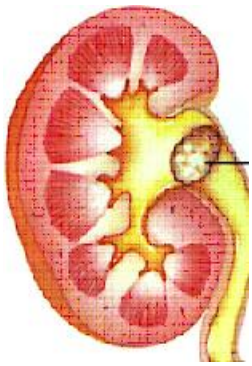
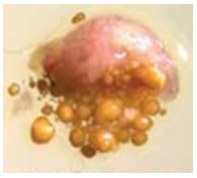
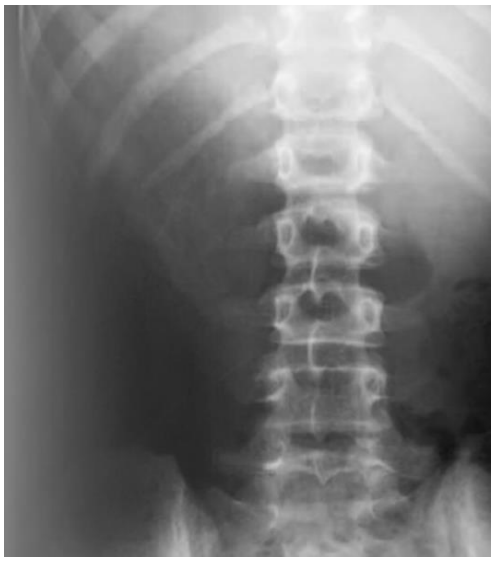
Internal Medicine Grand Rounds

Bariatric Surgery and Effects on Calcium and Bone Metabolism

June 26, 2015







Khashayar Sakhaee, MD
Department of Internal Medicine
Charles and Jane Pak Center for Mineral Metabolism and Clinical Research
University of Texas Southwestern Medical Center
Dallas, TX, USA

Biographic Information

Name: Khashayar Sakhaee, M.D.

Academic RANK: Professor, Internal Medicine

Division: Mineral Metabolism

Interest: Teaching, patient care, patient-oriented research with particular interest in pathophysiologic mechanisms and treatment of kidney stones and osteoporosis.

Purpose & Overview: Understanding the underlying pathophysiologic mechanisms of bone loss and kidney stone disease. Exploring appropriate countermeasures to slow bone loss and reduce the risk of kidney stones.

Educational Objectives:

1. To understand the prevalence of bone fracture and kidney stone disease among various bariatric surgeries.
2. To define underlined pathophysiologic mechanisms of Osteoporosis and kidney stone development in this population.
3. To define optimal management of osteoporosis and kidney stone disease in this population.

Conflict of Interest

Research support:

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Paid consultations for industry:

None

Co-inventor of patent:

Potassium Calcium Citrate

Grand Rounds Outline

- Introduction
- Prevalence of Bone Fracture After Bariatric Surgery
- Changes in Bone Mineral Density at Vertebral Spine & Proximal Hip Following Roux-en-Y Gastric Bypass (RYGB), Sleeve Gastrectomy (SG), and Adjustable Gastric Banding (AGB).
- Pathophysiologic Mechanisms of Bone Loss Following Bariatric Surgery
    a) Role of Mechanical Unloading on a Skeleton
    b) Role of Defective Gastric-acid Secretion and its Contribution to Impaired Calcium Absorption
    c) Role of Calciotropic Hormone Metabolism
- Energy Metabolism & Bone
    a) Role of Leptin in Bone & Metabolism
    b) Role of Adiponectin in Bone Metabolism
    c) Role of Gastrointestinal Peptides in Bone Metabolism
- Prevalence of Kidney Stone Formation Following Bariatric Surgery
- Pathophysiologic Mechanisms of Kidney Stone Formation Following Bariatric Surgery
    a) Role of High Urinary Oxalate following RYGB
    b) Role of Hypocitrauria following RYGB
    c) Role of Low urinary Volume, Acidic Urine pH and Urinary Calcium Following RYGB Procedure
- Potential Unified Treatment Approach towards Skeletal Bone Disease and Kidney Stone Formation Following Bariatric Surgery
- Conclusion

Introduction

Since the early 1960s, the prevalence of obesity among adults has more than doubled with an increase of 13.4 - 35.7% in U.S.[1]. The epidemic of obesity plateaued between 1999 – 2010, yet the prevalence of extreme obesity is significantly high as 14.5% of U.S. adults have body mass index (BMI) of 35 or greater. Compared with normal weight adults, the cost of health care in this population has been estimated to be significantly high.

Life style modifications and pharmacological treatments have been largely ineffective in treatment of extremely obese subjects. Bariatric surgery has emerged as the most effective treatment modality in promoting weight loss, morbidities, and mortalities (Figure 1) and has been well recognized in controlling body weight and ameliorating comorbidities in this population[2]. As a result, an increasing number of bariatric surgeries have been performed worldwide over the past decades. In recent years, Roux-en-Y gastric bypass (RYGB) exceeded the number of other procedures including sleeve gastrectomy (SG) and adjustable gastric banding (AGB). However, recent reports have established an increasing use of SG in this population (Figure 2). The highly significant impact of bariatric surgery on cardiovascular and diabetic complications accompanied with improvement in survival has overshadowed the adverse skeletal health and development of kidney stones.

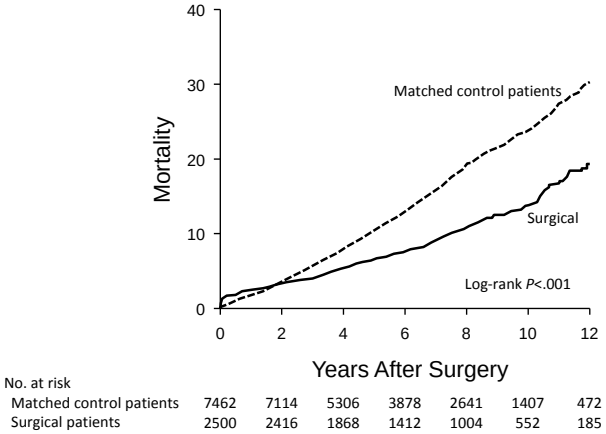

Figure 1. Association between Bariatric Surgery and Long-term Survival. Arterburn, JAMA, 2015.

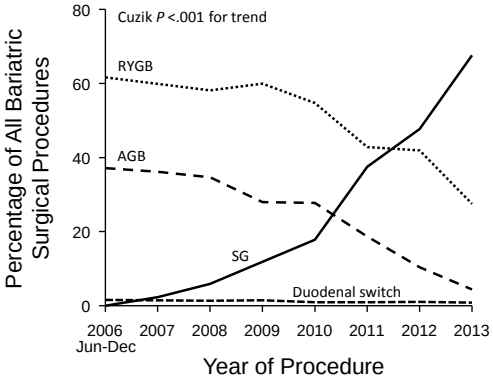

Figure 2. Relative use of Common Bariatric Procedures between June 2006- December 2013. Reames, JAMA, 2014.

Prevalence of Bone Fracture after Bariatric Surgery

To date, there are limited longitudinal population-based studies available to estimate the incidence of bone fractures in patients following bariatric surgery. In one retrospective cohort study in the United Kingdom, the record of 2,079 patients underwent bariatric surgery and matched controls were compared for 2.2 years[3] (Figure 3a). This study did not disclose an increase in fracture risk following surgery compared with obese weight match control subjects. To the contrary, in another population based study, residents of Olmsted County, Minnesota were followed for a median of 7.7 years displayed that bariatric surgery is associated with 2.3 fold increases the risk of the first fracture at any site[4] (Figure 3b). The discrepancies between these two studies are multifactorial and may be due to the younger population, short duration of follow-up, and inclusion of a large number of patients with ABG in the United Kingdom cohort.

[3] In contrast, the Minnesota cohort study included a significantly larger number of patients with RYGB and a longer duration of follow-up[4]. One limitation of the latter study was lack of involvement of weight matched control subjects to assess the independent confounding effect of obesity on increased fracture risks.

In a very recent study performed in U.S and Taiwan in which 120 uncontrolled diabetics were randomized into intensive lifestyle and medical management alone, or lifestyle and medical management plus RYGB. The achievement of triple endpoint control of glycemia, systolic blood pressure and LDL cholesterol were significantly higher in the RYGB cohort than in lifestyle and medical management alone. However, the RYGB cohort had prominently more fractures associated with falls compared with lifestyle and medical management alone. All fractures occurred in women and nutritional deficiencies were more prevalent in the RYGB group, despite use of nutritional support.[15]

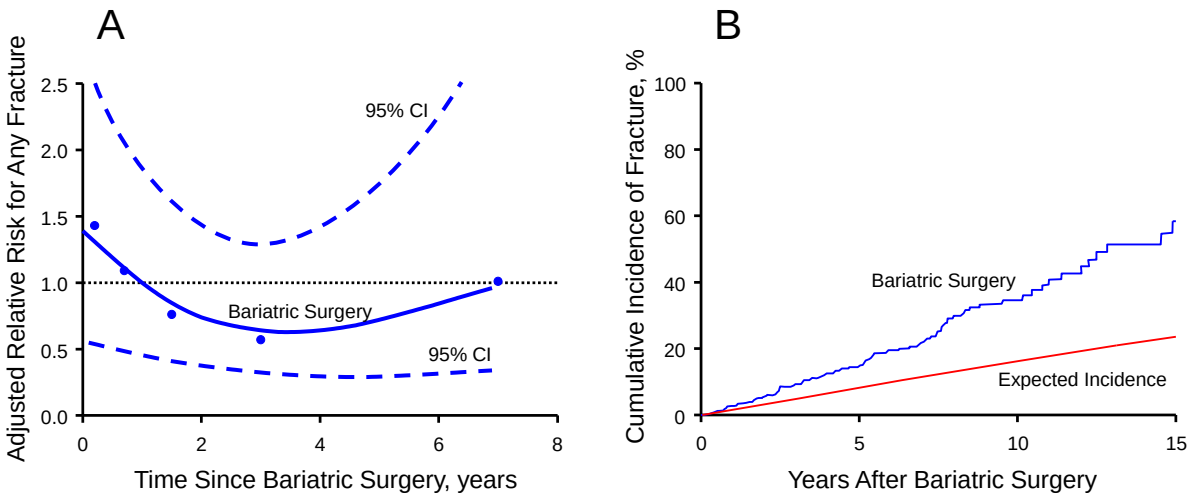

Figure 3. Skeletal Impact of Bariatric Surgery. A: Lalmohamed, BMJ, 2012; B: Nakamura, Osteoporosis Int., 2013.

Changes in Bone Mineral Density, Microarchitecture and Strength at Vertebral Spine & Proximal Hip Following RYGB

Bone is a dynamic tissue that constantly remodels in response to mechanical stresses and hormonal changes. Bone remodeling starts with bone resorption by osteoclast and ends with osteoblastic bone matrix synthesis which undergoes mineralization. An imbalance between bone resorption and bone formation will result in diminished bone strength and consequently increase bone fractures. Bone strength is now clinically determined by BMD analysis however, additional factors including alteration in microarchitecture, bone turnover, and bone mineralization will change the quality of the bone, which independently may increase the risk of bone fragility fractures.

It has been misconstrued that modern bariatric surgeries will overcome the skeletal complication imposed by jejunoileal bypass and biliopancreatic diversions, which were abandoned in the 1980s. Over the past decade, 12 studies have demonstrated changes in vertebral bone mineral density (BMD) ranging from -0.03 to -12.0% in a total of 289 subjects with ages ranging from 17 - 47 years old with female predominance ranging between 78 - 100% followed for 9 months- 2 yrs[5-15]. These studies showed that changes at hip BMD varied from 0 to -11% following the 9 - 24 months post RYGB (Figure 4). The fall in BMD was robust during the first 6 - 12 months, commensurate with rapid weight loss in most but not all studies[10,13,16].

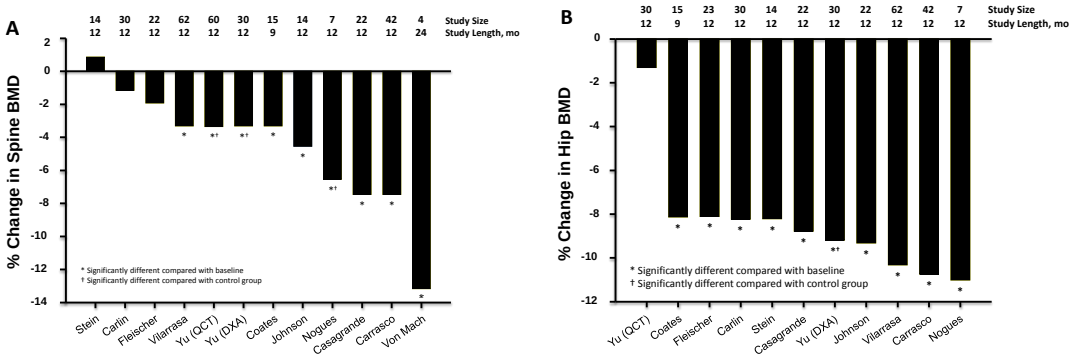

Figure 4. Bone mineral density changes at the hip and vertebral spine following RYGB. Adapted from Yu, JBMR, 2014.

In a recent longitudinal study of RYGB patients and matched obese subjects, bone density using DXA and volumetric BMD with quantitative computed tomography (QCT) showed persistent bone loss at both trabecular and cortical bone in RYGB patients compared to obese-controls.[11] This finding specifies that fall of BMD reported in previous studies is not due to the technical error imposed by increased body fat. These changes were associated with alterations in microarchitecture and bone strength using high-resolution peripheral QCT (HR-pQCT). The microarchiteratural changes were accompanied by significant trabecular involvement at radius bone and prominent increase in cortical porosity at the tibia.[11] The changes in the cortical bone property of the tibia were consistent with previous studies suggesting similar changes following bariatric surgery.[15] In addition, bone strength, assessed by microfinite element analysis used to estimate failure load was significantly lower at both the radius and tibia in RYGB patients compared to the obese-controls. These changes were demonstrated despite normalization of PTH and Vitamin D levels suggesting that factors other than calciotropic hormone may contribute to perturbed micoarchitectural and mechanical strength in the RYGB population.

Changes in Bone Mineral Density at Spine & Proximal Hip Following SG & AGB

With an increasing trend to perform SG, concern has been aroused towards the development of bone loss in this population. The clinical experiences with BMD changes following SG and AGB have been very limited. The results of the three reported studies in literature have been inconsistent, two studies demonstrated BMD changes at vertebral spine ranging from -1.2 to -4.6% [8,17].On the contrary, one study showed an increase of BMD at +7.9% one year after SG procedure [18] (Figure 5). Two studies have evaluated changes in hip BMD after SG over 6-12 months. Both studies found that SG led to significant loss of hip BMD.[8,17].

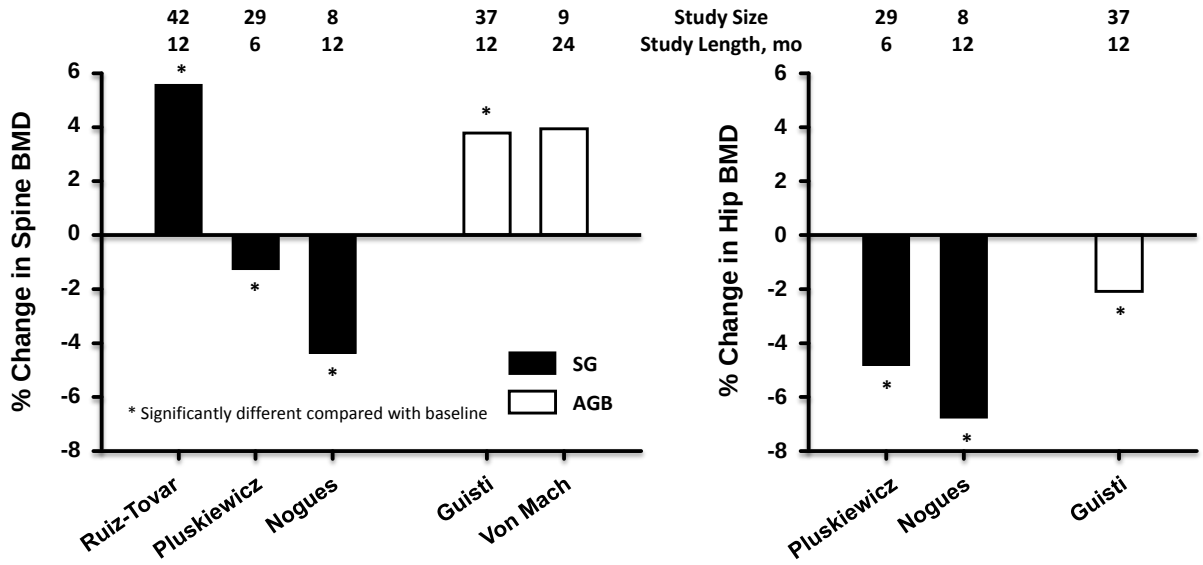

Figure 5. Bone mineral density changes at the spine and hip following sleeve gastrectomy and adjustable gastric banding. Adapated from Yu, JBMR, 2014.

Pathophysiologic Mechanisms of Bone Loss Following Bariatric Surgery

Pathophysiologic mechanisms of bone loss following bariatric surgery are complex and diverse including alterations in mechanical unloading on a skeleton, defective gastric acid secretion, derangements in calcium, calciotropic hormone metabolisms, and modulations in energy metabolism.

Role of Mechanical Unloading on a Skeleton

Mechanical loading, under normal physiological conditions, participates in the principal role of maintaining bone mass, bone strength, and bone size. Clinical studies exploring the effect of weight loss on BMD following bariatric surgery have been controversial. Few studies demonstrated a direct correlation between weight loss and fall in BMD at weight bearing skeletal sites including the proximal hip[10,12,13]. However, in one recent study, bone loss at both the axial and appendicular skeleton was reported to persist for 24 months following RYGB despite stabilization of weight.[19]

The underlying molecular mechanism of skeletal unloading has been linked to up-regulation of the mRNA of sclerostin (SOST)[20]. Sclerostin is a protein produced principally by osteocytes which possess mechanoreceptors which transmit the mechanical to biological signals[20]. Sclerostin produced by osteocytes inhibits osteoblastic cell differentiation and function by inhibiting Wnt/beta-catenin. The potential role of sclerostin and its association with bone loss has been recently shown in one study of 90 pre-menopausal women following RYGB and SG procedures[21]. This study demonstrated rapid and sustained increase of sclerostin level associated with increased bone turnover markers and fall of BMD in this population (Figure 6).

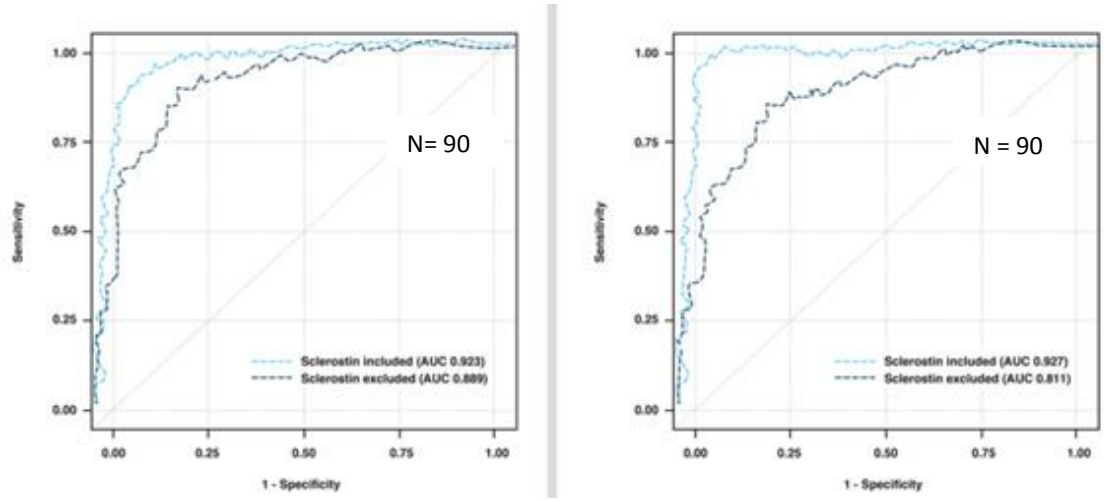

Figure 6. ROCC of the multiple regression models predicting Bone Mineral Density with and without following RYGB and SG. Muschitz, JCEM, 2015.

Role of Defective Gastric-acid Secretion and its Contribution to Impaired Calcium Absorption

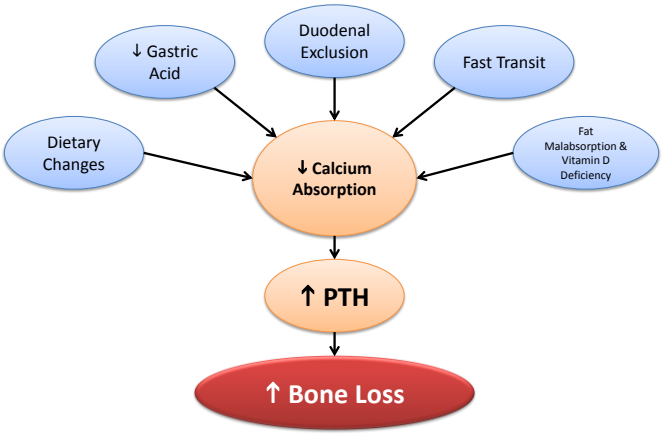

Figure 7. Impaired Calcium Absorption Following Bariatric Surgery.

Multiple factors including dietary changes, impaired gastric excretion, exclusion of duodenum, fast transit time, intestinal fat malabsorption and vitamin D deficiency will contribute to low intestinal calcium absorption in this population (Figure 7). Intestinal calcium absorption is affected by gastric pH, whereby an acidic pH enhances intestinal calcium absorption.[22,23] Limited studies investigating intestinal calcium absorption following bariatric surgery reported conflicting results with one study showing true fractional intestinal calcium absorption decreasing following RYGB surgery, however it remained within the normal range[42]. In a separate study following RYGB, despite normal vitamin D status intestinal calcium absorption was significantly decreased (Figure 8). This decline in intestinal calcium absorption was associated with a significant fall in 24-hour urine calcium excretion, and significant rise in serum PTH levels[24]. Gastric pH was not assessed in either of these studies.

To date, no study has alluded to whether bariatric surgery will influence gastric pH. In a recent study, in RYGB treated rats compared with sham operated control rats, the role of the rise in gastric pH was examined. RYGB resulted in a significant rise in gastric pH in RYGB rats associated with lower bone volume and strength as analyzed by microcomputed tomography. This study highlights the importance of impaired gastric secretions in the development of bone disease.

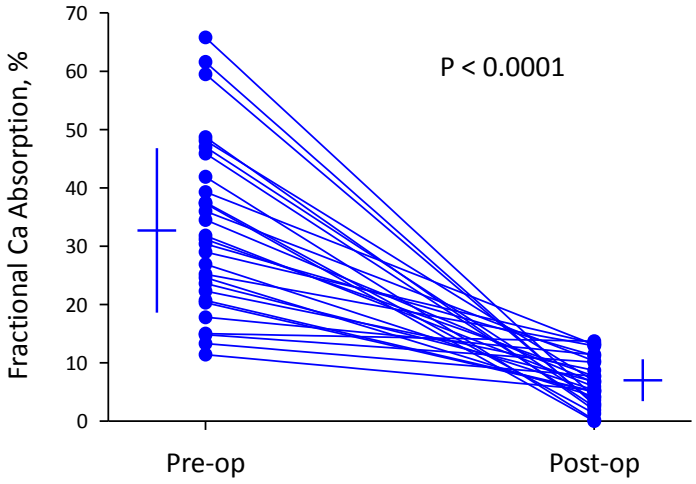

Figure 8. Fractional Ca absorption before and following 6 months of RYGB. Schafer, JBMR, 2015.

Role of the Calciotropic Hormone Metabolism

The derangement in calciotropic hormone metabolism has been described in obese subjects before bariatric surgery. An elevated serum parathyroid hormone (PTH) in severely obese subjects compared with non-obese subjects has been shown to decline with weight loss. Moreover, obese individuals suffer from vitamin D deficiency. The derangement in vitamin D metabolism has been linked to redistribution of vitamin D into fat tissue and also due in part to lifestyles[25]. However, conflicting results have been reported showing serum vitamin D levels in patients following RYGB and SG to be low or normal (Figure 9)[10,19].

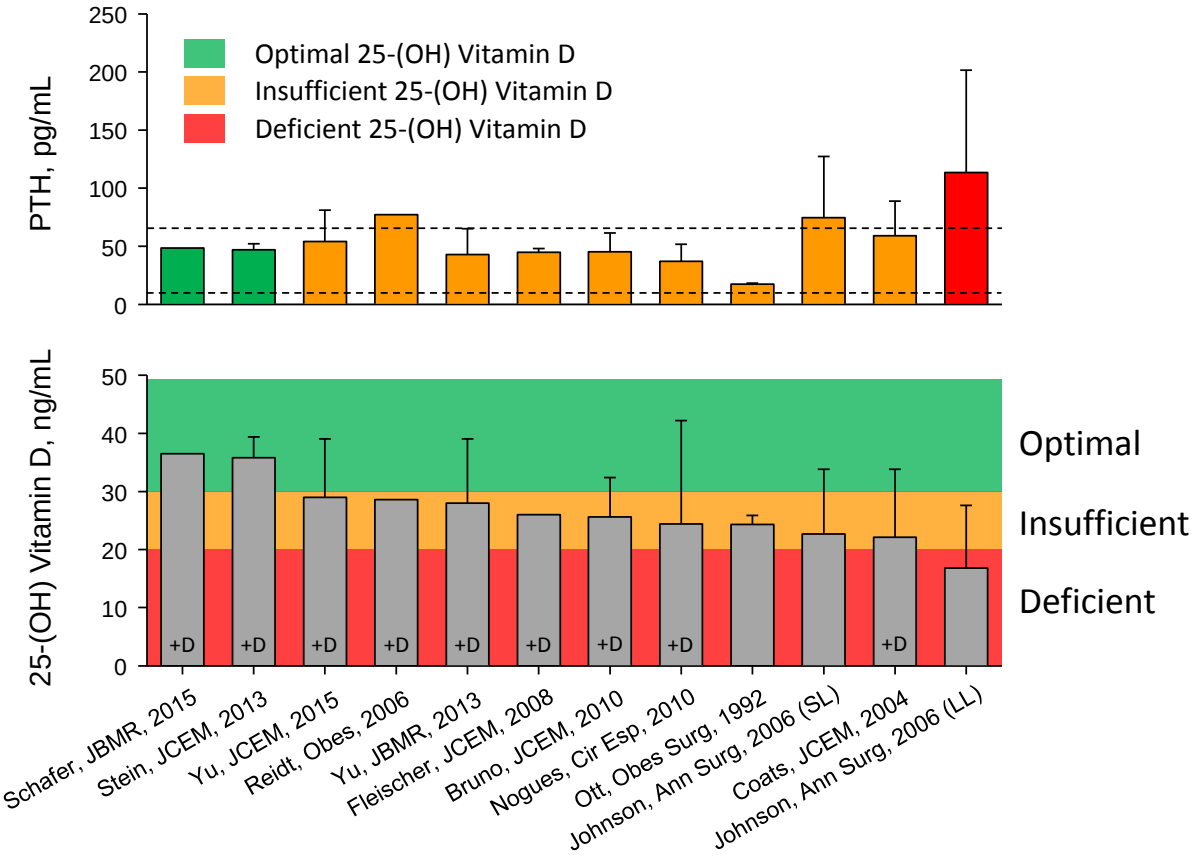

Figure 9. Serum PTH and 25(OH)D following RYGB and SG.

On the contrary, serum PTH has been shown to be overall persistently elevated following bariatric surgery[10] and is responsible for an increase in bone turnover, and decrease bone strength in this population. The significance of PTH in alterations in bone strength was supported in a study of 22 women who underwent RYGB using HR-pQCT to determine the microfinite element of the bone[15] (Figure 10). The results of this study indicated no alteration in tubercular compartment of the bone, but more particularly significant impairment in cortical bone compartment as manifested

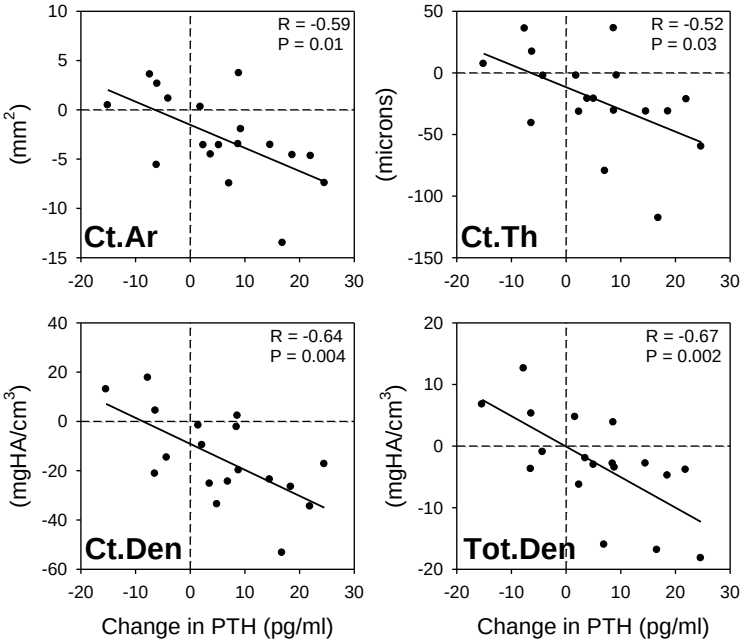

Figure 10. Association between changes in PTH and cortical microarchitecture. Stein, JCEM, 2013.

by prominent changes in the tibial cortical area, total density, cortical density, and cortical thickness.[15]

Energy Metabolism & Bone

Role of Leptin in Bone Metabolism

The inverse relationship between adipogenesis and osteoblastic bone formation has been known for many years. Since the discovery of leptin [26]it has been shown that this adipocyte-derived hormone may not only participate in controlling food intake, energy expenditure, and body-weight, but also in bone metabolism[27]. The experimental studies in animals on the role of leptin in bone metabolism have been contradicting whereas CNS administration of leptin was shown to be antiosteogenic however, its systemic delivery has been shown to increase bone growth and reduce bone loss.[27] Study in ob/ob mice with bone histomorphometric analysis of vertebral and femoral bone demonstrated an increase in bone mass compared with wild-type control.[27] In this model intracerebral leptin infusion resulted in reduced bone mass and mechanical strength in ob/ob mice. This study confirms an inverse relationship between adipogenesis and osteogenesis.

Table 1. Changes in bone turnover markers and leptin following RYGB. Bruno, JCEM, 2010.

n=20	Baseline	18 months	*P* Value
Age (yr)	46.6±9.0 (29.0-60.0)		
BMI (kg/m^2)	47.2±6.6 (39.5-60.0)	27.6±3.0 (23-33)	<0.0001
BAP (ng/ml)	17.6±5.3 (9.9-30.4)	22.2±7.8 (11.8-41.1)	0.0017
NTX (nM BCE)	10.8±2.7 (7.1-18.5)	16.9±5.5 (10.5-33.7)	<0.0001
PTH (pg/ml)	36.3±23.6 (12.3-75.0)	45.3±16.1 (26.5-77.8)	0.11
Leptin (ng/ml)	54.9±21.0 (18.8-90.2)	7.4±6.4 (1.1-28.9)	<0.0001

BAP = Bone Alkaline Phosphatase; NTX = N-Telopeptide

Our knowledge of the role of leptin on skeletal bone remodeling in humans and specifically its contribution to potential bone loss following bariatric surgery have not been fully elucidated. In one study, subcutaneous leptin administration in patients with generalized lipodystrophy with hypoleptinemia demonstrated no significant change in BMD following 16 - 18 months of treatment. Simultaneously, leptin treatment did not affect serum or urinary markers of bone formation and bone resorption. In a study of 20 RYGB patients, fall in BMI and serum leptin levels were associated with significantly increased serum N-telopeptide

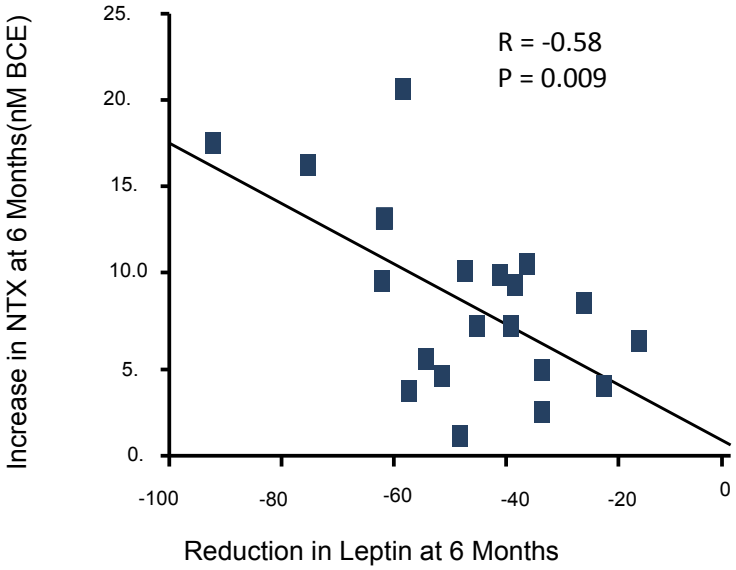

Figure 11. Correlation between serum NTX and Leptin six months following RYGB. Bruno, JCEM, 2010.

of type 1 collage (NTX)[28] (Table 1 and Figure 11).

Over the past decade, it has emerged that complex interplay among leptin, the central nervous system and bone play a principal role in bone remodeling. The action of leptin has been demonstrated to be mediated centrally in the brain stem and hypothalamus to mediate sympathetic stimuli to the skeleton. The release of norepinephrine (NE) via sympathetic nerve signals activate beta-2 adrenergic receptors (beta2AR) in osteoblasts which then modulates bone formation and also inhibits bone resorption[29,30]. This model contradicts the previously proposed inverse relationship between fat and bone.

Role of Adiponectin in Bone Metabolism

Adiponectin is a 30 kD protein which was first described in 1995[31]. It has been shown that adiponectin levels significantly increase following RYGB. The rise of adiponectin 12 months following RYGB was associated with significant reduction of BMD[6]. Studies *in vitro* have linked the effect of adiponectin to the stimulation of RANK-L and inhibition of osteoprotegerin in human osteoblasts.[32]

Role of Gastrointestinal Peptides in Bone Metabolism

Ghrelin is a peptide produced by the stomach fundus, which induces hunger in humans. After RYGB, and SG, ghrelin levels significantly declined. The effect of this peptide in bone turnover and BMD has not yet been reported following bariatric surgery. However, it has been shown that ghrelin *in vitro* increases osteoblastic cell proliferation and differentiation.
Glucagon-like peptides (GLP-1 and GLP-2) are secreted postprandially by the intestinal L-cells[33]. The serum levels of these peptides increases significantly after RYGB procedures. In only one study, it has been demonstrated that administration of GLP-1 is associated with a rise in BMD.

Prevalence of Kidney Stone Formation Following Bariatric Surgery

Since abandonment of the jejunoileal bypass, it was thought that the prevalence of kidney stone disease following modern bariatric surgery would be low. An initial report using data from a national private insurance claim demonstrated among a large cohort consisting of 4,690 patients following RYGB, a significantly high prevalence of kidney stones of 7.5% compared with 4.6% in obese controls.[34] The result of this study was later supported by another cross-sectional study of 762 patients from Olmsted County, Minnesota following bariatric surgery matched for the obese controls who did not undergo surgery. More than 2/3 of those treated in this study underwent RYGB with the remaining consisting of other malabsorptive or restrictive operations (Figure 12)[35]. Although prevalence of kidney stone episodes were similar between the two populations at the baseline, following RYGB the incidence of kidney stones more than doubled (11%)

Figure 12. Risk of incidence stones following RYGB and all malabsorptive bariatric surgery procedures compared with matched obese controls. Lieske, Kidney Int, 2015.

compared with obese non-surgical patients (4.3%). Although the rate of the RYGB procedures in recent years has diminished, in one 2008 estimate there were over 830,000 persons who underwent RYGB procedure.

Unlike RYGB, the incidence of kidney stones following restrictive surgeries has been found to be low. In one study of 201 patients following gastric-banding procedures, compared with 201 morbidly obese-control patients over 2.5 years showed a significantly lower rate of stone formation (1.5%) vs. (6%), respectively. Another retrospective study of 332 patients following AGB and 85 patients with SG over a 54 - month period, demonstrated a very low stone incidence in the two cohorts.[36] Within the AGB cohort, a person-time incidence rate of 3.40 stone diagnoses per 1000 person-years, however, within the SG group a person-time incidence rate of 5.25 stone diagnosis per 1000 person - years was found.[36] These results highlight a much lower incidence of kidney stones following restrictive bariatric procedures compared to RYGB.[34,35]

Pathophysiologic Mechanisms of Kidney Stone Formation Following Bariatric Surgery

The underlying pathophysiologic mechanisms of kidney stone formation following bariatric surgery are complex and diverse, including hyperoxaluria, hypocitraturia, and abnormally acid urine increasing the risk for kidney stone formation.

Role of High Urinary Oxalate following RYGB

A high incidence of hyperoxaluria has been reported among 2/3 of patients with kidney stones who have undergone RYGB. The onset of development of hyperoxaluria varies and may occur either early or late following bariatric surgery, depending on the type of surgical procedure, the differences in dietary intake and patient's health status. Oxalate homeostasis is maintained through hepatic oxalate synthesis, dietary oxalate intake, intestinal absorption, and renal excretion (Figure 13).[37]

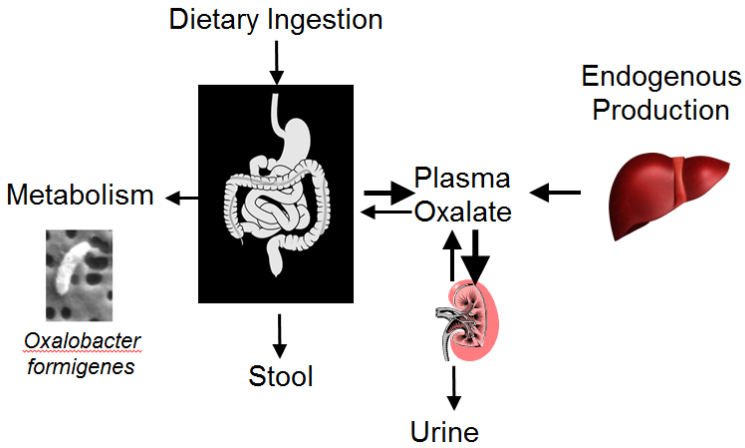

Figure 13- Oxalate Homeostasis

The underlying pathophysiologic mechanism of hyperoxaluria has not been fully understood. Increased fecal fat content has been shown in only one study of 11 patients following RYGB. Intestinal fat malabsorption in this study was associated with the rise of plasma concentration of oxalate and thereby significantly elevated urinary calcium oxalate supersaturation.[38] A study of a rat model of RYGB with high-fat feeding also supported the latter study by showing that fat malabsorption in this animal was associated with hyperoxaluria as well as acidic urine.[39] However, dietary oxalate and fat restriction did not fully rescue the high urinary oxalate excretion in this model; this suggests that hyperoxaluria may not be totally due to intestinal fat malabsorption. From these findings, it was suggested that (1) complexation of unabsorbed fatty acids to calcium and magnesium in the intestinal lumen increases intestinal oxalate content and absorption. Validity of this scheme has been confirmed with oral oxalate load following bariatric surgery, showing an increase in urinary oxalate excretion 2-4 hours after oxalate load.[13] (2) It has been suggested but not validated that alterations in intestinal microbial flora following bariatric surgery could potentially modify the colonization of lower intestinal flora with respect to oxalobacter formigenes, which are known to degrade luminal oxalate (Figure 14). (3) Yet, another pathway has been suggested to be due to increased permeability of the colonic mucosa epithelial cells as a consequence of exposure to unconjugated bile acids and long-chain fatty acids following RYGB. Hyperoxaluria and kidney stone formation following restrictive bariatric surgery has not been significant.

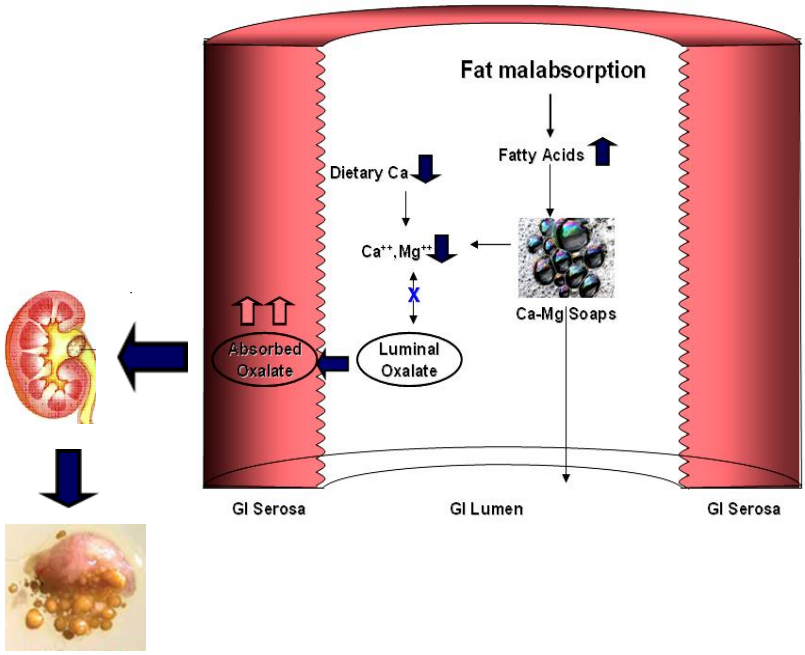

Figure 14. Intestinal fat malabsorption and hyperoxaluria.

Role of Hypocitrauria following RYGB

Hypocitrauria is a principal finding, but not for all patients following RYGB. Its prevalence varies ranging from 24 - 63%.[25] Hypocitrauria is commonly encountered in metabolic acidosis. Citrates play an important inhibitory role against calcium oxalate and calcium phosphate crystallization. The inhibitory action involves the formation of soluble complexes of these salts and thereby reduces the urinary supersaturation and also exerts direct inhibition effects against the calcium oxalate crystallization processes. One distinction in the hypocitraturic population is the absence of overt metabolic acidosis which may be attenuated implying participation of bone in the buffering of excessive acid load imposed by intestinal fluid loss. Consistent with this

scheme, the study in RYGB rats compared with sham rats showed a rise in the anion gap and lactate levels as well as significant and inverse correlation with bone loss.

Role of Low Urinary Volume, Acidic Urine pH and Urinary Calcium Following RYGB Procedure

Due to a limited gastric pouch reservoir, low urinary volume is commonly detected in most of the bariatric population. In two studies, acidic urine pH has been shown but not uniformly following RYGB, accompanied with supersaturation of dissociated uric acid.

Hypocalciuria is frequently detected following RYGB, which plays a protective role against calcium oxalate crystallization by overriding the effect of hypocitraturia and hyperoxaluria.[13] The underlying mechanism of hypocalciuria has been linked to impaired intestinal calcium absorption.

Potential Unified Treatment Approach towards Skeletal Bone Disease and Kidney Stone Formation Following Bariatric Surgery

Given concern with nutritional deficiencies and impaired intestinal calcium absorption, the American Association of Clinical Endocrinologist, The Obesity Society, The American Society of Metabolic and Bariatric Surgery have all recommended calcium supplementation in this population. In these guidelines, they proposed the daily treatment consisting of 1,200 - 2,000 mg of calcium and ergocalciferol 50,000 IU once or twice a week and a higher dose for those subjects with severe vitamin D deficiency of approximately 50,000 - 150,000 IU per day.

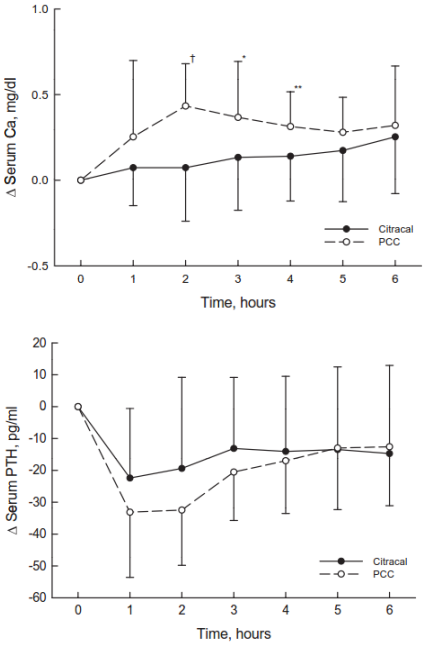

Figure 15. Changes in serum calcium and serum PTH after single dose of Citracal tablet and PCC. Sakhaee and Pak, Significance between 2 phases at corresponding time points is indicated by *P<0.05, **P<0.01, †P<0.001. Surg Obes Rel Dis, 2013.

These societies specifically recommend that this population be supplemented with calcium citrate tablets due to its high intestinal bioavailability, based on study of post-menopausal women comparing the tablet formulation of calcium citrate and calcium carbonate. The validity of this recommendation was contradicted in a study of 23 obese subjects following RYGB showing that supplementation with calcium citrate of 1,500 - 1,800 mg/daily in addition with 600-800 IU/daily did not change serum 25(OH) D levels and serum PTH concentration[13]. It was shown that a single dose of calcium citrate in tablet form was not effective in suppressing PTH secretion in this population[40]. In contrast, administration of a single dose pre-solubilized effervescent (liquid) potassium calcium citrate (PCC) conferred bioavailable calcium and was effective to significantly inhibit PTH secretion (Figure 15)[40]. The effervescent pre-solubilized

PCC supplementation is novel since it may reverse the pathophysiologic derangements operative for the skeletal bone loss and kidney stone formation.

Supporting evidence came from a short-term, randomized cross-over placebo controlled study in 24 patients following RYGB[41], demonstrating that PCC significantly inhibited bone turnover by lowering PTH secretion (Figure16). Additionally, treatment with PCC conferred alkali load resulting in increased urinary pH and citrate, commensurate with attenuating urinary calcium excretion. These changes were accompanied with inhibition against calcium oxalate crystal agglomerations and reduction in urinary supersaturation of uric acid. Future long-term studies are needed to support the clinical efficacy of this medication against bone fractures and kidney stone incidence in this population.

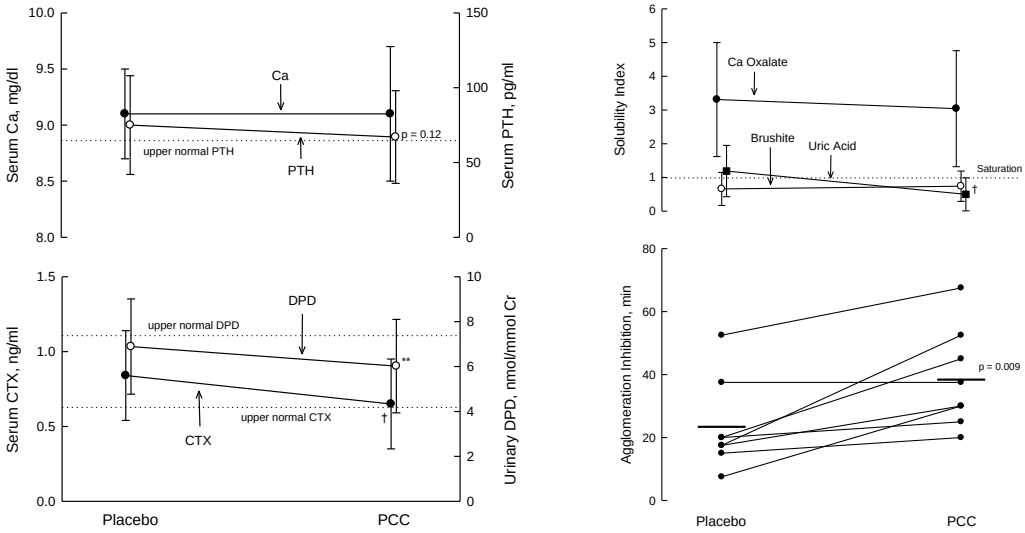

Figure 16. Effects of PCC on serum Ca, PTH, bone turnover marker and saturation indices. Sakhaee & Pak, Surg Obesity Rel Dis, 2012.

Bisphosphonates are used as the first drug of choice in the treatment of senile osteoporosis. At present time there is not report of use of these drugs following bariatric surgery. However, bisphosphonates have been used following gastric bypass surgery in patients with gastric cancer. In a study of 13 patients with gastric cancer who developed progressive bone loss with severe osteopenia unresponsive to vitamin D treatment, alendronate treatment for 2 years improved BMD significantly. In rat model of gastrectomy and gastric bypass induced osteoporosis/osteomalacia, treatment with oral bisphosphonate showed improvement in bone density and biochemical marker in bone turnover. However, there is a concern with the use of this drug following bariatric surgery due to an underlying intestinal calcium malabsorption and prevalent vitamin D deficiency, which potentially increased the risk for severe hypocalcemia in this population.

Conclusion

Bariatric surgery has been established to diminish cardiovascular risks, improve type 2 diabetes and reduce all/causes of mortality in morbidly obese patients[2], with an enormous impact on health and economy of the nation. However, it has emerged that, it carries a high risk of bone fracture and kidney stones.[4,34,35] Therefore, it is crucial that this population receives prophylactic measures to avoid these complications. At this time, treatment with PCC appears to be rational since it may avert both skeletal and kidney stone complications the feasibility of this treatment should be tested in long-term study in prevention of kidney stone incidence and bone fractures.

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