Master's thesis

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The prevalence of osteoporosis and osteoporotic fractures 10-15 years after RYGB surgery compared to the HUNT3 study

Master's thesis in Medical Studies (CMED)
Supervisor: Lars Gunnar Johnsen
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Abstract

Background: Bariatric surgery has proved to be the most effective therapy for sustained loss weight in patients with severe obesity. Until recently, Roux-en-Y gastric bypass (RYGB) was the most performed bariatric procedure worldwide. Accumulating number of studies suggest a detrimental consequence of RYGB surgery on bone health, but there is need of more studies with long-term follow-up. The aim of the study is to evaluate the prevalence of osteoporosis and major osteoporotic fractures in a patient cohort 11.5 years after RYGB surgery and compare with the rates in the HUNT3 study.

Methods: Patients who underwent RYGB surgery during 2003 – 2009 in three hospitals in Middle Norway were invited to a follow-up visit between 2018 – 2020 (the BAROBS study). The follow-up consisted of clinical exams, blood tests, dual-energy X-ray absorptiometry (DXA) examination, self-administered questionnaire, and interview conducted by physicians. As a control group in this study, 1000 randomly selected participants with equivalent age and sex distribution as the BAROBS participants were selected from the HUNT3-study.

Results: Median follow-up in BAROBS was 11.5 (range 9.1-16.8) years. Osteoporosis was identified in 12% of the BAROBS participants, and 1.8% of HUNT3-participants. A total of 39 (8%) BAROBS participants suffered 45 major osteoporotic fractures during 10-15 years after RYGB surgery, while 124 (12.6%) HUNT3 participants experienced at least one osteoporotic fracture before the HUNT-study was conducted. Mean time to major osteoporotic fracture after RYGB was 7.9 (±3.2) years and the incidence rate of major osteoporotic fracture was 7 pr 1000 person-years. The most frequent fracture in BAROBS and HUNT3 was at the forearm/wrist.

Conclusion: There were higher rates of osteoporotic fractures in the control group (HUNT3) compared to the BAROBS-population. However, when compared to HUNT3 the prevalence of osteoporosis was significantly increased 10-15 years after RYGB surgery. Consequently, the BAROBS-participants are at greater risk of suffering low-energy fractures than the general population.

Bakgrunn: Bariatrisk kirurgi er den mest effektive metoden for å behandle alvorlig fedme og fører til vedvarende vektreduksjon. Inntil nylig var Roux-en-Y gastrisk bypass (RYGB) den bariatriske prosedyren som var mest utført på verdensbasis. Et økende antall studier tyder nå på at RYGB medfører skadelige konsekvenser for skjeletthelsen, men det er behov for flere studier med lang oppfølgingstid. Hensikten med denne studien er å evaluere prevalensen av osteoporose og osteoporotiske brudd 11.5 år etter RYGB operasjon og å sammenligne med forekomstene i HUNT3.

Metode: Pasienter som gjennomgikk RYGB operasjon mellom 2003 – 2009 hos tre sykehus i Midt-Norge ble invitert til en oppfølgingsstudie i 2018 – 2020 (BAROBS-studien). Oppfølgingen bestod av kliniske undersøkelser, blodprøver, dual-energy X-ray absorptiometry (DXA) undersøkelser, spørreskjema fylt ut på egenhånd og intervju med lege. Tusen tilfeldig utvalgte deltakere av HUNT3 med tilsvarende alders- og kjønnsfordeling som BAROBS-gruppen ble valgt som kontrollgruppe i denne studien.

Resultat: Median oppfølgingstid i BAROBS var 11.5 år (område 9.1-16.8) år. Tolv prosent av BAROBS-deltakerne hadde osteoporose ved oppfølgingstidspunktet, og 1.8% av HUNT3-deltakerne hadde osteoporose. Totalt sett fikk 39 (8%) BAROBS-deltakere 45 osteoporotiske brudd i løpet av 10-15 år etter RYGB, mens 124 (12.6%) HUNT3-deltakere hadde opplevd 132 osteoporotiske brudd før HUNT3-studien ble utført. Gjennomsnittlig tid fra RYGB-operasjon til et osteoporotisk brudd oppstod var 7.9 (±3.2) år, og insidenraten for osteoporotisk brudd var 7 pr 1000 person-år. Den hyppigst forekommende frakturlokalisasjonen i BAROBS og i HUNT3 var i håndleddet/underarmen.

Konklusjon: Det var høyere forekomst av osteoporotiske beinbrudd i kontrollgruppen (HUNT3) enn i BAROBS-populasjonen. Prevalensen av osteoporose var signifikant høyere 10-15 år etter RYGB-kirurgi sammenlignet med forekomsten i HUNT3, og BAROBS-deltakerne har dermed større risiko for å gjennomgå lavenergibrudd sammenlignet med normalpopulasjonen.

Introduction

Worldwide the prevalence of obesity has near tripled since 1975 and has now reached such dimensions that the World Health Organization (WHO) in 2016 classified more than 1.9 billion (39%) adults as overweight, where people with obesity constitute over 650 million (1). The global epidemic of obesity is a serious issue both for the public health and for the individual. For patients with severe obesity (BMI $\geq$ 40 kg/m^2, or $\geq$ 35 kg/m^2 with at least one serious comorbidity) bariatric surgery has proved to be the most effective therapy for sustained weight loss providing additional benefits for obesity related comorbidities, such as type 2 diabetes mellitus, dyslipidaemia, hypertension (2), obstructive sleep apnea (3), resulting in reduced long-term all-cause mortality (4, 5). Nevertheless, growing evidence show that bariatric surgery, especially malabsorptive procedures, has deleterious effects on bone health (6) and increases bone fracture risk (7). Bariatric surgery has been found to result in decrease in bone mineral density (BMD), increase in bone turnover markers, microarchitecture deterioration, and an early and sustained bone loss post-surgery. However, while numerous studies imply that bariatric surgery poses detrimental consequences for bone health, there are inconsistent results between studies. These inconsistencies may be explained by differences in matching of control groups, follow-up time, bariatric procedures or number of study participants (8).

Roux-en-Y gastric bypass (RYGB)

In Norway approximately 2000 bariatric operations are performed annually (9), and globally the mean age at bariatric surgery is typically 40-45 years. Most studies report a considerable gender disparity among bariatric patients, generally 70-80% are female (10). Consensual indications for bariatric surgery are BMI $\geq$ 40 kg/m^2, or BMI $\geq$ 35 kg/m^2 accompanied by at least one serious obesity related comorbidity (11). RYGB is historically the most performed bariatric procedure globally, now surpassed by sleeve gastrectomy (SG) (12), and is considered a mixed bariatric operation, i.e., with restrictive and malabsorptive features. The general steps include creation of a gastric pouch, a biliopancreatic limb, a jejunojejunostomy, and a gastrojejunostomy (13). Thus, the duodenum and proximal jejunum, in addition to the acid-producing part of the stomach, are bypassed (Fig. 1). These are important areas for nutrient absorption and bypassing them leaves the patient susceptible to malabsorption of vital vitamins and minerals for bone formation and maintenance of bone mineral density, such as vitamin D and calcium. Consequently, bariatric patients are recommended supplements of calcium and

vitamin D post-surgery, in addition to other vitamins and minerals such as vitamin B12, iron, folate, thiamine, and zinc (14).

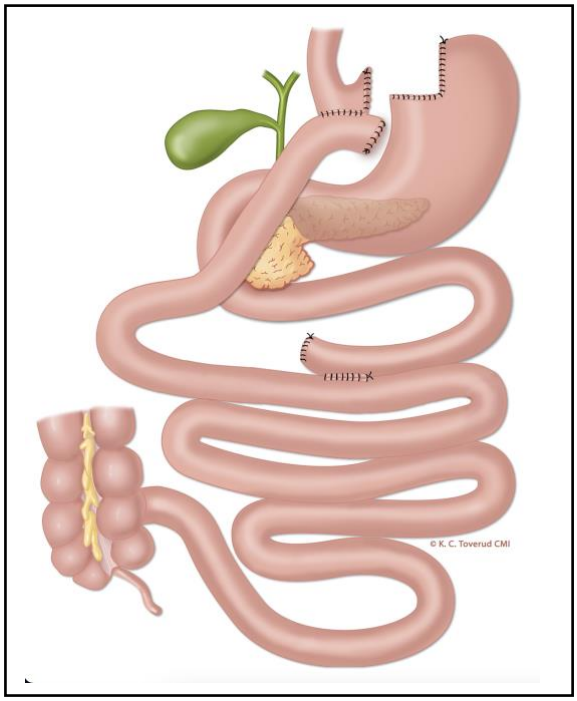


Figure 1. Roux-en-Y gastric bypass.

Osteoporosis

Osteoporosis, acknowledged as the most prevalent bone disorder worldwide, is a systemic skeletal disease characterized by reduced bone mass, microarchitecture deterioration and compromised bone strength (15), resulting in higher risk of bone fracture (16). Defined by WHO, osteoporosis is present when bone mineral density (BMD) is -2.5 standard deviations or more below reference values for young healthy women (T-score $\leq$ 2.5 SD). The most serious clinical outcome of osteoporosis is osteoporotic fractures (17), and Norway has the highest hip fracture rates in the world as a Norwegian on average suffers a hip fracture every hour (18). Some risk factors for osteoporosis include inadequate nutritional absorption, weight loss, little weight-bearing physical activity, history of fracture, age, and gender. Additionally, certain drugs may adversely affect bone health, such as glucocorticoids or proton pump inhibitors (19, 20).

Obesity and bone mineral density

Historically obesity is considered to be a protective factor against osteoporosis (21). Several mechanisms have been proposed, mainly that increasing mechanical loading from obesity stimulates bone formation as a compensating mechanism to the gained load. This belief is supported by the positive correlation between BMI and BMD and has led to the understanding that weight loss may lead to decrease in BMD. Furthermore, the fracture risk assessment tool (FRAX®) includes BMI as a parameter, and higher BMI leads to lower fracture risk (22). Furthermore, adipocytes are important sources of estrogen production, a hormone which inhibits bone resorption from osteoclasts, posing a positive consequence of adiposity on post-menopausal bone health (23). However, recent studies challenge the notion of BMI resulting in increasing BMD, suggesting a more complex interaction between bone metabolism and obesity, interactions which are not fully understood. Bone health is positively influenced by mechanical loading, but this effect may not suffice in obesity (24). Theories include a possible negative effect of obesity on bone microarchitecture, that obesity might result in site-specific fracture risk, and that hormonal and biochemical factors may influence the bone health (24). Further, obesity is associated with several factors which may adversely affect skeletal health, such as increased bone marrow adipogenesis, visceral fat, and vitamin D deficiency, a factor which is inversely related to BMI (22, 25).

There is need of more studies with long follow-up time assessing the relationship between RYGB, osteoporosis and osteoporotic fractures. The aim of the present study was to determine the prevalence of osteoporosis and major osteoporotic fractures 10-15 years after RYGB surgery performed during 2003-2009 in Central Norway, and to compare with the rates in the HUNT3 study, which reflects the general population in the county of Nord-Trøndelag in Central Norway.

Materials and methods

This study is a retrospective analysis of data collected from the Bariatric Surgery Observation Study (BAROBS). BAROBS is a retrospective cross-sectional observational study of patients who underwent RYGB for severe obesity at three hospitals in Central Norway Regional Health Authority (Helse Midt-Norge) during 2003-2009. The objective was to assess the long-term effects of primary RYGB on weight loss, comorbidities associated with severe obesity, quality of life, and overall health. A total of 930 patients were invited to a clinical follow-up between 2018 and 2020, of which 546 (58.7%) accepted. Of these we excluded 19 patients due to

secondary bariatric surgery, 21 patients due to missing data regarding fracture history, and 21 patients due to lacking dual-energy X-ray absorptiometry (DXA) examination, resulting in 485 participants that were found eligible for this study (Fig. 2). The follow-up consisted of clinical exams, blood tests, DXA examination, self-administered questionnaire, and interview conducted by physicians. The participants were asked about fracture history, time and site of fracture, history of osteoporosis. Participants were not asked about the traumatic nature of their fractures. Compliance regarding supplementation of calcium and vitamin D was documented, in addition to collection of blood samples analyzed for serum 25(OH) vitamin D, serum ionized calcium and serum parathyroid hormone (PTH). Additional data were collected from electronic patient record (EPR) regarding missing registration of time to fracture. Information about use of medications in the BAROBS-group was registered and relevant drugs are presented to display the status of comorbidities in BAROBS and to show use of important drugs regarding bone health.

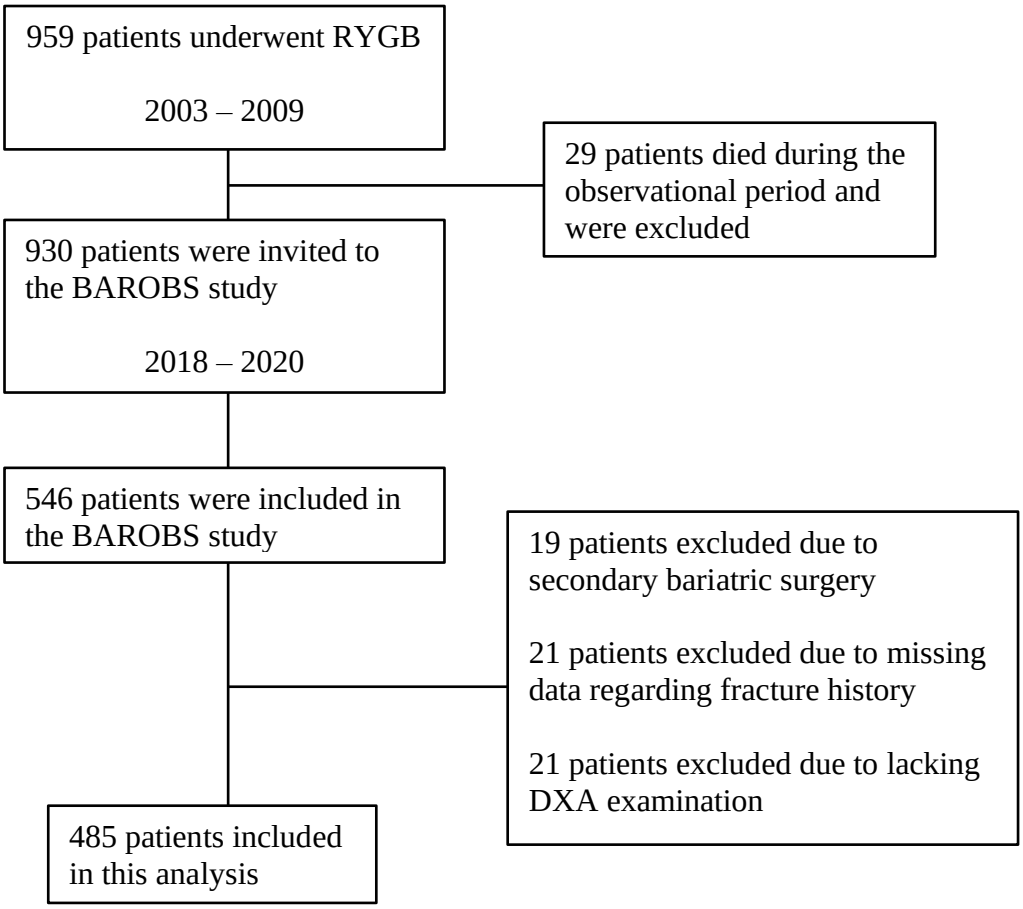


Figure 2. Flow-chart of the study population.

Control group HUNT

The Trøndelag Health Study (The HUNT Study) is a longitudinal population-based study in Nord-Trøndelag County in Norway. It constitutes a large database of questionnaire data, clinical measurements, and samples from 1984 and onwards. HUNT has high participation rates and has become a great base for health research. Several surveys have been performed throughout the decades, and the HUNT3 Study was performed during 2006 – 2008. The total county population was invited (n=93860) and 54.1% (n=50807) participated (26). The questionnaire included questions regarding osteoporosis, years of diagnosis, and if the participants had experienced radius fracture, hip fracture or vertebral compression fracture, including year of fracture (27). In addition, the study includes DXA scans for a selection of the participants. As a control group in this study, 1000 randomly selected participants with equivalent age and sex distribution as the BAROBS participants were selected from the HUNT3-study.

Definition of outcomes

In the BAROBS-group major osteoporotic fractures were defined as fractures at the hip, wrist/forearm, vertebrae, and humerus. When counting participants with fractures they were prioritized in that order. Incidence rates were calculated by dividing number of fractures by the total person-years at risk. Participants with only finger or toe fractures after RYGB were not regarded as relevant fracture events. If they had several fractures, the first one was counted in "time-to-fracture". BMD was assessed by DXA measurements and osteoporosis was defined by T-score $\leq$ -2,5 SD in participants aged 50 years or older, and Z-score was used when participants were aged below 50 years. Osteopenia was defined by T-score between -2.5 and -1 SD.

In the HUNT-group information regarding fractures was collected from questionnaires, and major osteoporotic fractures includes fractures at the hip, wrist/forearm, and vertebrae. Fracture at humerus was not included in the HUNT3-questionnaire. Fractures occurring before the age of 18 years were not considered relevant in this study and were not included. Because of low validity regarding osteoporosis-status in the questionnaire, we used DXA measurements to assess the occurrence of osteoporosis in the HUNT3-population. For participants aged 50 years or older, mean values of bone mineral density were calculated from right and left hip total T-score. For participants aged below 50 years we used Z-score derived from DTX200 when available, and T-scores when Z-scores were missing.

Statistical analysis

Statistical analyses were performed sing IBM SPSS version 27 (SPSS Inc., Chicago, IL, USA) software. Continuous variables are presented as means ±SD if normally distributed, if not by median and range. Normality was assessed through Shapiro-Wilk test. Categorical data are presented as numbers and percentages, and the Pearson χ^2 test was used for comparison of independent categorical variables. For assessment of independent non-parametric continuous variables for variables with two categories, Mann-Whitney U test was used. *P*-values < .05 were considered statistically significant for all analyses.

Ethics

This study was approved by Regional Committee for Medical and Health Research Ethics in November 2022 (2017/1828/REK sør-øst).

Results

Participant characteristics BAROBS

We retrospectively evaluated 485 BAROBS-participants with a median follow-up of 11.5 (range 9.1 – 16.8) years. Median age at RYGB surgery was 39.0 (range 19 – 65) years, median age at follow-up was 51.2 (range 30 – 78) years, and 391 (81%) participants were female. Median BMI was 44.0 (range 34.0 – 66.0) preoperatively, 29.0 (range 20.0 – 47.0) at nadir 1-2 years after surgery, and 33.9 (range 20.3 – 59.7) 11.5 years after surgery (Fig. 3). A total of 84 (17%) patients were using anti-hypertensive drugs, 56 (12%) patients were using antithrombotic drugs, 33 (7%) were under medical treatment for type 2 diabetes mellitus, 34 (7%) patients were using statins, and 66 (14%) patients were using proton pump inhibitors. Thirteen (3%) patients were under hormone replacement therapy, 10 (2%) were using prednisolone, and 9 (2%) participants received oral or intravenous bisphosphonates at the time of follow-up (Tab. 1).

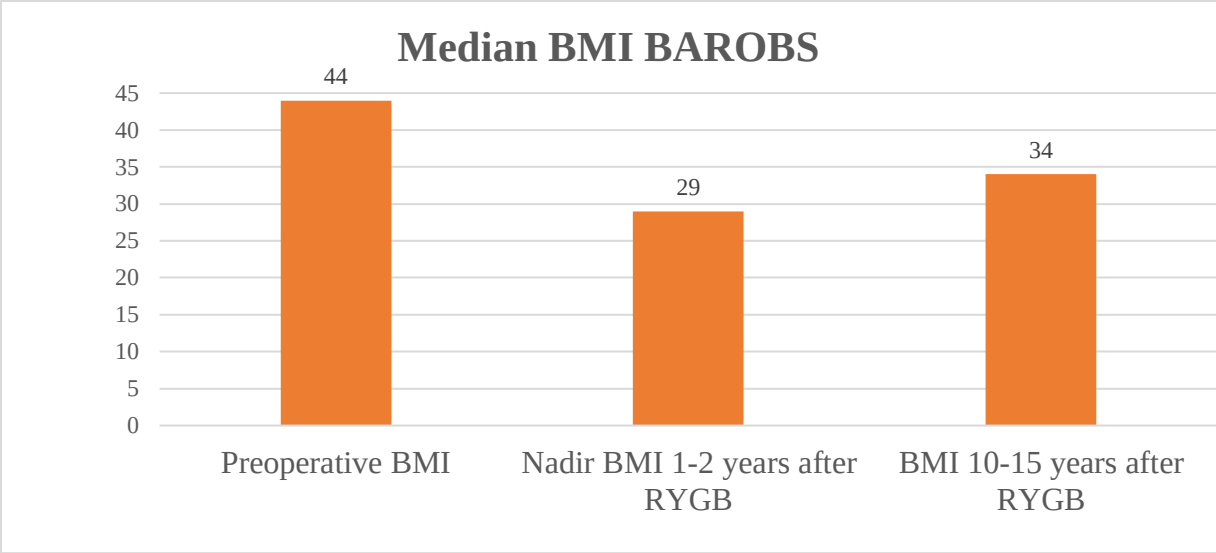


Figure 3. Median BMI preoperatively, at nadir, and 10-15 years after RYGB.

Table 1. Medication BAROBS	Number of participants (%)
ACEi, CCB, ARB	84 (17)
Proton pump inhibitors	66 (14)
Antithrombotic drugs	56 (12)
Statins	34 (7)
Antidiabetic drugs	33 (7)
Hormone replacement therapy	13 (3)
Prednisolone	10 (2)
Bisphosphonates	9 (2)

Abbreviations: ACEi, Angiotensin-converting-enzyme inhibitor; CCB, calcium channel blocker; ARB, angiotensin receptor blocker; antidiabetic drugs, metformin/glucagon-like peptide-1 analogue/dipeptidyl peptidase-4 inhibitor/sodium-glucose cotransporter-2 inhibitor

Fractures BAROBS

A total of 77 (16%) participants suffered 103 fractures at all sites during 10-15 years after RYGB surgery, of which 21 (27%) patients experienced multiple fractures. Altogether 39 (8%) patients experienced 45 major osteoporotic fractures (MOF). Mean time to MOF was 7.9 (±3.2) years and mean time to fracture at all sites was 7.8 (±3.2) years (fig. 4). Mean age at MOF was 52.2 (±10.5) years and 50.5 (±10.4) years at fracture at all sites. Fracture events before RYGB surgery occurred in 96 (19.8%) participants. The incidence rates of major osteoporotic fracture and fracture at all sites were 7 and 14 per 1000 person-years, respectively. The most frequent fracture was at the wrist/forearm and the second most common was at the ankle (Fig. 5)

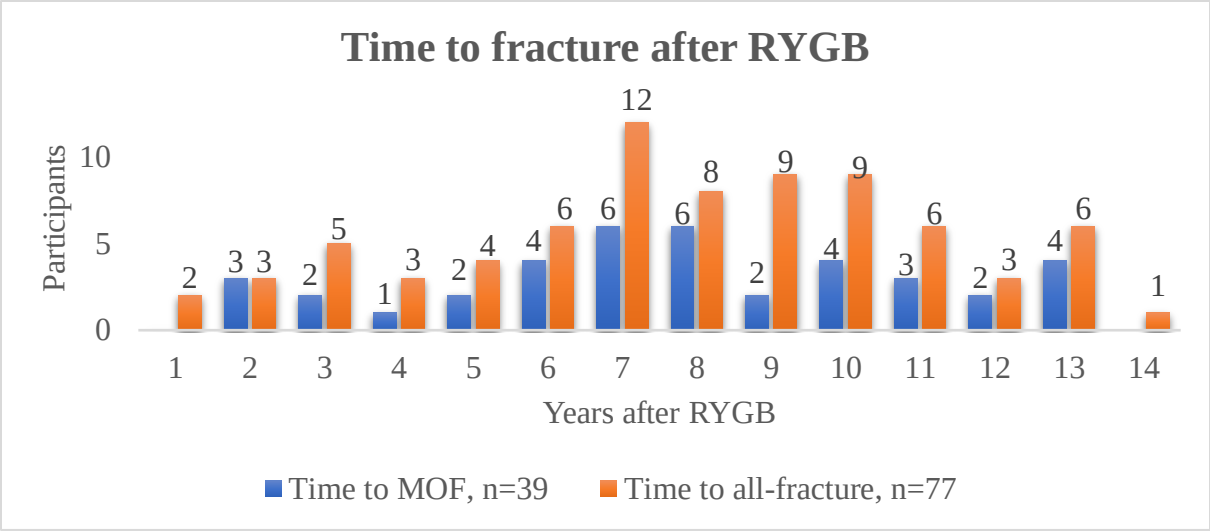


Figure 4. Time to major osteoporotic fracture (MOF) and time to all-fracture.

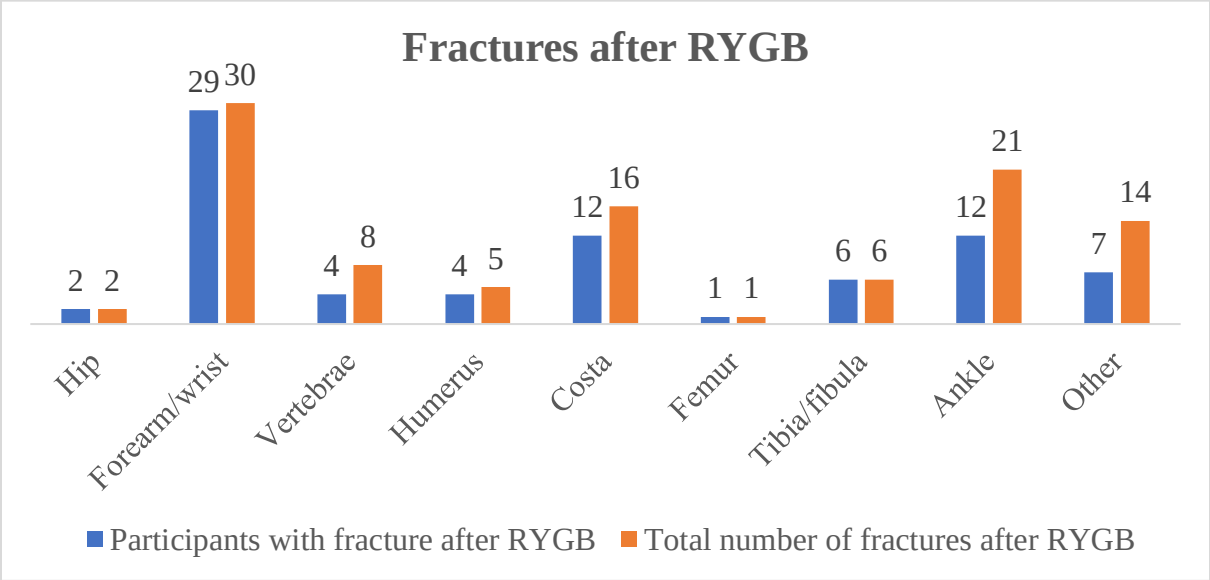
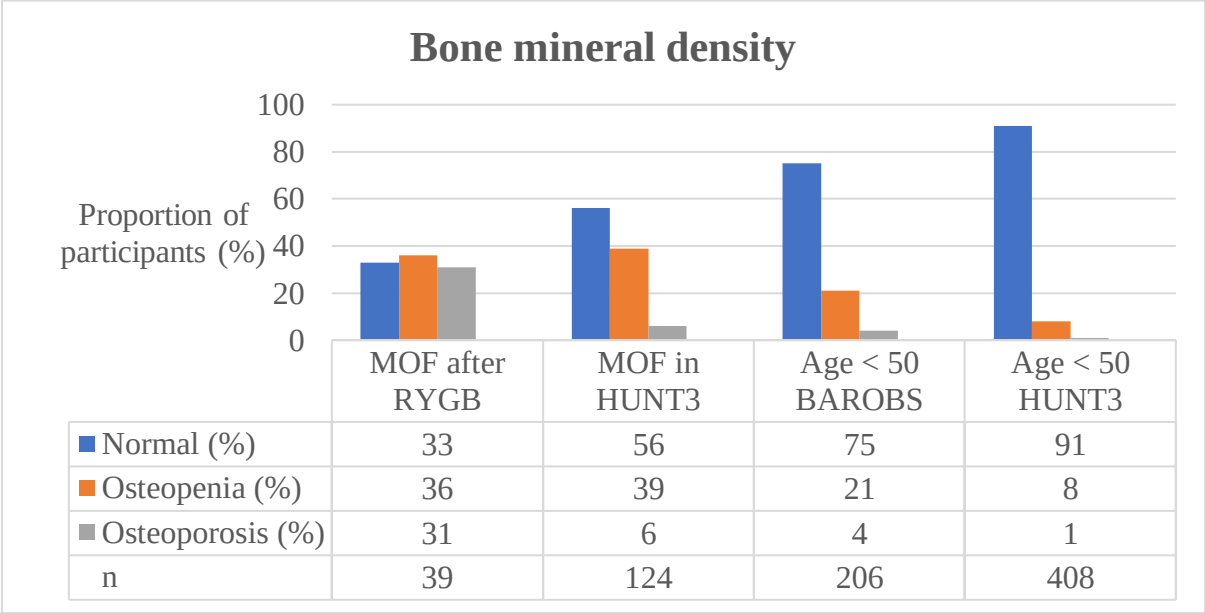


Figure 5. Frequency and sites of all fractures after RYGB. Other: Fracture at clavicula, shoulder, knee, or pelvis.

Osteoporosis BAROBS

In the total population 57 (12%) participants were diagnosed with osteoporosis at the time of follow-up, 168 (35%) with osteopenia, and 26 (5.4%) were under treatment for osteoporosis before the follow-up visit. Within the group which experienced at least one osteoporotic fracture 10-15 years after RYGB (n=39), 26 (66.7%) participants had osteopenia (35.9%) or osteoporosis (30.8%) (fig. 7), and 30 (76.9%) were 50 years or older at follow-up. Median age among participants with osteoporosis or osteopenia was 57.9 (range 38 – 78) years and 53.8 (range 34 – 73) years, respectively. When assessing the occurrence of major osteoporotic

fractures in relation to age, we found significantly higher age in those who experienced a MOF after RYGB compared to those who did not (p = .007). We also found statistically significant difference in occurrence of osteoporotic fractures when comparing participants with normal BMD with osteoporotic and osteopenic participants (p < .000). There was no significant difference between females and males regarding occurrence of major osteoporotic fracture (p = .133) or fracture at all sites (p = .122). However, we found significantly higher frequency of osteoporosis and osteopenia among women compared to men (p = .044). Furthermore, when assessing the association between BMI reduction after surgery to nadir and occurrence of MOF after RYGB, we found that the participants who suffered MOF after surgery had lower reduction in BMI after surgery (p = .023). However, there was no significant difference in BMI-reduction over the span of 10-15 years after surgery when comparing the same groups (p = .809).



	MOF after RYGB	MOF in HUNT3	Age < 50 BAROBS	Age < 50 HUNT3
Normal (%)	33	56	75	91
Osteopenia (%)	36	39	21	8
Osteoporosis (%)	31	6	4	1
n	39	124	206	408

Figure 7. Normal: T-score > -1.0; Osteopenia: T-score ≤ -1 to > -2.5; Osteoporosis: T-score ≤ -2.5.

Vitamin D, calcium, and hyperparathyroidism in BAROBS

We evaluated the relationship between serum 25(OH) vitamin D, serum ionized calcium, and serum parathyroid hormone with MOF post RYGB surgery. The respective serum levels are shown in figure 6. A total of 253 (52%) participants reported daily intake of calcium and vitamin D supplements, up to 60% when including intake 4-6 days a week, and 80 (17%) reported no intake. Vitamin D insufficiency, defined as levels below 75 mmol/L, was registered in 283 (59.1%) of the BAROBS-participants, of which 19 (6.7%) experienced at least one major osteoporotic fracture post-surgery. That is, 48.7% of the participants who experienced at least

one MOF had vitamin D insufficiency at follow-up. However, we did not find significant difference in vitamin D levels when comparing participants with MOF after RYGB with participants with no MOF (p = .331). Nor did we find significant difference in serum ionized calcium (p = .676) or serum PTH (p = .892). Nevertheless, participants reporting weekly intake of calcium and vitamin D supplements, presented higher serum 25(OH) vitamin D levels (p < .001), but there was no significant difference in serum calcium levels when comparing these groups (p = .602).

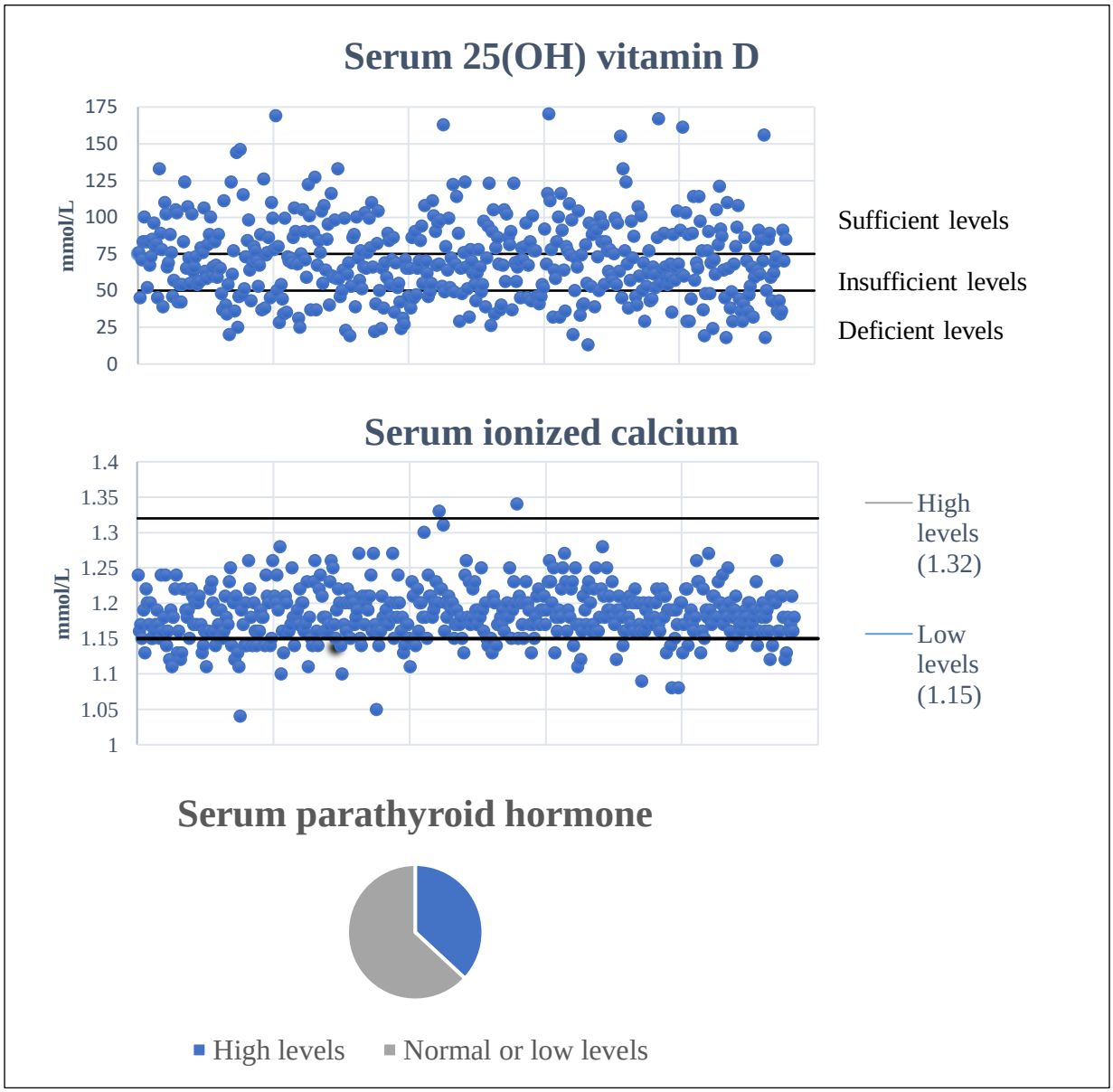


Figure 6. Measurements from 485 BAROBS-participants at follow-up of 25(OH) vitamin D, serum ionized calcium, and parathyroid hormone. Reference ranges: 25(OH) vitamin D: 31 – 98 nmol/L; serum ionized calcium 1.15 – 1.32 mmol/L; serum parathyroid hormone: There was different normal values for PTH between the respective hospitals, consequently the values are noted as high or normal/low.

HUNT3

Median age among the 1000 HUNT3 participants was 53.0 (range 29 – 70) years and 800 (80%) were females. Median BMI was 26.7 (range 17.0 – 52.6). A total of 124 (12.6%) participants suffered 132 osteoporotic fractures after the age of 18 years, and median age at first osteoporotic fracture was 45.0 (range 18 – 69) years. Fracture at the wrist/forearm occurred most frequently, i.e., in 83 (8.6%) participants. DXA measurements revealed 18 (1.8%) participants with osteoporosis, and 224 (22.6%) with osteopenia. Median age among participants with osteoporosis or osteopenia was 63.0 (range 39 – 69) years and 62.0 (range 31 – 70), respectively. In the HUNT group there was significantly higher age in participants who suffered a MOF compared to those who did not ($p < .001$), and there was significant difference in occurrence of MOF when comparing participants with normal BMD with osteoporotic or osteopenic participants ($p < .001$). There was no significant difference in BMI between participants suffering fractures compared to those who did not ($p = .167$).

Table 2. Characteristics of study participants

Characteristics at follow-up	RYGB group (n=485)	HUNT group (n=1000)	*p* values
Female, *N* (%)	391 (80.6)	800 (80.0)	.779
Median age (range), years	51.2 (30 - 78)	53.0 (29 - 70)	.328
Median follow-up (range)	11.5 (9.1 - 16.8)		
Median preoperative BMI[a] (range), kg/m^2	44.0 (34 - 66)		
Median BMI (range), kg/m^2	33.9 (20.3 - 59.7)	26.7 (17.0 - 52.6)	< .001
History of any fracture, *N (%)*	173 (35.7)		
Any fracture after RYGB, *N* (%)	77 (15.9)		
Osteoporotic fracture, *N* (%)	39 (8.0)	124 (12.6)	.008
Median age at osteoporotic fracture (range)	49.0 (26 - 73)	45.0 (18 - 69)	.006
Osteoporosis	57 (11.8)	18 (1.8)	< .001
Osteopenia	168 (34.6)	224 (22.6)	< .001
Only RYGB participants	MOF after RYGB (n=39)	No MOF after RYGB (n=446)	*p* values
Female, *N* (%)	35 (89.7)	356 (79.8)	.133
Median age (range), years	52.8 (30-78)	51.0 (30-74)	.007
Median BMI (range), kg/m^2	33.4 (22.3-41.9)	33.9 (20.3-59.7)	.077
Median BMI reduction from RYGB to nadir (range), kg/m^2	13 (6 - 25)	15 (5 - 36)	.023
Mean BMI reduction from RYGB to follow-up (SD), kg/m^2	9.7 (±5.8)	9.4 (±5.7)	.809
Daily supplementation of vitamin D and calcium (%)*	24 (61.5)	294 (66.2)	.555
Mean time to MOF, years	7.9 (±3.2)		
Incidence rate MOF, events, person-year	7 pr 1000 py		

[a]Baseline variable

*Calcigran forte 500-1000 mg

Discussion

Fracture rates and osteoporosis in BAROBS compared to HUNT3

Is the present study we found significantly higher rates of osteoporosis and osteopenia among participants who underwent RYGB surgery compared to the prevalence in the normal population in the county of Nord Trøndelag (HUNT3). However, we found significantly higher rates of osteoporotic fractures in HUNT3 (12%) than in BAROBS (8%). This result appears to conflict with the former stated notion that bariatric surgery increases the fracture risk, but essential characteristics regarding the study populations need to be highlighted. First, the time frames in the two groups are different. The BAROBS participants were followed up from a median age of 39 - 51 years, creating a defined time frame of 11.5 years for the osteoporotic fractures to occur during. In contrast, the HUNT participants answered the questionnaire at a specific time point (median age of 53 years), resulting in many more years at risk of fracture compared to the BAROBS patients. Second, the definition of osteoporotic fracture in this study included fractures at the hip, wrist/forearm, vertebrae, and humerus (in BAROBS), but there was lacking information regarding the traumatic nature of the fractures, particularly in HUNT3. Consequently, we were not able to differentiate between low-energy fractures and high-energy fractures, though the traumatic nature was described in some of the BAROBS patients. Thus, lacking information regarding the traumatic nature of the fractures comprises a confounding factor when comparing fracture events in the two groups. However, the rate of osteoporotic fractures in HUNT3 that occurred in participants at the age of 39 – 51 years, that is, the median ages at baseline and follow-up in BAROBS, the prevalence was 2.4%, which is numerically lower than the prevalence in BAROBS (8%).

There were similar results in the BAROBS and HUNT groups when assessing the relationship between age and MOF, age and BMD, and differences between women and men. That is, in both groups participants that suffered an osteoporotic fracture were significantly older and had lower BMD compared to those who did not suffer osteoporotic fracture. In addition, there was no significant difference between men and women regarding occurrence of osteoporotic fractures. Figure 7. shows the distribution of osteoporosis, osteopenia, and normal BMD among participants of BAROBS and HUNT3 categorized in groups that suffered MOF or were 50 years or younger. Figure 7, which shows the proportions of participants of BAROBS and HUNT3 with osteoporosis, osteopenia, or normal BMD categorized in groups of participants that suffered MOF or were younger than 50 years of age, reveals that 31% of the participants

who experienced a MOF after RYGB were osteoporotic, whereas in HUNT osteoporotic participants only counted for 6%. Furthermore, 21% of the BAROBS participants aged under 50 years were osteopenic and 4% osteoporotic, versus 8% and 1% in HUNT, respectively. In addition, osteoporotic or osteopenic participants of BAROBS were numerically younger than HUNT-participants, i.e., median age of 58 and 54 years among osteoporotic or osteopenic BAROBS-participants, versus 63 or 62 years in HUNT3. Hence, the higher proportion of osteoporotic participants who suffered a MOF in BAROBS versus HUNT3, may indicate that more of the osteoporotic fractures in BAROBS could originate from low-energy traumas compared to HUNT3. However, this is an assumption.

Evaluation of rates of osteoporosis and osteopenia in the two groups are more readily compared than the fracture rates, because of smaller contribution from the younger part of the normal population regarding osteoporosis compared to fractures, that might be traumatic, as low bone density is less frequent among the young. In both groups, T-scores were used to evaluate osteoporosis. The prevalence of osteoporosis was significantly higher in BAROBS (12%) compared to HUNT3 (1.8%). The BAROBS group also presented significantly higher rates of osteopenia. These findings reflect results of other studies showing a decrease in BMD after RYGB surgery, particularly when evaluating BMD by T-scores derived from total hip, a site known for decrease in BMD after RYGB surgery as opposed to lumbar spine which do not reveal significant difference after surgery (28).

Fracture rates and osteoporosis in BAROBS compared to other studies

Increasing number of studies have been published addressing the fracture risk after bariatric surgery. A Swedish study by Ahlin et al. (29) assessed the fracture risk up to 19 years after gastric bypass surgery and calculated the incidence rates for major osteoporotic fracture, fracture at all sites, and in obese controls. Their respective incidence rates were 11.9 MOFs per 1000 person-years, 22.9 all-fractures per 1000 person-years, and 4.0 MOFs per 1000 person-years in the control group. These fracture rates are higher than we found in the BAROBS population; 7 MOFs per 1000 person-years and 14 all-fractures per 1000 person-years, but the longer follow-up period in the Swedish study could explain some of the differences in fracture rates as other studies have found fracture risk to increase over time. Epidemiologic studies suggest that the risk of osteoporotic fracture after mixed bariatric procedures starts to increase 2-5 years after surgery (6), and several studies suggest that the fracture risk continues to increase the following years (29, 30). Similar to our study, Fashandi et al. found a time to fracture after

surgery of 7.6 years (31), as we found a mean time to osteoporotic fracture after RYGB of 7.9 years. Most of the osteoporotic fractures in BAROBS occurred during the 7th year after surgery (fig. 4).

In a study of 124 patients undergoing RYGB surgery at Oslo University Hospital during 2004 - 2006, Blom-Høgestøl et al. evaluated the rates of low-energy fractures and changes in BMD up to 10 years after RYGB surgery (32). They report a higher proportion of clinical low-energy fractures compared to our study, i.e., 15% vs our 8% (MOF). They found a time to fracture of 8.4 years; thus, similar to our results. When assessing BMD, they found 17% with osteoporosis (T-score ≤ -2.5 for postmenopausal women or men 50 years or older, or Z-score ≤ -2.0 for premenopausal women or men under 50 years) and 40% were osteopenic (T-score -1.1 to -2.4 for postmenopausal women or men 50 years or older, or Z-score -1.1 to -1.9 for premenopausal women or men under 50 years). These results are numerically higher than the prevalence of osteoporosis and osteopenia in our study of 12% and 35%, respectively. Our studies represent Norwegian populations from different counties with similar age- and sex-distribution, but there are differences between the populations regarding vitamin D and calcium supplementation. In BAROBS 60% were reporting vitamin D and calcium supplementation at least 4-6 days a week compared to 24% reporting regular (at least 5 days a week) intake of calcium and 31% of vitamin D in the study from Oslo. Consequently, they report a rate of vitamin D insufficiency of 75% compared to BAROBS' 60%.

Dual-energy X-ray absorptiometry after bariatric surgery

DXA scanning is a commonly used method of assessing aBMD changes after bariatric surgery. Bariatric patients experience substantial weight loss after surgery, which may lead to artefactual changes in DXA-derived areal bone mineral density (aBMD) results due to drastic changes in body size and composition leading to measurement errors (33). A meta-analysis evaluated differences in aBMD by comparing results derived from DXA with quantitative computed tomography (QCT) or high-resolution peripheral QCT (HR-pQCT) and found DXA to overestimate BMD loss after RYGB surgery (34). Yu et al. observed similar differences between DXA and QCT, and report discordant results particularly at the hip, suggesting that substantial weight loss after bariatric surgery may impact DXA-results (35). These studies pose a mechanism of which DXA-results are impacted by drastic changes in body composition after bariatric surgery.

Vitamin D

Vitamin D is established as an important factor against development of osteoporosis and bone fracture (36) and is inversely correlated to increasing BMI, leading to the inference that obesity is associated with vitamin D deficiency. As reported in the results, 59% of the BAROBS participants presented with serum 25 (OH) vitamin D levels below 75 nmol/L (insufficient levels), which applied to 49% of the participants who suffered a MOF after RYGB. We did not find significant difference in vitamin D levels when comparing participants who suffered a MOF and those who did not. This result seems to conflict with the forementioned association between vitamin D insufficiency and osteoporotic fractures. Some studies suggest a lack of adverse effects of vitamin D deficiency on bone health in people with obesity and have presented theories that vitamin D deficiency in obese individuals may not always represent true deficiency, a phenomenon that might be explained by the sequestration of this fat-soluble vitamin in adipose tissue (24). Another hypothesis is that vitamin D deficient people with obesity may develop compensating mechanisms through inter-related regulatory pathways of bone active hormones, such as estrogens and leptins (37). The main effect of vitamin D regarding bone health is to facilitate the absorption of calcium (36), however, only 9% of the BAROBS-participants with vitamin D insufficiency presented with hypocalcemia.

Control group

The choice of control group when evaluating bariatric patients remain a matter of discussion. Paccou et al. state that the selection of control group is one of the most important confounding factors in retrospective controlled studies and that results may differ between studies regarding fracture events due to differences in matching by obesity comorbidities (38). Particularly matching of cases and controls by BMI. However, Nakamura et al. compared their results with fracture outcomes expected in the normal population in general and did not match by BMI. They claim this makes a better basis for counseling the obese patients about their fracture risk after surgery (30).

Strengths and weaknesses

The major strength of the study is the long follow-up period of 11.5 years. Many studies have a follow-up time of 2-3 years and may have missed important results, as studies with longer follow-up have found fracture risk to increase over time. Furthermore, the BAROBS project comprises a solid base for evaluation of RYGB's effects on health outcomes as the broad approach to potential outcomes after surgery enables many associations to be found. Among

others, BAROBS includes measurements of serum 25(OH) vitamin D and serum ionized calcium and even information regarding compliance to the recommended supplementation. Numerous studies do not report supplementation of these substances, and do not include information regarding coherence. The study does, however, have limitations as it does not include a large number of subjects who suffered a MOF after surgery, which could influence the statistical power of the study to assess the impact of RYGB on major osteoporotic fractures. Further, the traumatic nature of the fractures was not documented in BAROBS or HUNT3. However, the future holds possibilities for improved quality of the comparison of BAROBS and HUNT, as HUNT4 also includes DXA measurements. This enables assessment of bone mineral density in the general population over the span of 9-13 years, which would create an improved basis for comparison.

Conclusion

There were higher rates of osteoporotic fractures in the control group (HUNT3) compared to the BAROBS-population. However, when compared to HUNT3 the prevalence of osteoporosis was significantly increased 10-15 years after RYGB surgery. Consequently, the BAROBS-participants are at greater risk of suffering low-energy fractures than the general population.

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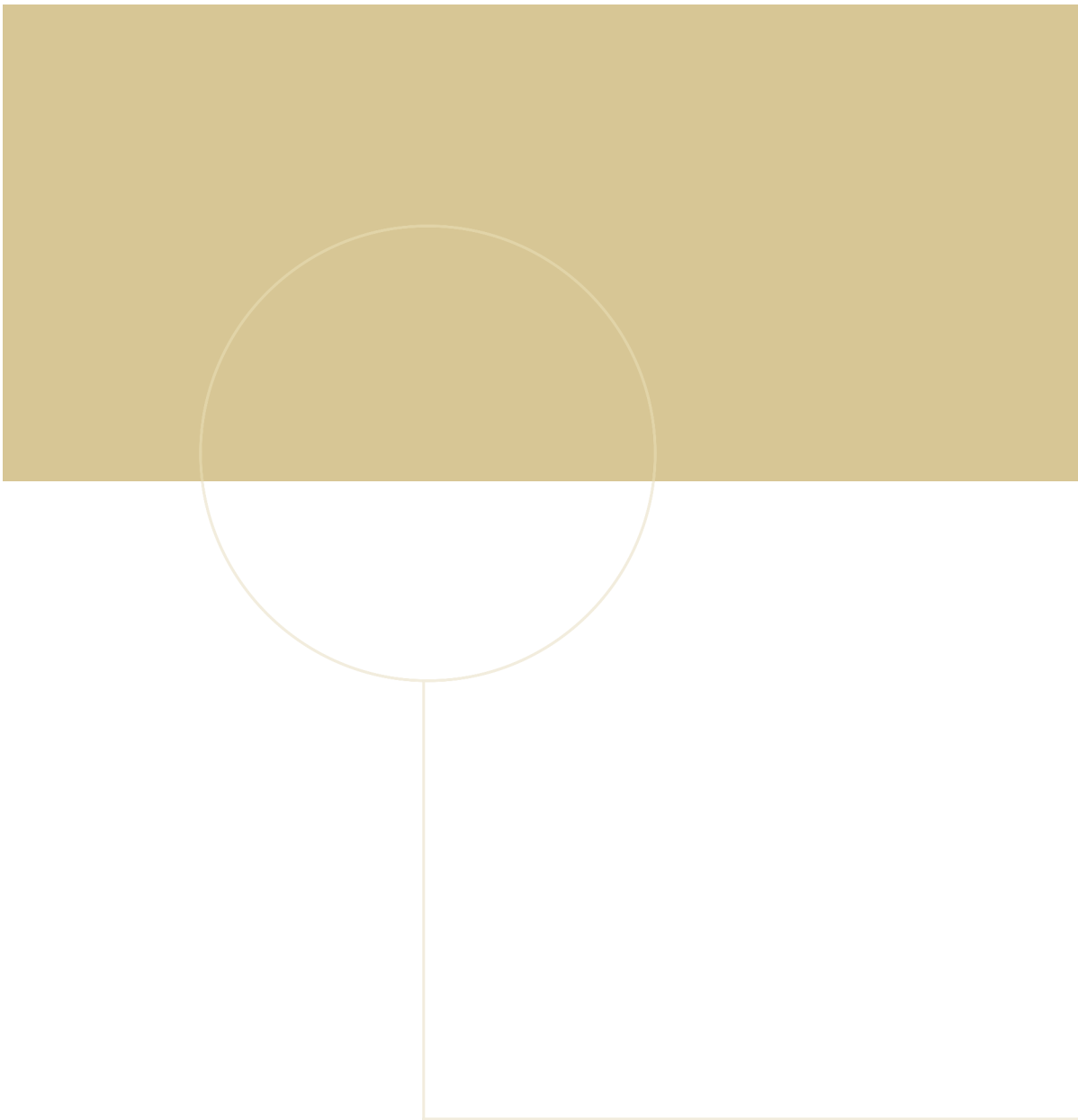

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