

Bariatric Surgery: What the Rheumatologist Needs to Know

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ABSTRACT. A staggering 76 million adults are obese in the United States. It is known that obesity contributes to increased incidence and worse disease outcomes in many rheumatic conditions. Bariatric surgery has emerged as the most effective treatment modality for the morbidly obese, leading to substantial and sustained weight loss. The purpose of this review article is to summarize the findings of studies investigating the effect of substantial weight loss achieved through bariatric surgery on rheumatic disease and outcomes. Second, with an increasing number of patients undergoing bariatric surgery, it is important for the rheumatologist to have a basic understanding of the commonly performed bariatric procedures and to be aware of important nutritional deficiencies and medication restrictions that apply to this patient population. (J Rheumatol First Release May 1 2016; doi:10.3899/jrheum.160075)

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OBESITY

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According to the US National Health and Nutrition Examination Survey data from 2011 to 2012, one-third of the US population was obese¹. In comparison to behavioral and pharmacological treatments, bariatric surgery results in a more sustained and significant weight loss of 50%–70% of excess body weight, making it the most effective treatment for obesity^{2,3}. Further, bariatric surgery decreases overall mortality and effectively manages obesity-related comorbidities⁴.

Currently, surgery is reserved for patients with a body mass index (BMI) > 40 kg/m² or those with BMI > 35 kg/m² with 1 or more severe obesity-related conditions⁵. Because of the high rates of remission of chronic metabolic disorders such as type 2 diabetes mellitus (T2DM) that occur within days of surgery and by mechanisms independent of weight loss, the term “metabolic surgery” has gained popularity.

Obesity has been linked to an increased incidence of rheumatic diseases such as osteoarthritis (OA), gout, psoriatic arthritis (PsA), and rheumatoid arthritis (RA)^{6,7,8,9}. Adipose tissue is considered a potent endocrine organ, releasing proinflammatory cytokines such as interleukin (IL)-6, IL-1, and tumor necrosis factor, macrophages, and adipokines. In

addition to their effects on appetite regulation and fat metabolism, adipokines such as leptin and adiponectin exert and modulate inflammatory effects on synovium, bone, and cartilage, and contribute to the development of rheumatic disease^{10,11}. Following bariatric surgery procedures, a decrease in proinflammatory cytokine and leptin levels has been demonstrated¹². Therefore, the effect of substantial weight loss achieved through bariatric surgery on outcomes of rheumatic disease is an area of growing interest that will be reviewed in our paper. In addition, because more of our patients will be undergoing bariatric surgery, it is important to provide the rheumatologist with a basic understanding of the commonly performed procedures and highlight important nutritional deficits and medication restrictions that may affect patient management.

BARIATRIC PROCEDURES EXPLAINED

Bariatric procedures have significantly evolved from the time of the first jejunoileal bypasses performed in 1954. This procedure is no longer performed because of a high complication rate that interestingly included the development of an inflammatory arthritis¹³. Antibodies to bacterial antigens residing in the redundant loop of the small intestine were found in the serum of some affected patients and reversal of the intestinal bypass resulted in amelioration of arthritis along with the disappearance of these antibodies¹⁴.

Bariatric procedures performed at this time include the Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy, gastric band, and duodenal switch with or without biliopancreatic diversion. Most surgeries are now performed using minimally invasive (laparoscopic) techniques.

RYGB was the most popular weight loss procedure until

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2013. In this surgery, the proximal stomach is divided from the rest of the stomach, resulting in the formation of a new, small 2-ounce pouch. Next, the jejunum is divided and the distal end is brought up and connected to the newly created small stomach pouch, creating a gastrojejunostomy. The standard length of this Roux or alimentary limb is usually 150 cm, but short and long variants exist, with the latter resulting in more malabsorption. The procedure is completed by connecting the proximal part of the divided jejunum (biliopancreatic limb) to the Roux limb so that gastric, liver, and pancreatic secretions from the bypassed stomach and duodenum will eventually mix with food in the common channel (Figure 1).

Laparoscopic sleeve gastrectomy (LSG) is now the most commonly performed procedure in medical centers in the United States. In LSG, about 80% of the stomach is removed, leaving a small tubular stomach (Figure 2). LSG is perceived to be technically easier to perform than the RYGB and results in an equivalent amount of excess weight loss (EWL) and similar improvement in comorbid conditions. Other benefits of this procedure compared with the RYGB are the lower risks of nutritional deficits and the avoidance of dumping syndrome. However, gastroesophageal reflux disease is more common after LSG.

The laparoscopic-adjustable gastric band (LAGB) involves the placement of an adjustable band creating a small gastric pouch, thus limiting daily food intake. LAGB has

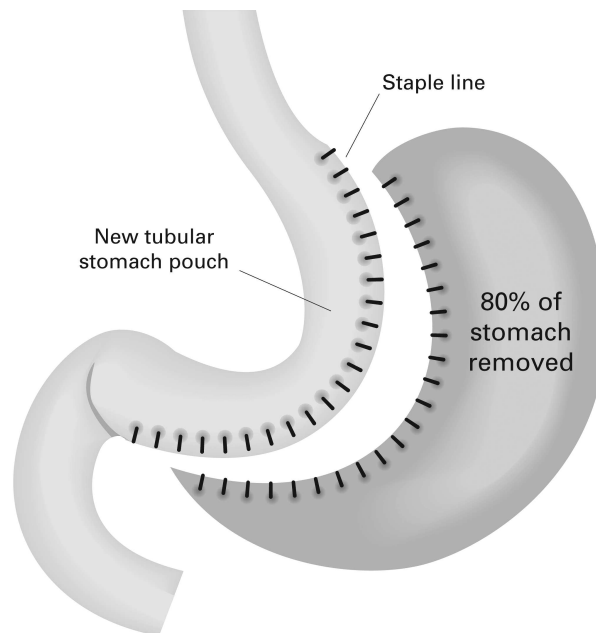


Figure 2. Sleeve gastrectomy.

fallen out of favor because of insufficient weight loss and higher rates of reoperation.

Other less commonly performed procedures are the duodenal switch (DS) with or without biliopancreatic diversion (BPD/DS). This involves the creation of a smaller tubular stomach pouch by removing two-thirds of the stomach and then bypassing a large portion of small intestine (three-fourths). Although BPD/DS results in the most EWL and highest rates of T2DM remission, it is very selectively performed because of the higher complication rates, including greater nutritional risks.

The mechanisms by which bariatric surgery are thought to induce weight loss and exert its beneficial metabolic effects are complex and still not completely understood. They include reduction in gastric size, anatomical gut rearrangement, altered flow of nutrients, and vagal manipulation¹⁵. Another important factor is alteration of gut hormones, including peptide YY (PYY), glucagon-like peptide 1 (GLP-1), and ghrelin. These hormones are appetite-regulating hormones. Ghrelin, produced by the fundus of the stomach, is significantly reduced after LSG, leading to loss of appetite. Secretion of GLP-1 and PYY is increased following bariatric surgery, and these incretins increase insulin sensitivity and stimulate β cell proliferation in the pancreas, hence offering an explanation for the early improvement seen in T2DM. These incretins also cause early satiety, which helps promote weight loss¹⁵.

Recently, bile acids and their receptors (FXR and TGR5) have emerged as key signaling molecules with effects on satiety, incretin and glucose homeostasis, and gut microbiota following bariatric surgery¹⁶.

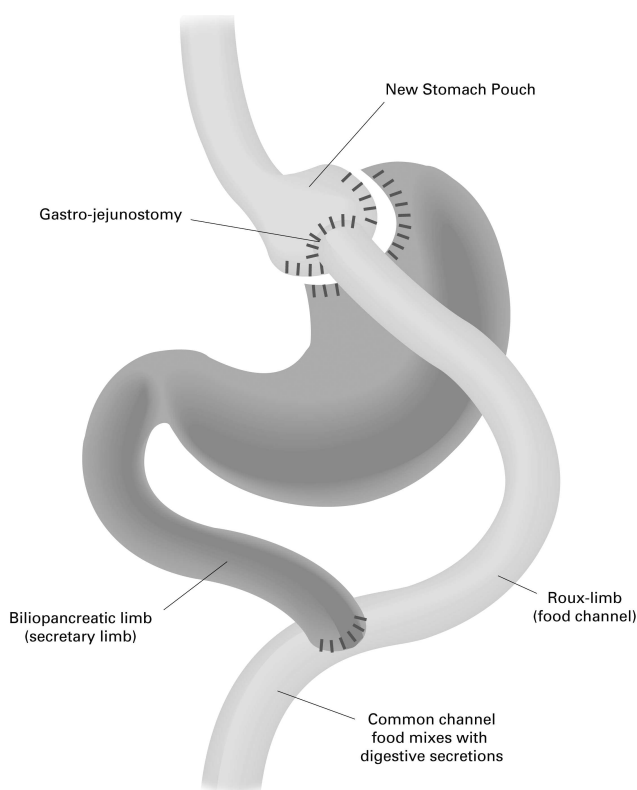


Figure 1. Roux-en-Y gastric bypass.

EFFECT OF BARIATRIC SURGERY ON RHEUMATIC DISEASE

Osteoarthritis. Individuals with a BMI > 30 are 7 times more likely to have knee OA than those with BMI < 25, and obesity is the main modifiable risk factor for knee OA¹⁷. An increase in mechanical loading is felt to be the main contributor to the development of knee OA. Obesity has also been linked to the development of OA in non-weight bearing joints and may be related to the release of proinflammatory cytokines from adipokines that participate in cartilage degradation¹⁸.

In a study by Hacken, *et al*, 24 patients with symptomatic knee arthritis underwent bariatric surgery and achieved an average weight loss of 27% at the 2-year followup. All variables from the Knee Osteoarthritis Outcome Score (KOOS) and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) assessments were significantly improved at 6, 12, and 24 months when compared with baseline. There was a positive correlation between changes in the KOOS/WOMAC scores and the change in BMI¹⁹.

Richette, *et al* also found similar improvement in WOMAC scores in 44 obese patients with moderate/severe knee OA who underwent bariatric surgery. They found that weight loss surgery resulted in a significant decrease in IL-6, high-sensitivity C-reactive protein (CRP), fibrinogen, and orosomucoid. There was also a significant increase in N-terminal propeptide type IIA collagen (+32%), a biomarker of cartilage synthesis, and a significant decrease in cartilage oligomeric matrix protein (COMP; -36%), a biomarker of cartilage degradation. Changes in COMP were correlated with changes in insulin levels and insulin resistance, but not adipokine levels. Therefore, weight loss after bariatric surgery appears to result in structural effects on cartilage, and changes in insulin resistance may be involved in this²⁰.

Abu-Abaid, *et al* demonstrated radiographic structural changes in 64 patients with knee pain and early radiograph OA who underwent bariatric surgery. An average increase in joint space of about 0.655 mm was seen and was associated with an average BMI reduction of 6.3 kg/m² at the 3-month followup²¹.

Joint replacement. Morbid obesity is considered a relative contraindication to unilateral knee joint replacement because of the higher rates of wound infection, dehiscence, prosthetic loosening, and thromboembolic complications. Severson, *et al* divided 125 patients into 3 groups: group 1 had total knee arthroplasty (TKA) before bariatric surgery, group 2 had TKA within 2 years of bariatric surgery, and group 3 had TKA more than 2 years after bariatric surgery. The highest complication rate was seen in group 1. Patients in group 3 had significantly shorter anesthesia, operation, and tourniquet times, but also the highest number of revisions. No revisions were seen in group 2²².

Another study looked at 143 patients undergoing bariatric surgery and hip or knee joint replacements. Bariatric surgery

was performed first in 53 of the patients and arthroplasty first in 90 patients. Wound infection and hospital readmission rates were 3.5 and 7 times lower, respectively, in the group of patients who had bariatric surgery prior to joint replacement²³.

In contradiction to the studies above, Martin, *et al* found that bariatric patients who underwent TKA had a higher risk of reoperation (HR 2.6) compared with patients of a higher prebariatric BMI who did not undergo bariatric surgery²⁴.

Gout and hyperuricemia. Obesity has contributed to the increasing prevalence of gout, and a strong-graded association between successive BMI category and gout prevalence can be demonstrated⁸.

Acute gout attacks are common in the immediate postoperative period following bariatric surgery, and prophylactic treatment for gouty attacks should be considered in all preoperative patients with gout. In 1 study, a third of 21 patients with gout had an acute gout attack following bariatric surgery²⁵, and another study found an increased frequency of acute gout attacks in patients undergoing bariatric compared with nonbariatric upper abdominal surgeries (18% vs 2%)²⁶. In the latter study, however, the number of gout attacks and serum uric acid (SUA) levels started to decrease after the first postoperative month. The SUA decreased from 9.1 mg/dl at baseline to 5.6 mg/dl 13 months after surgery, and the number of patients with gout attacks decreased from 23% in the year before surgery to 8% in postoperative months 1 to 13²⁶.

Improvement in hyperuricemia was also demonstrated in over 2000 patients studied in the Swedish Obese Subjects Study. SUA levels decreased by 15% at 2 years and 9% at 10 years in patients who underwent bariatric surgery compared with controls⁴. In their study, Dalbeth, *et al* also documented reductions in SUA in 60 obese diabetics who achieved an average weight loss of 34 kg 1 year after bariatric surgery. After an initial postoperative increase in SUA that was partly attributed to renal dysfunction, SUA started to decrease from the third month after surgery. The mean SUA decreased from 0.38 mmol/l (6.4 mg/dl) at baseline to 0.30 mmol/l (5.0 mg/dl) 1 year after bariatric surgery, and the majority of patients were able to achieve SUA below that of the SUA saturation limit. Out of 12 patients with gout included in the study, mean SUA decreased from 0.44 mmol/l to 0.33 mmol/l (7.4 mmol/l to 5.55 mg/dl) 1 year after surgery, and the majority of patients were able to achieve SUA below the target therapeutic level of 0.36 mmol/l (6 mg/dl). In addition, 8 patients (67%) were not receiving any urate-lowering therapy a year after surgery²⁷. Interestingly, the same investigators isolated peripheral blood mononuclear cells (PBMC) from the blood of obese patients before and after surgery, and incubated them with monosodium urate (MSU) crystals. There was a significant reduction in PBMC IL-1 β , IL-8, and IL-6 responses to MSU crystals after surgery²⁸.

Rheumatoid arthritis. A recent metaanalysis of 11 studies exploring the association between BMI and RA risk showed

that obese individuals had a 24% increased risk for RA development compared with nonobese individuals⁷.

Obese patients with RA also appear to have higher disease activity and are less likely to remain in sustained remission²⁹.

Sparks, *et al* conducted a retrospective cohort study of 53 patients with RA who underwent bariatric surgery and had a mean weight loss of 41 kg 1 year postsurgery. Of the patients, 57% had moderate to high disease activity prior to surgery and this dropped to 6% twelve months after surgery. Then 5.8 years after surgery, 74% of patients were in remission compared with 26% at baseline. In addition, fewer RA medications were prescribed and lower ESR and CRP were documented in the postsurgery group³⁰.

Psoriatic arthritis. Sethi, *et al* analyzed a retrospective database of bariatric surgeries performed at a single center between 2002 and 2013, and identified 86 patients with a preoperative diagnosis of psoriasis, 21 of whom also had a diagnosis of PsA. Disease severity ratings (0–10 scale) in patients with psoriasis decreased from 5.6 prior to surgery to 4.4 one year after surgery and from 6.6 to 4.5 in patients with PsA (both groups $p < 0.01$). The patients with the worst disease and greatest EWL experienced the most improvement³¹.

Systemic lupus erythematosus (SLE). There are limited data investigating the effect of bariatric surgery on SLE. A retrospective study of 31 patients with SLE who underwent bariatric surgery from 2005 to 2013 (23 had RYGB, 3 LSG, 5 other) demonstrated that 42% of patients were able to reduce the number of immunosuppressive medications they were taking at the 3-year followup and 19% were not receiving steroids completely. However, 13% of patients had major postoperative complications, and perioperative immunosuppressive use was significantly associated with postoperative complication³².

Bone and mineral metabolism. Because preoperative Vitamin D deficiency is seen in up to 60%–70% of patients, it should be screened and treated for prior to surgery^{33,34}.

Vitamin D is absorbed by the jejunum and ileum and therefore procedures that bypass this part of the intestine such as the RYGB and BPD further exacerbate Vitamin D deficiency. The same procedures also affect calcium absorption. In response to low calcium ions or Vitamin D, there is a compensatory increase in parathyroid hormone (PTH).

LAGB and LSG cause minimal to no change in Vitamin D, calcium, or PTH³⁵.

Studies looking at bone mineral density (BMD) changes in post-RYGB patients demonstrate decreases in BMD at the hip of about 8% to 10%, but no apparent decline of lumbar BMD^{36,37,38}. Postmenopausal status and amount of weight loss were important factors in BMD decline^{37,38}. These studies also show evidence of early bone remodeling with elevations in urinary N-telopeptide cross-linked collagen type 1, a marker of bone resorption, occurring at 3 months and persisting at least a year after surgery. More modest elevations

of bone formation markers were seen^{36,37,38}. Vitamin D malabsorption and secondary hyperparathyroidism were seen in some of these studies despite increased levels of calcium/Vitamin D supplementation^{37,38}.

Two prospective studies carried out on patients undergoing BPD/DS showed a decrease in lumbar spine BMD of about 4% to 8%^{39,40}.

The effects of LAGB and LSG on bone density and bone turnover markers are less clear. One study demonstrated an increase in bone resorption markers and a decrease in hip BMD of about 6%, but no change in lumbar spine BMD 2 years after LAGB⁴¹.

A study by Vilarrasa, *et al* comparing the effects of LSG with RYGB on bone density at 1 year found no difference in the percentage of patients with osteopenia or osteoporosis (OP) between the 2 groups. Menopausal women were at higher risk of having low bone mass, but the presence of OP was uncommon, being seen in 1 patient from each group⁴².

Overall, despite the reduction in BMD seen in these studies, values often remain within or above normal⁴³.

Bariatric surgery can affect bone through reduced skeletal mechanical loading, decrease in estrogen levels, and secondary hyperparathyroidism. Changes in the levels of adipokines and gut hormones following bariatric surgery are also involved because these hormones have been shown to affect bone metabolism^{44,45}. Leptin concentrations decrease in proportion to loss of total body fat and are inversely correlated with increased levels of bone resorption markers⁴⁵.

But are the changes in bone density and bone resorption markers following bariatric surgery clinically relevant in terms of fracture risk? Lalmohamed, *et al* did not find increased rates of osteoporotic fracture in patients 2.2 years after bariatric surgery when compared with controls, although there was a trend toward increased fracture risk 3–5 years postsurgery and in patients who had a greater EWL⁴⁶.

A historical cohort study of 258 Olmsted County, Minnesota, residents followed for an average of 7.7 years after bariatric surgery demonstrated a 2-fold increased risk of fracture at the traditional osteoporotic sites⁴⁷.

Recommendations for calcium/Vitamin D and BMD monitoring. Clinical practice guidelines published by the American Association of Clinical Endocrinologists, The Obesity Society, and the American Society for Metabolic and Bariatric Surgery in 2013 recommended annual testing of albumin, calcium, PTH, 25-hydroxy Vitamin D levels, and 24-h urinary calcium excretion⁵. A combined dietary and supplementary calcium intake of 1500–2000 mg/day in RYGB patients and 1800–2400 mg/day in BPD patients is recommended. Because there is minimal acid secretion by the stomach pouch created after RYGB, calcium citrate is the preferred form of calcium supplementation because it does not depend on an acid environment for optimal absorption.

In the early postoperative period, at least 3000 units/day of Vitamin D in the form of ergocalciferol or cholecalciferol

may be required to titrate levels to > 30 ng/ml. In cases of severe Vitamin D malabsorption, oral doses as high as 50,000 units 1–3 times weekly to daily may be required⁵.

The guidelines also suggested that in patients undergoing RYGB or BPD, BMD measurements may be indicated to monitor for OP at baseline and at about 2 years. However, it was acknowledged that at this time there are insufficient data to warrant preoperative assessment of BMD in all patients, outside of the formal National Osteoporosis Foundation recommendations⁵.

Of note, there are technical problems with BMD measurement in morbidly obese patients because the variability in areal BMD increases significantly with tissue depths greater than 25 cm⁴⁸. For the very obese or those with secondary hyperparathyroidism, which appears to be catabolic at cortical sites, BMD measurements of the distal one-third of the forearm should be considered⁴⁹.

If therapy for OP is required, intravenous bisphosphonate therapy is preferred because of the concern about adequate oral absorption and potential anastomotic ulcerations seen after oral bisphosphonate use⁵.

MEDICATION CONSIDERATIONS

Nonsteroidal antiinflammatory drugs have also been implicated in the development of anastomotic ulcerations and perforations in gastric bypass patients and should be avoided if possible⁵⁰. There are no specific guidelines pertaining to the

pre- or postoperative optimization of disease-modifying antirheumatic drugs (DMARD) or other immunosuppressants in the bariatric population. Case reports from transplant patients receiving cyclosporine, tacrolimus, or mycophenolate show that decreased drug absorption rather than toxicity is the main consideration in the postbariatric population⁵¹. Reduction in drug absorption is more frequent in patients who have undergone procedures such as the RYGB or DS because of decreased intestinal length, which reduces the surface area available for drug absorption. For the same reasons, absorption of enteric, extended, or time-release medications is reduced after malabsorptive procedures, and immediate-release formulations should be used instead. Rheumatologists should monitor their patients closely for therapeutic effect and if concerns about adequate drug absorption arise, alternative agents or modes of delivery should be considered (for example, liquid formulations or subcutaneous delivery, although obesity itself may limit subcutaneous delivery of some medications). Further studies looking at the pharmacokinetics of commonly prescribed DMARD/immunosuppressants after various bariatric procedures are clearly needed to clarify this important area.

DISCUSSION

From the preliminary studies presented in our paper, it appears that obese patients with rheumatic diseases such as RA, PsA, gout, and OA experience improved outcomes

Table 1. Summary of rheumatic disease outcomes following bariatric surgery in selected studies.

Disease	Study	Subjects/Surgery	Outcomes
OA	Hacken, <i>et al</i> ¹⁹	24 pts with knee OA (19 RYGB, 4 GB, 1 with SG)	↓ all variables KOOS and WOMAC at 6, 12, and 24 mos
	Richette, <i>et al</i> ²⁰ Abu-Abeid, <i>et al</i> ²¹	44 pts with knee OA (38 RYGB, 6 GB) 64 pts with knee pain and early radiographic OA	↓ all variables WOMAC and ↓ pain score from 50 to 25 (VAS) ↑ 0.655-mm joint space at 3 mos Function score ↑ from 78.5 to 90.69 (out of 100)
Gout	Romero-Talamás, <i>et al</i> ²⁶	99 pts with gout (69 RYGB, 22 SG, 8 GB) compared with 56 pts with gout undergoing nonbariatric abdominal surgery	↑ “early” gout attacks (18% in bariatric surgery group compared with 2% in abdominal surgery group) % of pts with at least 1 gout attack ↓ from 24 prior to surgery to 8 during postop mos 1–13
RA	Sparks, <i>et al</i> ³⁰	53 pts with RA (43 RYGB, 7 GB, 3 SG)	↓ in no. pts with moderate/high disease activity from 57% to 6% No. pts in remission ↑ from 26% to 74% at 5.8 yrs Fewer RA medications, lower ESR and CRP
Psoriasis and PsA	Sethi, <i>et al</i> ³¹	86 pts with psoriasis 21 also with PsA	Disease severity score ↓ from 5.6 to 4.4 (0–10 scale) ↓ score 6.6 to 4.5
SLE	Corcelles, <i>et al</i> ³²	31 pts with SLE (23 RYGB, 3 SG, 5 other)	42% pts ↓ IS medication 3 yrs postsurgery 19% not receiving steroids 13% major postop complication
OP	Lalmohamed, <i>et al</i> ⁴⁶	2079 pts (1249 GB, 613 RYGB, 217 other), 10,442 controls	No increase in OP fracture rate at 2.2 yrs Trend to ↑ fracture risk 3–5 yrs postsurgery in those with most EWL
	Nakamura, <i>et al</i> ⁴⁷	258 pts (243 RYGB, 15 other)	79 pts with 132 fractures 2-fold ↑ risk of fracture

OA: osteoarthritis; pts: patients; RYGB: Roux-en-Y gastric bypass; GB: gastric band; SG: sleeve gastrectomy; KOOS: Knee OA Outcome Score; WOMAC: Western Ontario and McMaster Universities OA Index; VAS: visual analog scale; postop: postoperative; RA: rheumatoid arthritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PsA: psoriatic arthritis; IS: immunosuppressive; SLE: systemic lupus erythematosus; OP: osteoporosis; EWL: excess weight loss.

following bariatric surgery (Table 1)^{19,20,21,26,30,31,32,46,47}. However, these findings need to be validated by larger prospective studies with longer followup times.

Whether newer bariatric procedures have deleterious effects on bone homeostasis and the clinical relevance of this in OP and fracture risk are areas that need further study.

The exact mechanisms behind the beneficial effects seen after bariatric surgery need further clarification, but it appears that a complex interplay exists of weight loss, changes in adipokines, gut hormones, glucose/insulin homeostasis, the gut microbiota, and inflammatory mediators.

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