Original Article

Vitamin D Deficiency Does Not Impair Metabolic Improvements After Gastric Bypass

A Deficiência de Vitamina D Não Compromete as Melhorias Metabólicas Após *Bypass* Gástrico

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ABSTRACT

Introduction: Vitamin D deficiency is a long-known cause of calcium metabolism and bone disorders. More recently, it has also been identified as a potential risk factor for obesity and diabetes. Surgical alterations of the gastrointestinal tract associated with lipid malabsorption can conceivably contribute to vitamin D deficiency. We aimed to assess the prevalence of vitamin D deficiency and secondary hyperparathyroidism in patients with obesity before and after gastric bypass (RYGB) surgery and their impact on weight loss and glycemic profile.
Methods: Patients (n=553) were subjected either to classic RYGB (n=415) or to long biliopancreatic limb metabolic RYGB (n=138). Anthropometric and biochemical parameters related to calcium and glucose metabolism were prospectively evaluated for up to 36 months after the procedure.
Results: Both RYGB variants were effective in achieving sustained weight loss and long-term improvement in glycemic control. At 36 months, vitamin D deficiency and secondary hyperparathyroidism were present in 91.9% and 72.5% of patients, respectively,

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compared with 87.1% and 10.5% before surgery. 25-hydroxyvitamin D (25(OH)D) levels were negatively correlated with parathyroid hormone concentrations, but showed no significant correlations with excess weight loss, fasting glucose or HbA1c.
Conclusion: Vitamin D deficiency and secondary hyperparathyroidism are highly prevalent before and after RYGB. However, these conditions do not appear to adversely affect postoperative weight loss or glycemic improvement.

Keywords: Bariatric Surgery; Obesity/surgery; Vitamin D Deficiency; Vitamin D

RESUMO

Introdução: A deficiência de vitamina D é uma causa conhecida há muito tempo de distúrbios no metabolismo do cálcio e na saúde óssea. Mais recentemente, também foi identificada como um potencial fator de risco para obesidade e diabetes. Alterações cirúrgicas do trato gastrointestinal associadas à má absorção de lipídios podem, possivelmente, contribuir para a deficiência de vitamina D. O nosso objetivo foi avaliar a prevalência de deficiência de vitamina D e hiperparatireoidismo secundário em pacientes com obesidade antes e depois da cirurgia de bypass gástrico em Y de Roux (RYGB) e seu impacto na perda de peso e no perfil glicémico.
Métodos: Os doentes (n=553) foram submetidos a *bypass* gástrico em Y de Roux clássico (RYGB) (n=415) ou a RYGB metabólico com alça biliopancreática longa (n=138). Parâmetros antropométricos e bioquímicos relacionados ao metabolismo do cálcio e da glicose foram avaliados prospectivamente por até 36 meses após o procedimento.
Resultados: Ambas as variantes de RYGB foram eficazes na obtenção de perda de peso sustentada e melhora a longo prazo no controlo glicémico. Aos 36 meses, a deficiência de vitamina D e o hiperparatireoidismo secundário estavam presentes em 91,9% e 72,5% dos pacientes, respectivamente, em comparação com 87,1% e 10,5% antes da cirurgia. Os níveis de 25-hidroxivitamina D (25(OH)D) apresentaram correlação negativa com as concentrações de hormona da paratireoide, mas não mostraram correlações significativas com a perda de excesso de peso, glicemia de jejum ou HbA1c.
Conclusão: A deficiência de vitamina D e o hiperparatireoidismo secundário são altamente prevalentes antes e depois da cirurgia de *bypass* gástrico em Y de Roux (RYGB). No entanto, essas condições não parecem afetar negativamente a perda de peso pós-operatória ou a melhora do controlo glicémico.

Palavras-chave: Cirurgia Bariátrica; Deficiência de Vitamina D; Obesidade/cirurgia; Vitamina D

INTRODUCTION

Cutaneous synthesis upon ultraviolet sunlight exposure is the major source of vitamin D.[1] It stimulates calcium absorption in the gut, calcium reabsorption from the glomerular filtrate in the kidney, and regulates bone remodeling by activating osteoblasts and promoting osteoclast maturation.[1] Vitamin D deficiency leads to decreased intestinal absorption of calcium, which in turn stimulates parathyroid hormone (PTH) secretion.[1,2] Secondary hyperparathyroidism induced by vitamin D deficiency enhances osteoclast activity and bone resorption in attempt to maintain normal circulating calcium levels, although at the expense of reducing bone mineral density and increasing the risk of osteoporosis and fractures.[1,2]

Depending on the population studied, vitamin D deficiency affects approximately 18% to 57% of individuals.[3] The inverse relationship between the 25-hydroxyvitamin D (25(OH) D) levels and body mass index (BMI) above 30 kg/m^2 has led to the recognition of obesity as a risk factor for vitamin D deficiency.[4,5] Moreover, conditions associated with impaired fat absorption, such malabsorption syndromes, also predispose to fat-soluble vitamins deficiency, including those from iatrogenic origin such as metabolic bariatric surgery (MBS).[1] Therefore, individuals who have undergone MBS are considered a high-risk group with indication for systematic screening of vitamin D deficiency.[1]

Since the increasing prevalence of obesity has been accompanied by the exponential rise in the number of patients undergoing MBS,[6] this can contribute to the continuous upsurge of patients at risk of developing vitamin D deficiency, secondary hyperparathyroidism, and metabolic bone disease.[7-9]

In addition, vitamin D has a role in several other biological actions besides calcium metabolism, which include immune system modulation and the stimulation of insulin secretion and insulin sensitivity.[2] Furthermore, vitamin D deficiency has also been associated with obesity, metabolic syndrome and type 2 diabetes (T2DM).[10,11]

Our current study aimed to assess the impact of gastric bypass surgery (RYGB) on the prevalence of vitamin D deficiency and secondary hyperparathyroidism, as well as their consequences in weight loss and glucose profile.

METHODS

Patients who underwent RYGB for obesity refractory to conservative medical therapy with a BMI greater than 40 kg/m^2 or 35 kg/m^2 in the presence of comorbidities, between January 2009 and December 2011 at a single surgical center, were prospectively evaluated as a cohort. Among the universe of patients submitted to RYGB at our institution during this period (n=721), those who did not comply with the vitamin D supplementation recommendations were selected for inclusion in this study (n=553), allowing us to access the natural history of vitamin D status in this population. Patients underwent either the classical RYGB (n=415) or the long biliopancreatic limb metabolic variant of the RYGB (n=138), procedures that differed only in the length of biliopancreatic limb of the Roux-en-Y, which was of 72.7 ± 15.5 cm (minimum 50 and maximum 120 cm) for the classical procedure and 200 cm for the metabolic variant as previously described.[12] All patients were followed at the Multidisciplinary Clinic for Obesity Treatment at the same institution for up to three years postoperatively. They received routine postoperative multivitamin supplementation, with vitamin D prescribed only to those with documented deficiency. Patients who complied with vitamin D supplementation recommendation or became pregnant during follow-up were excluded from the study.

Anthropometric and fasting biochemical parameters - including urea, creatinine, calcium, inorganic phosphorus, albumin, 25(OH)D, PTH, glucose and glycated hemoglobin (HbA1c) - were assessed before surgery and up to 36 months. Patients with 25(OH)D levels below 30 ng/mL were classified as vitamin D insufficiency and further subdivided into categories corresponding to severe (<10 ng/mL), moderate (10-20 ng/mL) or light (> 20-30 ng/mL). A PTH level above 7.2 pmol/L, in the presence of normal calcium and renal function, was considered diagnostic of secondary hyperparathyroidism. For data analysis, patients were further grouped according to the surgical technique and the presence of T2DM in: (i) patients without T2DM undergoing classic RYGB, (ii) patients without T2DM undergoing metabolic RYGB, (iii) patients with T2DM undergoing classic RYGB and (iv) patients with T2DM undergoing metabolic RYGB. Patients lost to follow-up at 24 (n=16) and 36 months (n=50) were evenly distributed across the four groups.

1. STATISTICAL ANALYSIS

Qualitative variables were expressed as number of cases and percentage (%), while quantitative variables were expressed as mean and standard error of the mean. Differences between two independent experimental groups were evaluated using the unpaired Student's t-test for normally distributed variables, and the Mann-Whitney U test for non-normally distributed variables. Comparisons among three or more independent groups with normal distribution were performed using one-way analysis of variance (ANOVA) followed by the Newman-Keuls post hoc test. The Kruskal-Wallis ANOVA with Dunn's post hoc was used to compare three or more groups when the assumption of normality was not met. The chi-square test was applied to compare two or more nominal variables. Correlations between variables were assessed using either Pearson's or Spearman's correlation coefficients, depending on the normality of the data distribution. A p-value < 0.05 was considered statistically significant. All statistical analyzes were performed using GraphPad Prism software version 6 and IBM SPSS Statistics version 22, both for Windows.

RESULTS

This study enrolled a total of 553 patients, the majority of whom were female (F:M ratio 91.5:8.5%). Among them, 21.9% (n=121) met T2DM criteria. Patients underwent either the classical variant of RYGB (n=415) or the metabolic variant of RYGB (n=138). A higher proportion of patients without T2DM underwent classical RYGB (82.6%), whereas most patients with T2DM received the metabolic variant (66.9%). The choice of surgical technique was determined by the surgeon based on individual patient characteristics.

In the preoperative period, the four groups were comparable in demographic, anthropometric, and biochemical characteristics, except for age, fasting glucose, and HbA1c. Patients with T2DM were significantly older (47.2 ± 0.8 years *vs* 39.3 ± 0.5 years) and presented with higher fasting glucose (149.46 ± 5.76 mg/dL *vs* 94.39 ± 0.70 mg/dL) and HbA1c levels (7.32 ± 0.21% *vs* 5.57 ± 0.04%) compared to those without T2DM.

Following surgery, all four groups experienced a significant reduction in BMI and a corresponding increase in the percentage of excess BMI loss (%EBMIL) over the 36-month follow-up compared to preoperative values (Fig. 1). At 6 months, %EBMIL was significantly higher in patients without

T2DM who underwent metabolic RYGB compared with the group without T2DM submitted to the classical procedure (78.69 ± 2.68% *vs* 70.38 ± 1.03%, $p < 0.05$). However, this difference was no longer evident during the subsequent follow-up up to 36 months (Fig. 1).

Preoperatively, 87.1% of patients exhibited some degree of vitamin D insufficiency (<30 ng/mL), with 6.5% showing 25(OH)D levels consistent with severe deficiency (Fig. 2). Postoperatively, serum 25(OH)D concentrations showed a progressive, though non-significant, decrease, a trend that was similar across all groups (21.56 ± 1.71 ng/mL *vs* 18.43 ± 0.66 ng/mL at 36 months, $p > 0.05$). At 36 months, 91.9% of patients had some degree of vitamin D deficiency, including 17.5% with severe deficiency (Fig. 2).

Before surgery, 10.5% of patients presented elevated PTH levels. This proportion increased significantly from 12 months

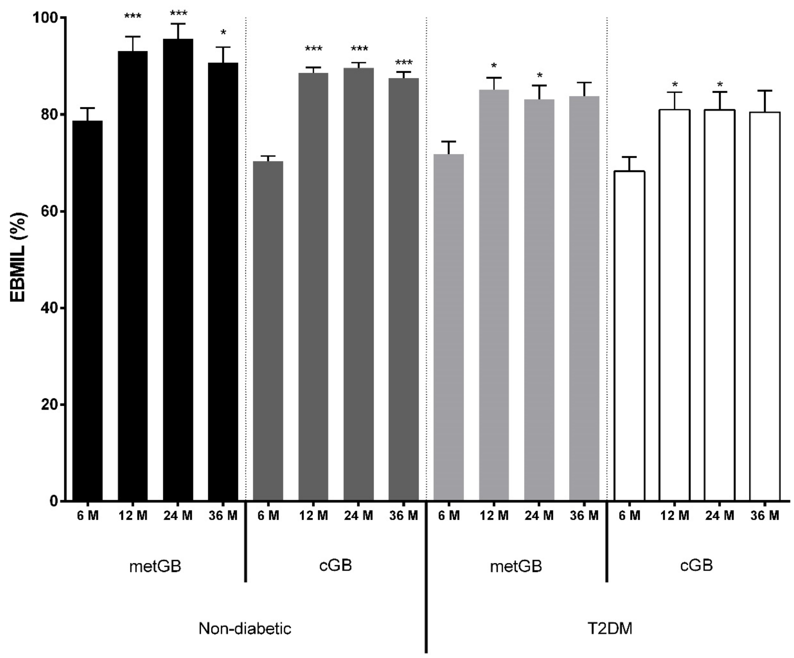

Figure 1 – Variation of the EBMIL (%) up to 36 months after metabolic bariatric surgery in the different studied groups, non-diabetic submitted to classic gastric bypass (cGB), non-diabetic submitted to metabolic gastric bypass (metGB), T2DM submitted to classic gastric bypass (DcGB) and T2DM submitted to metabolic gastric bypass (DmetGB). (* *vs* 6M, *p*<0.05; ** *vs* 6M, *p*<0.01; *** vs 6M, *p*<0.001).

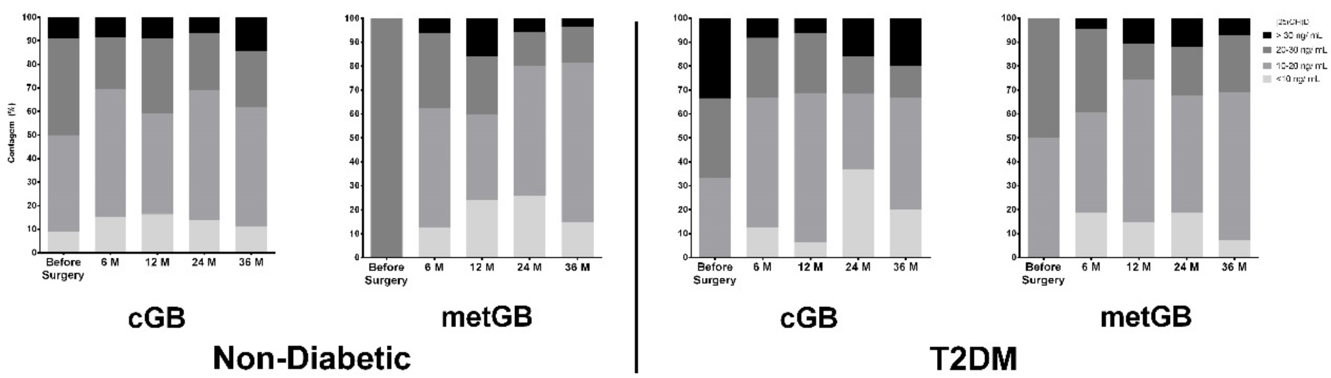

Figure 2 – Distribution of the 25(OH)D levels before and up to 36 months after metabolic bariatric surgery in the different studied groups, non-diabetic submitted to classic gastric bypass (cGB), non-diabetic submitted to metabolic gastric bypass (metGB), T2DM submitted to classic gastric bypass (DcGB) and T2DM submitted to metabolic gastric bypass (DmetGB).

onward, regardless of the surgical procedure or the presence of T2DM, reaching its peak at 36 months (5.56 ± 0.46 pmol/L vs 10.16 ± 0.35 pmol/L, $p < 0.001$), when 72.5% of patients presented secondary hyperparathyroidism (Table 1). Serum total and corrected calcium, phosphate, urea, and creatinine remained stable over the follow-up, with no significant differences between groups (Table 1). Across both surgical procedures, 25(OH)D levels correlated positively with total and corrected calcium levels ($p = 0.133$, $p < 0.01$ and $p = 0.095$, $p < 0.01$, respectively) and negatively with PTH ($p = -0.213$, $p < 0.01$); while calcium levels correlated negatively with PTH ($p = -0.242$, $p < 0.01$).

Fasting glucose and HbA1c decreased significantly after surgery, although patients with T2DM maintained significantly higher values throughout the follow-up. HbA1c was negatively correlated with %EBMIL, with a stronger correlation observed in the T2DM group ($p = -0.167$, $p < 0.01$ *vs* $p = -0.339$, $p < 0.01$). No correlations were found between the biochemical parameters associated with calcium metabolism and the anthropometric or glycemic parameters, regardless of the patient group analyzed.

DISCUSSION

Vitamin D levels in the obese population have not been given due relevance until the last decade, since it has been assumed that the negative correlation between BMI and serum 25(OH)D levels was secondary to the decrease in fat-soluble vitamins' bioavailability that was sequestered in adipose tissue, which would be normalized in the event of weight loss as observed after MBS.[13-15] However, despite the conceivable increase in vitamin D bioavailability associated with the decrease in adipose reserves,[16,17] anatomical and functional alterations induced by the different MBS techniques are also liable to induce variable degrees of malabsorption that can be responsible for micronutrient

Table 1 – Evolution of biochemical parameters before and after surgery

	Before surgery	6 months	12 months	24 months	36 months
BMI	$41.95 \pm 0.19^{***}$	$30.30 \pm 0.18^{***}$	$27.49 \pm 0.17^{***,\dagger\dagger\dagger}$	$27.32 \pm 0.17^{***,\dagger\dagger\dagger}$	$27.56 \pm 0.66^{***,\dagger\dagger\dagger}$
% EBMIL	NA	71.28 ± 0.87	$88.01 \pm 0.91^{\dagger\dagger\dagger}$	$88.56 \pm 0.99^{\dagger\dagger\dagger}$	$87.27 \pm 0.02^{\dagger\dagger\dagger}$
%TWL	NA	27.72 ± 0.28	$34.35 \pm 0.30^{\dagger\dagger\dagger}$	$34.66 \pm 0.35^{\dagger\dagger\dagger}$	$34.15 \pm 0.39^{\dagger\dagger\dagger}$
25(OH)D (ng/mL)	21.56 ± 1.71	17.99 ± 0.54	18.50 ± 0.54	17.38 ± 0.55	18.43 ± 0.66
Ca_{total} (mg/dL)	9.28 ± 0.10	9.34 ± 0.02	$9.20 \pm 0.02^{\dagger\dagger\dagger}$	$9.14 \pm 0.02^{\dagger\dagger\dagger}$	$9.16 \pm 0.02^{\dagger\dagger\dagger}$
Ca_c (mg/dL)	9.08 ± 0.09	9.25 ± 0.03	$9.13 \pm 0.02^{\dagger\dagger}$	$9.12 \pm 0.02^{\dagger\dagger\dagger}$	9.17 ± 0.02
PTH (pmol/L)	5.56 ± 0.46	7.41 ± 0.17	$8.19 \pm 0.18^{**,\dagger}$	$9.20 \pm 0.22^{**,\dagger\dagger}$	$10.16 \pm 0.35^{***,\dagger\dagger}$
Fasting Glycemia (mg/dL)	106.81 ± 1.73	$87.82 \pm 0.80^{***}$	$85.27 \pm 0.51^{***,\dagger}$	$86.30 \pm 0.55^{***}$	$88.21 \pm 0.69^{***}$
HbA1c (%)	5.94 ± 0.06	$5.45 \pm 0.04^{***}$	$5.45 \pm 0.03^{***}$	$5.51 \pm 0.03^{***}$	$5.52 \pm 0.03^{***}$

Results presented in number or mean ± standard error of the mean. BMI: body mass index; %EBMIL: percentage of excess body mass index loss; NA not applicable; PTH: parathyroid hormone; %TWL: percentage of total weight loss; 25(OH)D: 25-hydroxyvitamin D.

** $p<0.01$; *** $p<0.001$ *vs* before surgery.

† $p<0.05$; †† $p<0.01$; ††† $p<0.001$ *vs* 6 months.

deficits[18] and contribute to 25(OH)D depletion.[8,19] Reduced sun exposure and inadequate nutritional intake may also predispose to vitamin D insufficiency and disorders of calcium metabolism, as observed in the obese and post-bariatric population.[20-22] Depending on the type of MBS performed, there is a variable risk of nutritional deficits in frequency and severity, usually higher for procedures with longer bypassed segments and shorter common channels, particularly prone to iron and calcium deficiencies, which are mostly absorbed at the proximal jejunum.[8,23] Elicited by calcium and vitamin D deficiency in order to maintain homeostasis, a compensatory rise in PTH occurs to stimulate calcium mobilization from the skeleton, leading to a decrease in bone mineral density and thus increasing the risk of osteopenia and osteoporosis.[22,24] Although the threshold for parathyroid stimulation varies widely, it is more often when 25(OH)D levels fall below 30 ng/mL.[1,2,25]

RYGB is one of the most popular bariatric surgical techniques[6] since it carries a low risk of surgical morbimortality[26] and is highly effective in attaining long-term weight loss and remission of obesity-associated comorbidities.[27] RYGB combines a restrictive component with a slightly hypoabsorptive component in the same surgical procedure. Since its original description, the optimal length of the Roux-en-Y limbs has been a matter of ongoing debate. Nowadays, standard RYGB consists of constructing a Roux-en-Y with a biliopancreatic limb measuring 67.4 ± 32.2 cm long and an alimentary limb measuring 124.1 ± 29.4 cm long.[28] Technical variants employing longer biliopancreatic limbs have demonstrated greater efficacy in improving obesity-associated metabolic comorbidities and are therefore referred to as metabolic bypass.[12,29]

In our cohort, patients had a significant reduction of their excess BMI that reached a maximum of 88% at 24 months, while remaining above 82% at 36 months after surgery. No significant differences in weight trajectories were found between the two techniques, except that among patients without T2DM, the metabolic variant was associated with a higher %EBMIL during the first six months after surgery compared to the classical procedure. Before surgery, 87.1% of patients had some degree of vitamin D insufficiency, which was associated with secondary hyperparathyroidism in 10.5% of the cases. Following surgery, there was a nonsignificant decrease in 25(OH)D levels up to 36 months, at which point vitamin D deficiency reached a maximum of 91.9%. This trend was accompanied by a gradual and significant increase in PTH levels throughout the three postoperative years, with hyperparathyroidism observed in 72.5% of patients. Vitamin D and PTH patterns were similar regardless of the surgical technic or diabetes condition. Calcium homeostasis regulation mechanisms seem to be preserved after the surgery, as vitamin D and PTH, as well as calcium and PTH, were negatively correlated, while calcium and vitamin D were positively correlated, as would have been expected.[22,25] Although few reports have documented an increase in vitamin D levels in the first six to 24 months after MBS,[13,16,17,30] or no significant variation in the vitamin D status,[31] several others have found vitamin D deficiency to occur in over 50% of patients, as well as the need for supplementation with increasing doses to achieve adequate replacement.[8,19,22,24,32] Hyperparathyroidism has been reported in 30 to 50% of patients following RYGB,[22,25,33] with a prevalence rate exceeding 50% after five years of follow-up.[9] Thus, our findings corroborate previous reports stating that vitamin D deficiency and secondary hyperparathyroidism are common in the post-MBS population.[22,32,34] There were no differences in vitamin D deficiency or hyperparathyroidism prevalence between the two RYGB procedures; this could possibly be attributed to the fact that increasing the length of the biliopancreatic limb does not significantly compromise the absorptive capacity, opposite to what is observed with variants that increase the alimentary limb length or decrease common channel length.[22,35] This hypothesis is further corroborated by the absence of additional weight loss after the metabolic RYGB compared to the classical procedure.

Besides the weight reduction effects, MBS is also the most effective therapy for patients with T2DM with poor glycemic control and BMI > 35 kg/m^2, as it allows them to induce clinical remission or to improve metabolic control.[36] In our study, non-diabetic and T2DM patients' weight loss, despite displaying distinctive patterns, was similar after both surgical procedures. Likewise, regardless of the RYGB technique used, BMI and HbA1c were positively correlated, and T2DM patients had their fasting glucose and HbA1c levels reduced to below 6.5%, reflecting the good metabolic control.

A role for vitamin D in glucose homeostasis has also been attributed. By affecting insulin secretion and sensitivity, vitamin D deficiency has been associated with a higher risk for obesity, metabolic syndrome, and diabetes.[37-39] However, our data does not support such a hypothesis, as we have found no correlation between vitamin D or PTH levels and HbA1c levels, BMI, or EBMIL to suggest that calcium metabolism status could influence the efficacy of the surgery in inducing weight loss or metabolic improvement.

One of the major strengths of this study was having performed a characterization of the impact of vitamin D status in a post-bariatric population cohort on weight loss and glycemic control without the interference of any specific therapeutic intervention. As biochemical parameters reflecting vitamin D status were also evaluated throughout the year, the effect of seasonal fluctuations as confounding factors has also been minimized. The major limitation of this study was the inability to evaluate the consequences of vitamin D deficiency and hyperparathyroidism on bone metabolism, since no bone turnover markers or bone mineral densitometries were routinely performed before or after surgery that would allow assessment of the skeletal consequences of these alterations on their major target organ.[40]

CONCLUSION

In conclusion, the herein study demonstrates that although vitamin D deficiency and secondary hyperparathyroidism prevalence are high in the obese and post-bariatric population, these do not have a clinically significant impact on the efficacy of gastric bypass regarding weight loss or diabetes metabolic control. Still, it reinforces the need for periodic assessment of vitamin D status, while procedure-specific recommendations for supplementation and treatment of vitamin D deficiency in the post-bariatric patient are still needed.

LEARNING POINTS/TAKE HOME MESSAGES

- Vitamin D deficiency is highly prevalent in patients with obesity before and after RYGB, and its status should be assessed in these populations.
- Secondary hyperparathyroidism significantly increases after RYGB without vitamin D supplementation.
- Vitamin D deficiency and secondary hyperparathyroidism do not have an impact on weight loss or glycemic improvement.

ETHICAL DISCLOSURES

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2024).

Provenance and Peer Review: Not commissioned; externally peer-reviewed.

RESPONSABILIDADES ÉTICAS

Conflitos de Interesse: Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

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Confidencialidade dos Dados: Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

Proteção de Pessoas e Animais: Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pela Comissão de Ética responsável e de acordo com a Declaração de Helsínquia revista em 2024 e da Associação Médica Mundial.

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CONTRIBUTORSHIP STATEMENT

ACC: Investigation, data collection, and drafting of the manuscript.

TG and TM: Methodology and data collection.

SP: Formal analysis and reviewing and editing of the manuscript.

ER: Reviewing and editing of the manuscript.

MN: Methodology, resources, and reviewing and editing of the manuscript.

MG and MPM: Conceptualization, investigation, project administration, and reviewing and editing of the manuscript.

All authors approved the final version to be published.

DECLARAÇÃO DE CONTRIBUIÇÃO

ACC: Investigação, recolha de dados e redação do manuscrito.
TG e TM: Metodologia e recolha de dados.
SP: Análise formal, revisão e edição do manuscrito.
ER: Revisão e edição do manuscrito.
MN: Metodologia, recursos, revisão e edição do manuscrito.
MG e MPM: Conceitualização, investigação, administração do projeto, revisão e edição do manuscrito.
Todos os autores aprovaram a versão final a ser publicada.

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