefore, further investigation is warranted regarding the effect of BS on bone health in other surgical procedures, such as the sleeve gastrectomy,[86] which is currently the mostly performed BS technique, as well as new procedures that are rapidly gaining momentum in BS clinical practice.

The present study has limitations that must be underlined. First, our results regarding bone mass losses at the LS should be interpreted with caution due to the high heterogeneity identified between studies. Second, we did not include a comparator group in our analyses, and therefore, some of the changes in bone mass and quality observed might also reflect the effect of ageing. Third, differences in BMD observed between DXA and QCT/HR-pQCT should also be interpreted with caution since, although both procedures grossly assess the same skeletal region (TH, LS, or radius), the specific region of interest under analysis may not coincide, as for the case of the radius, which may contribute, at least partially, to the disagreement identified between 2D and 3D imaging techniques.[87] However, this meta-analysis also presents several strengths, such as the use of a three-level hierarchical random effects meta-analytic model. This model allowed us to include data from multiple follow-up periods of the same study permitting, therefore, to decompose the heterogeneity and determine the amount of variance explained by follow-up time after RYGB. More importantly, the meta-regression models also allowed us to quantify this time effect and to estimate the yearly average amount of bone loss experienced by patients following BS, which may be an important information in clinical practice.

5 | CONCLUSION

The main findings of this systematic review and meta-analysis with meta-regression indicate that, after RYGB, there is a significant vBMD loss at the TH, LS, radius, and tibia. Importantly, there was an estimated annual vBMD loss of 5.0% at the LS, 2.8% at the radius, and 2.7% at the tibia during the assessed follow-up time after RYGB. Bone quality is also negatively affected by RYGB as shown by the deterioration of almost all cortical and trabecular bone parameters assessed at the radius and tibia. We also sought to determine the differences in aBMD assessed by DXA and vBMD assessed by QCT or HR-pQCT in these patients. With QCT and HR-pQCT as a reference, DXA significantly underestimated LS and overestimated TH post-BS BMD losses.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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