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Case Report

Treatment with bariatric surgery in patients with osteogenesis imperfecta and severe obesity

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1. Introduction

Osteogenesis imperfecta (OI) is a connective tissue disorder most commonly caused by defects in collagen type 1. Patients with OI suffer a life-long increased fracture risk. Skeletal deformities and pain impair physical function. Immobility and genetic susceptibility may lead to obesity.

Obesity (Body Mass Index (BMI) > 30 kg/m^2) is an expanding global health problem associated with an increased risk of developing comorbidities such as type 2 diabetes, cardio-vascular disease, various cancers, sleep apnea, osteoarthritis, and an overall increased mortality (Visaria and Setoguchi, 2023; Aune et al., 2016). Treatment options are lifestyle intervention, pharmacotherapy, and bariatric surgery.

Weight loss of >10–15 % is known to improve overall metabolism and ameliorate co-morbidity such as type 2 diabetes and sleep apnea (Magkos et al., 2016). New pharmacological treatment for obesity has demonstrated weight loss of up to 15 % (Jastreboff et al., 2022, 2023; Wilding et al., 2021); however, weight loss sufficient to improve *e.g.* osteoarthritis should be of >25–40 % of initial body weight, which currently is only accessible through bariatric surgery (Panunzi et al., 2021; Syn et al., 2021). Although weight loss *per se* has beneficial effects bariatric surgery is associated with several side effects including potential deleterious effects on bone health with a decrease in bone mass due to increased bone resorption (Muller et al., 2019; Thereaux et al., 2019). These bone-related changes have been reported to be associated with an increased risk of fractures, especially after Roux-en-Y Gastric Bypass (RYGB) (Khalid et al., 2020). On the other hand, in patients with OI and obesity, an optimization of physical function is crucial, and weight loss may be necessary to maintain mobility and prevent metabolic co-morbidity. Patients with OI are routinely followed by measures of bone mineral density (BMD) performed by dual x-ray absorptiometry (DEXA). In general, measures of BMD may be confounded by present obesity and changes in body weight.

OI cannot be cured, and treatment is supportive and fracture preventive. Bone protective treatment options are antiresorptives, such as zoledronic acid, or bone anabolic treatment, such as teriparatide or sclerostin antibodies (Ralston and Gaston, 2020; McClung et al., 2022; Glorieux et al., 2024).

Sclerostin antibodies (Romosozumab, Setrusumab) are relatively new bone anabolic drugs that improve bone formation and suppress bone resorption and thereby improve bone strength (Ralston and Gaston, 2020; Glorieux et al., 2024).

This report presents two cases of patients with OI and concomitant severe obesity (BMI >40 kg/m^2), where bariatric surgery was performed after careful consideration of the benefits and risks.

2. Cases

2.1. Case 1

A 49-year-old perimenopausal female with OI type 1 due to a COL1A1 mutation, c.3267_3268delinsTT(p.Gln1090*). She was living with severe obesity (*i.e.* BMI of 43 kg/m^2 and body weight of 120 kg) and suffered pain from degenerative osteoarthritis of both knees. She had reduced mobility due to multiple fractures ($n > 50$) with most recent fracture occurring 5 years previously. She did not have diabetes. She had several unsuccessful weight-loss attempts, including lifestyle interventions and dietary advice. Due to reduced mobility and pain from progressive osteoarthritis she was referred to and found eligible for a RYGB procedure.

Prior to referral to surgery, she had been treated for one year with Setrusumab in a clinical trial with the largest dose investigated (20 mg/

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kg) followed by two years of yearly zoledronate with last dose given 6 months before surgery (Glorieux et al., 2024). She lost 8 % body weight preoperatively as recommended and stopped smoking. Before and after surgery biochemical markers, HRpQCT and DEXA were performed. The preoperative BMD values at lumbar spine, hip, and forearm were in the normal range, *Z*-score lumbar spine +1.6, Z-score total hip +0.7, Z-score femoral neck +0.5 (Table 1).

There were no surgical or nutritional complications to the RYGB surgery and one year postoperatively she had lost 40 kg and thereby reduced BMI to 28 kg/m^2. She was followed by dietary and medical consultations and received supplements as recommended with vitamins, iron and calcium. Zoledronate treatment was repeated 6 months after surgery to prevent a potential loss of BMD and biochemical bone turnover markers were suppressed according to this treatment (Table 1). PTH, calcium and vitamin D3 remained normal, p-P1NP and p-CTX increased to low-normal values and BMD decreased 3–4 % at the lumbar spine and total hip after 6 months and 7.6–8.6 % during the first year and remained within the normal range.

Results of HR-pQCT showed three dimensional BMD(D100) and trabecular bone volume to tissue volume (BV/TV) that remained unchanged, whereas trabecular number (TB·N) decreased and trabecular separation (TB.Sp) increased. No clinical fractures occurred postoperatively.

2.2. Case 2

A 27-year-old male with a clinical diagnosis of OI type 1 (low energy fractures, blue sclera, triangular face) supported by results of abnormal collagen type I derived from dermal fibroblasts. He suffered 15 fractures with most recent fracture 12 years previously. He was living with very severe obesity (*i.e.* BMI of 75 kg/m^2 and body weight of 209 kg) and had sleep apnea, treated with nightly C-PAP. He did not have diabetes. He had a history of unsuccessful weight-loss attempts through lifestyle intervention, which in combination with sleep apnea made him eligible for a sleeve gastrectomy (SG) procedure.

To prevent potential increase in bone resorption he received treatment with zoledronate 2 months pre-operatively.

Due to the pre-operative body weight DEXA or HRpQCT were not performed. He had bone turnover markers measured pre- and postoperatively.

P1NP was low-normal and decreased postoperatively and remained suppressed 6 months after surgery. CTX was low preoperatively and remained below the lower reference range during the first year after surgery (Table 1).

Surgery was without complications. He was followed by dietary and medical consultations and received supplements as recommended with vitamins, iron and calcium. Two months after surgery he had lost 50 kg body weight, and six months post-operatively 75 kg. After one year his weight loss was 80 kg with a body weight of 129 kg (*i.e.* BMI of 48 kg/m^2). Six months post-operatively the DEXA showed a lumbar BMD of 0.880 g/cm^2, *Z*-score − 1.9 and a total hip BMD of 1.084 g/cm^2, Z-score + 0.4, femoral neck BMD 1.084 g/cm^2, Z-score − 0.3. PTH was slightly increased just after surgery, and thereafter PTH, vitamin D3, and calcium levels remained within the normal range. His mobility improved and he started working. No clinical fractures occurred.

3. Discussion

This short communication presents two cases with mild OI and severe obesity (BMI > 40 kg/m^2) with obesity-related complications. Both patients were referred to and successfully treated with bariatric procedures RYGB and SG, respectively. Bariatric surgery may be an option in patients with mild OI and concomitant severe obesity with obesity-related complications. Eligibility for bariatric surgery rests upon a BMI > 35 kg/m^2 and at least one obesity-related comorbidity but in relation to patients with OI, BMI is not an optimal measure for obesity, since body composition with a relative short stature may overestimate BMI.

It is important to emphasize that even though bariatric surgery leads to substantial weight loss, often >30 % of the initial bodyweight, it may also lead to adverse outcomes including malabsorption, hypoglycemia, acid reflux, and an overall negative impact on skeletal health (Magkos et al., 2016). There is a significant reduction in nutrient absorption such as calcium and vitamin D following both RYGB and SG. This may lead to secondary hyperparathyroidism and thus theoretically increased bone resorption. On the other hand, post-prandial incretin hormones such as GLP-1 and GLP-2 has been reported to increase especially following a RYGB and both GLP-1 and GLP-2 have been reported to inhibit bone resorption (Schiellerup et al., 2019). The effect of bariatric surgery on bone quality in non-OI individuals has been shown in several studies. A

Table 1
Biochemical markers and measures of bone mineral densities.

	Bone markers		Pre surgery (6*)	2 months post surgery	4 months post surgery	6 months post surgery (12*)	12 months post surgery (6*)
Case 1	p-Osteocalcin (10–47 μg/L)		19	26	33	31	
	p-P1NP (17–124 μg/L)		<13	16	26	28	
	p-CTX (<0.59 μg/L)		0.08	0.21	0.27	0.31	
Case 2	p-P1NP (17–124 μg/L)		31	14	<13	<13	<13
	p-CTX (<0.59 μg/L)		0.11	0.15	0.19	0.20	0.18
Areal BMD case 1	Total lumbar spine(g/cm^2)/%		1.151		1.148/−0.3 %	1.101/−4.4 %	1.062/−7.8 %
	Hip femoral neck (g/cm^2) %		0.833		0.811/−2.6 %	0.805/−3.3 %	0.794/−4.7 %
	Total hip (g/cm^2)/%		0.977		0.961/−1.7 %	0.933/−4.5 %	0.893/−8.6 %
	Left forarm (g/cm^2)/%		0.518		0.515/−0.5 %	0.520/+0.4 %	
Volumetric BMD Case 1	D100 (mg HA/cm^3)/ %	R	253.6		258.1/+1.7 %	255.1/+0.6 %	
		T	211.1		215.6/+2.1 %	214.3/+1.5 %	
	Trab BV/TV (l)/%	R	0.119		0.124/+4.5 %	0.124/+3.9 %	
		T	0.113		0.118/+4.2 %	0.117/+4 %	
	Tb. N (l/mm)/%	R	2.09		1.99/−4.8 %	2.06/−1.2 %	
		T	2.27		1.95/−14 %	1.83/−20 %	
	Tb.Sp (mm)/%	R	0.421		0.440/+4.4 %	0.424/+0.7 %	
		T	0.390		0.451/+16 %	0.483/+23.7 %	

P1NP: Procollagen N-terminal propeptide. CTX: Collagen 1 crosslink. BMD: areal bone mineral density. R: radius. T: tibia.D100: volumetric bone mineral density. Trab BV/TV: Trabecular bone volume to tissue volume. TbN: Number of trabeculae. TbSp: Trabecular separation. % indicates change from baseline values. (6*) and (12*) indicates time in months after last zoledronate infusion.

meta-analysis demonstrated a 45 % higher fracture risk in individuals after bariatric surgery such as RYGB compared to obese controls. The overall negative effect on bone quality was seen as a deterioration of both trabecular and cortical bone parameters in radius and tibia, and thus not only in weight bearing bone (Tomey et al., 1987). A meta-analysis from 2020 showed similar results and concluded that fractures were primarily located at the upper limbs, spine, and hips (Mendonça et al., 2022). BMD declines one year after RYGB by 6–11 % in populations without OI that did not receive pre-treatment with zoledronate (Mendonça et al., 2022).

The first case reduced body weight by one-third postoperatively, with a concomitant increase in bone resorption and 8 % reduction in bone mineral density but without major skeletal events. The preoperatively bone anabolic treatment (*i.e.* setrusumab), followed by two doses of antiresorptive treatment may have mitigated the negative skeletal effect of RYGB, however, bone turnover increased, and HRpQCT demonstrated a negative effect on trabecular bone structure with an increased tibial trabecular separation (23 %) and a decreased trabecular number (20 %) (Table 1).

The second case also reduced body weight by one-third postoperatively. The preoperative antiresorptive treatment resulted in a suppressed p-CTX, and the postoperative measurements remained low, indicating continuously suppressed bone resorption. P-P1NP was also low and decreased further during the follow-up (Table 1).

These two cases demonstrate significant body weight reductions, paralleled by alleviation in the obesity-related comorbidities. BMD decreased significantly in case 1 and none of the two patients experiences any fractures in response to bariatric surgery. Both patients had mild OI, were calcium and vitamin D sufficient and were pretreated with zoledronate and in case 1 also with setrusumab.

Finally, weight loss-induced improvement in mobility may in both cases affect bone quality as well as quality of life positively, resulting in long term benefit for the skeleton.

The two cases demonstrate bariatric surgery as a possible treatment of severe obesity in mild OI. Pre- and postoperative treatment with antiresorptives and securing sufficient intake of vitamin D and calcium are recommended to minimize bone deterioration. Further studies are needed to investigate skeletal health following bariatric surgery. When caring for patients with OI, it is of outmost importance to ensure increased mobility for as long as possible, encourage healthy lifestyle in terms of balanced calory intake as well as individualized training facilities despite obvious disabilities to avoid severe obesity. Bariatric surgery in OI patients is a team effort involving bone-, metabolic- and surgical experts.

CRediT authorship contribution statement

Jannie Dahl Hald: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Asta-Marie Welander Hald:** Writing – review & editing, Investigation, Formal analysis, Data curation, Conceptualization. **Torben Harsløf:** Writing – review & editing, Visualization, Methodology, Investigation, Conceptualization. **Bente Langdahl:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation, Conceptualization. **Jens Meldgaard Bruun:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Data curation, Conceptualization.

Declaration of competing interest

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Ethical Considerations: Involved cases were informed and consented to this publication.

Data availability

Data will be made available on request.

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