Excess risk and predictors of fracture/s following bariatric surgery for obese patients in the NHS: a real-world self-controlled case series and cohort study

NIHR RfPB PB-PG-1215-20017

16/01/2018, v1.0

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Sponsor: University of Oxford

Funder: National Institute for Health Research (NIHR), Research for Patient Benefit (RfPB) Programme

Lay Summary

BACKGROUND: While bariatric surgery (weight loss surgery) is effective for severe obesity, some research suggests that it might double fracture risk. However, most of the previous studies compare patients undergoing surgery to those not offered such treatments, making the results difficult to interpret. In addition, we do not know which patients who receive bariatric surgery are at highest risk of breaking their bone/s. The lack of convincing evidence means screening for bone health is not routinely carried out in the National Health Service in patients undergoing bariatric surgery.

PURPOSE: We aim to study if there is an increased risk of bone fracture/s following bariatric surgery. In addition, we will look for key factors to identify those most likely to suffer such fractures.

DESIGN/METHODS: We will use anonymised general practice and hospital records to study these associations. According to figures provided by the Clinical Practice Research Datalink, >10,900 patients undergoing bariatric surgery for obesity are available. To avoid the biases mentioned above we will use advanced methods applied in vaccine safety studies (called 'self-controlled case series'), where the risk of fracture in the periods before and after surgery are compared for each patient.

POTENTIAL IMPORTANCE: Our findings will help target patients in need for bone health assessment and/or treatment/s at the time before undergoing bariatric surgery.

Technical Summary

To further understand whether bariatric surgery affects the risk of fracture, as some studies have previously suggested, we propose to examine this relationship using Clinical Practice Research Datalink (CPRD)- Hospital Episode Statistics (HES) linked data of patients aged ≥18 and with a body mass index of 35+. To address this question there are three phases: (i) to assess the accuracy of CPRD reporting of bariatric surgery using positive predictive value calculations of the agreement between CPRD and HES. HES will be taken as the gold standard. (ii) to undertake a self-controlled case series analysis to assess whether the risk of fracture in the 5 years post-surgery is different to the risk pre-surgery for bariatric surgery patients. (iii) to determine predictors of post-operative fracture in a cohort study using logistic regression analyses and hence produce a fracture risk prediction tool.

For phases (ii) and (iii) three combinations for fracture will be considered 1. osteoporotic fracture (excluding skull, face, or digits), 2. major fracture (hip, wrist/forearm, spine, and proximal humerus) and 3. peripheral fracture/s (wrist-forearm, ankle, and proximal humerus). Should the prediction tool (phase iii) accurately predict fracture risk it is hoped that it will be used to identify whether a patient needs bone therapy or bone density scanning prior to undergoing bariatric surgery.

Objectives, Specific Aims and Rationale

RATIONALE

Despite the lack of randomised data on this issue, some (but not all) previous cohort and case-control studies have speculated that patients undergoing bariatric surgery might be at an increased risk of bone fractures post-operatively. Possible mechanisms for the increase in bone fragility include a decrease in mechanical loading secondary to weight loss, and/or calcium/vitamin D malabsorption in the operated stomach and duodenum.

OBJECTIVE/S

Our overarching aim is to assess whether there is a need for specific bone assessment and (when needed) fracture prevention treatment for patients undergoing bariatric surgery for severe obesity. To achieve this aim assessment of the accuracy of bariatric surgery reporting is CPRD is necessary.

SPECIFIC AIMS

1. To study the risk of post-operative fracture risk amongst severely obese NHS patients undergoing bariatric surgery; AND 2. To determine key risk factors of post-operative fracture, and to derive a prediction tool for the case-finding of high-risk patients at the time of pre-operative bariatric surgery assessment; AND 3. To assess the accuracy of bariatric surgery reporting in CPRD.

Study Background

OBESITY, BARIATRIC SURGERY, AND FRACTURES

Obesity has been traditionally considered a protective factor against osteoporosis and related fragility fractures.

Current NICE-recommended fracture prediction tools (i.e. FRAX and QFracture) do treat overweight/obesity as a protective factor. However, recent research has demonstrated that although indeed hip fractures are less common amongst the obese, they are more prone to fracture at peripheral sites (ankle, wrist, proximal humerus) (4, 5). This paradox has become more clinically relevant in recent years, after the implementation of NHS funded bariatric surgery units, and an increasing uptake of the technique at a national level. The current proposal is in fact the result of conversations between bariatric surgery clinicians and metabolic bone specialists in our hospitals trust on the need and –if so- the design of guidelines and local care pathways for patients who fracture (or at high risk of fracturing) in the years following obesity surgery. Following these discussions, clinical leads for the local metabolic bone and the bariatric surgery units agreed that there is a need for further research to fill the existing gap of evidence on 1. whether there is an increased risk of fracture/s post-operatively, and if so, what is the 'at risk' period; and 2. if there is such a risk, who -amongst patients undergoing bariatric surgery is most at risk of such fractures. Our current proposal aims to fill this gap under the NIHR themed call for research on 'Prevention and Treatment of Obesity'.

BARIATRIC SURGERY FOR SEVERE OBESITY – RISKS AND BENEFITS

Bariatric surgery (BS) has been proven very effective for the treatment of severe obesity, reducing long-term body weight by >65%(7) and inducing a 5-year body mass index loss of 12-17 kg/m2 on average(8). BS does therefore indirectly improve (sometimes leading to the resolution of) hypertension(9) and other cardiovascular risk factors(10); BS prevents(11), improves metabolic control(12), and induces remission of type 2 diabetes(8); and ultimately it produces a significant improvement in health-related quality of life(13). In addition, a Health Technology Assessment evaluation published in 2009 concluded that BS is cost-effective when compared to non-surgical interventions for moderate and severe obesity(14). NICE guidelines for the management of obesity (NICE CG 189) recommend bariatric surgery for patients with a BMI > 40 kg/m2, as well as for those with a BMI of 35 to 40 and a concomitant history of a "serious long-term condition that might improve as a consequence of weight loss (i.e. type 2 diabetes, hypertension)".

Despite these benefits, BS has –like all surgeries- also some known risks, including an increased risk of venous thrombo-embolism(15), surgical complications (infection, bleeding), and need for re-operation (17% and 7% at 1 month respectively)(8). However, the associated 90-day post-operative mortality is reassuringly low at 0.2%(11) shifting the focus on non-life threatening potential side effects. Despite clinical concerns, the lack of conclusive data on the association between BS and bone fragility is evident, as this is not a recognised risk in NHS-provided patient information materials(16).

BONE EFFECTS OF BARIATRIC SURGERY

It is well known that patients undergoing bariatric surgery experience nutrition deficits to include an insufficient absorption of calcium and vitamin D, potentially leading to alterations of bone metabolism and subsequently the development of osteopenia/osteoporosis(17). In parallel, the resulting weight loss has also detrimental effects on bone: the experienced reduction in mechanical load is associated with a decrease in the expression of sclerostin, which results in upregulation of the Wnt/beta-catenin pathway and thus a negative imbalance with increased bone resorption(18).

Despite all this, the data on the effects of bariatric surgery on bone mineral density are inconsistent, with studies ranging from no significant change to an up to 10% bone loss in the year following surgery compared to baseline(19). Even less clear is the existing literature on the association between bariatric surgery and fracture risk: although a systematic review published in 2010 concluded that there is an increase in fracture risk in the years following BS(20), more recent papers –including a BMJ published in 2012 and based on UK data(1)– have found no such relationship. All these studies are cohort (or in some cases case-control) analyses where important differences remain between participants undergoing surgery and those not receiving it: in the study by Lalmohamed et al(1), despite matching on BMI, those undergoing BS had a 3 kg/m2 higher BMI. Even more relevant might be the potentially existing differences in non-observed/analysed variables such as bone mineral density or socio-economic status, which the authors did therefore not manage to adjust for.

As a result of this controversy in the evidence, there is no clear guidance on reviewing bone health in BS patients as evidenced by the lack of inclusion of this patient group in the NICE CG 146 where bone risk assessment is targeted to those with a low not high body mass index.

WHY IS THIS RESEARCH IMPORTANT?

Locally, we (clinician scientists working in the Metabolic Bone unit) have recently been contacted by our colleagues from the BS unit with the aim to set up a clinical pathway or to establish shared care protocols or guidelines at the loco-regional level. The ongoing discussions between our unit members and the disappointing lack of consensus in the published evidence on the association between bariatric surgery and fracture/s have led to the drafting of the current application. We have jointly written the enclosed proposal, with the aims 1.to describe the association between BS and fracture risk after adequately adjusting for both observed and unobserved variables using novel pharmaco-epidemiological analyses (self-controlled case series(21)) , and 2.secondly, to identify key risk factors for post-BS fracture risk, and to derive a clinical prediction tool, which will be proposed to use for the identification and targeting of high-risk patients in need of specific bone assessment/s (eg DEXA scans for bone mineral density measurement) and/or treatment/s (eg calcium/vitamin D supplements) within the NHS. A meeting with local patient/carer groups have confirmed the relevance of this topic.

Study Type

Hypothesis testing (primary aim) and generating (secondary aim).

Study Design

Cohort and Self-Controlled Case Series

Feasibility counts

Feasibility counts were calculated on CPRD – linked HES data between 1/1/1997 and 31/3/2014 and identified patients with at least one OPCS4 code for bariatric surgery. The number of patients undergoing bariatric surgery according to this count is of n=10,989.

Sample size considerations

- Objective 1: According to the method proposed by Musonda et al(29) and implemented in the sampsi sccs command in Stata(30), 68 cases would be needed to detect as significant an incidence rate ratio (IRR) of 2 or above in a 2-sided SCCS analysis with alpha risk of 0.05, 80% power, and a 5-year (post-surgery) exposure period (main analysis). According to feasibility counts from the CPRD-HES linked data, the number of patients available with our inclusion criteria is of 10,989 (until end/2014). In previous analyses of CPRD data by Lalmohamed et al(1), incidence rate of fracture was 8.8/1,000 py, making a total of 494 cases (10,989 x 0.009 x 5) available in the 5-year post-operative (i.e. exposed) period. We therefore expect >90% power for the proposed analyses.

- Objective 2: In a log-rank 2-sided test, accepting an alpha risk of 0.05 and a beta risk of 0.2, and with a 20% prevalence of a given risk factor, 9,959 participants (1,993 “exposed” to the given risk factor) are required to detect as significant a rate ratio of 1.5 or above with 90% power. This calculation assumes a cumulative incidence of fracture of 0.9% and 4.5% at 1 and 5 years post-operatively as based on published UK data(1). A drop-out rate of 10% has been anticipated. More than 10,989 participants undergoing bariatric surgery will be available according to feasibility counts provided by the CPRD Knowledge Centre.

Data Linkage Required

We request access to the following linked datasets, and for the following reasons:

1.- HES inpatient data will be used to identify patients undergoing bariatric surgery (inclusion criterion and index date) using OPCS4 procedure codes.

2.- ONS death date will be used to censor patient follow-up in the cohort and SCCS analyses.

AND 3.- Patient-level Index of Multiple Deprivation will be used as a potential predictor of fracture risk

Study population

INCLUSION CRITERIA

All patients aged 18 or above registered in a CPRD-linked HES practice with up to standard (UTS) data available between 01/04/1997 and 31/03/2016 and a BMI of 35 or above, undergoing bariatric surgery according to CPRD or HES records will be eligible for Objectives 2 and 3.

Only those sustaining 1 or more fracture/s in the observation period (years before or after bariatric surgery) will be included for the SCCS (case-only) analysis (Objective 1).

EXCLUSION CRITERIA

Patients with less than 1 year of UTS data (since registration) available before the time of surgery will be excluded. In addition, those with a recent diagnosis (in the last year before surgery) of gastro-intestinal cancer will also be excluded to avoid misclassification (i.e. patients receiving gastrectomy for malignancy rather than for obesity).

START OF FOLLOW-UP

Follow up will begin upon the latest of BMI of 35 or higher, 1 year UTS follow-up at a registered practice, aged 18 and 01/04/1997.

END OF FOLLOW-UP

Patients will be followed until the earliest of patient exit from practice, death, practice no longer providing data, and 31/03/2016.

Selection of comparison group(s) or controls

N/A. A bariatric surgery cohort will be included, with no comparison/control group needed.

Exposures, Health Outcomes and Covariates

EXPOSURE/S

-Main exposure (Objective 1): Bariatric surgery is the main exposure (Objective 1), and it will be identified using previously published sets of READ codes in CPRD(1), which we will validate in the CPRD-HES linked population against HSCIC-approved lists of Operative Classification of Interventions and Procedure (OPCS-4) codes in the linked HES dataset: G27*, G28*, G31*, G32*, G33* (gastric bypass), G30.3, G38.7, G30.5 (gastric band), G48.1, G48.2, G48.5, G48.6 (gastric balloon/bubble), and G30.4 (stomach stapling). Previous UK studies(1) have only used primary care records (i.e. CPRD), and linking to HES and definitive ascertainment of bariatric surgery is a major advantage of our current proposal.

-Risk factors for post-operative fracture (Objective 2): a pre-specified list of risk factors from published studies will be included for the analysis of key predictors of fracture following surgery. The list will be limited to factors available from physical examination and medical history during pre-operative clinics, as these will be the basis for future risk assessments based on the proposed prediction tool. This list of predictors has been informed by expert consensus and a literature review, and it will include: 1.classic bone fragility risk factors (age, gender, previous systemic steroid use, body mass index (BMI), previous fracture history, smoking, alcohol drinking, history of inflammatory/rheumatoid arthritis, causes of secondary osteoporosis), 2.type 2 diabetes status and related treatments, 3.use of other drugs with an effect on fracture risk (aromatase inhibitors, anti-epiletics, antidepressants, hypnotics, calcium vitamin d supplements), AND 4.socio-economic deprivation. Time varying predictors will be assessed in the year before surgery with the value closest to Bariatric surgery date used in the prediction model if more than one value is available. Since patients undergoing Bariatric surgery are often required to lose weight prior to surgery, change in weight in the year before surgery will also be included as a covariate along with the last BMI value before surgery. Change in weight will be initially assessed as both change in BMI and change in excess body weight since the mechanisms of bariatric surgery leading to a change in fracture risk are unclear. In the final analysis only one of these two measures will be use if shown to be effective at predicting fracture risk.

All these will be ascertained using previously validated/used lists of READ codes (co-morbidities, clinical events),

British National Formulary (BNF) codes (drug therapies), and clinical measurements (weight, height, body mass index, smoking, etc) as provided in CPRD tables. Socio-economic deprivation is provided by CPRD and estimated at an ecologic level using the Index of Multiple Deprivation.

OUTCOMES

-Primary: primary outcome will be any osteoporotic fracture/s (any but skull, face, or digits) in the 5 years before or after bariatric surgery, with sensitivity analyses looking at 0-3 and >3 years before-after surgery respectively.

-Secondary outcomes will include: 1.major fracture (hip, wrist/forearm, spine, and proximal humerus), and 2.peripheral fracture/s (wrist/forearm, ankle, and proximal humerus) in the same time frames.

All the proposed study outcomes (i.e. bone fractures) will be ascertained using previously validated lists of READ/OXMIS (CPRD)(6) codes.

INTERACTION/S

Previous studies have suggested that excess risk attributable to bariatric surgery might differ by anti-osteoporosis drug/s use, age, weight loss, and the presence of type 2 diabetes. In addition, interactions by type of surgery will also be tested for. We will test for these interactions by introducing multiplicative terms in the SCCS equation/s. Stratified results will be reported for any borderline significant (p-val for an interaction<0.1) interaction/s.

Data/ Statistical Analysis

-Objective 1: A self-controlled case series (SCCS) analysis will be used to study the association between bariatric surgery and fracture risk. The SCCS method relies on intra-person comparisons in a population of subjects undergoing bariatric surgery who have sustained the event of interest (i.e. one or more fracture/s). Incidence rate ratios (IRR) of fracture will be derived comparing defined “exposure” intervals (time post-surgery) to “non-exposure” periods (pre-surgery). The start and end dates of the “exposure” period will be defined as the date of surgery (as recorded in GP records), and the end of follow-up (primary analysis), with sensitivity analyses redefining these “exposure” periods to 0-3, and >3 years post-operatively instead. All other observation time available in the dataset (the time from 12 months after registration in a CPRD practice to the day before surgery (pre-exposure) will be considered as “non-exposure” periods. We will control for age in this analysis using five-year bands. IRR and 95% confidence intervals will be calculated for incident events observed within the “exposure” period compared to baseline (“non-exposure”) using the SCCS method and assuming a Poisson distribution. Sensitivity analyses will be conducted where the duration of the exposure period will be set at 0-3 and >3 years (post-surgery) respectively.

-Objective 2: A retrospective cohort design will be used to estimate the incidence rates and cumulative incidence of fracture in the years after bariatric surgery, and to identify key risk factors associated with an increased fracture risk in this population.

As for the derivation of a clinical prediction tool for post-operative fracture risk, logistic regression analyses will be conducted, where fracture/s in the post-operative risk period (5-years initially but to be modified according to findings of the proposed subanalyses) will be a binary outcome. Stepwise backwards selection of key predictors (from the list of pre-specified

variables described above) with an exit p-value of <0.157(31) and bootstrap methods will be used to minimise chance findings, and only those variables retained in >80% of the resulting regression models will be considered. Multivariable-adjusted Odds Ratios (OR) and 95% Confidence Intervals will be reported for each of the identified key predictors.

Finally, the obtained coefficients (log-OR) will be combined to estimate 5-year fracture risk in a newly derived clinical prediction tool, which will be validated internally using c-statistic (discrimination) and observed vs expected ratios and plots stratified by risk deciles (calibration).

-Objective 3: We will use HES data to calculate the Positive Predictive Value of CPRD records of bariatric surgery. We will compare the date of surgery in CPRD (primary care) records to that in the linked hospital admission (HES) dataset. Differences in dates of less than 3 months will be considered to be the same episode and hence correctly by CPRD. HES will be considered a gold standard, and positive predictive values (PPV) for the proposed list of READ (CPRD) codes will be estimated. If PPV is low (<75%), a sensitivity analysis will be conducted restricted to the 60% of practices with linked HES data for Objectives 1 and 2, where exposure (date of surgery) will be defined based on OPCS4 codes (HES) only.

Plan for addressing confounding

A self-controlled case series design is proposed to minimise fixed confounding in the study of the effect of bariatric surgery on fracture risk. Under certain assumptions, SCCS methods are gold standard for controlling confounding.

Plans for addressing missing data

Missing data for any of the listed potential predictors (expected based on previous experience for BMI and smoking variables) will be handled using multiple imputation by chained equations (MICE) methods (32). Since alcohol use and smoking status have previously been shown to be missing not at random (1), a sensitivity study will be undertaken to identify whether the analyses remain robust despite violating the missing at random assumption.

Patient or user group involvement (if applicable)

A patient representative has collaborated in the drafting of the current protocol. In addition, two members of the research team had the opportunity to discuss our research aims and proposed methods with a group of 22 patients/carers from the local bariatric surgery patient

group. Verbal and written (anonymised) feedback was collected from the attendees, resulting in the following conclusions:

1. 19/22 (84%) were either supportive or 'fully supportive' that this is a relevant topic

2. 15/20 responders (75%) fully agreed with the proposed research methods, with only 2 being 'not sure'/'sort of', and 3 non-valid responses (blank text)

3. The need for individual (patient-level) risk estimation was raised by at least two patients, which led to the addition of a new aim to the project (i.e. to derive a risk prediction tool as part of Aim 2)

4. Written feedback encouraged dissemination of findings to both doctors and allied health professionals involved in bariatric surgery clinical management

AND 5. The need for testing for interactions with pre-existing co-morbidity and type of surgery was raised, which was discussed with the research team and added as additional interactions in the proposed protocol.

PPI (patient and public involvement) will benefit all stages of the research, including ensuring the focus and deliverables of the research map well to patient needs, the conduct and analysis of the research fulfils patient expectations and assisting in the dissemination of the study findings to reach interested sectors of the public.

A patient who had bariatric surgery has joined the team as a co-applicant and has been/will be involved in the application process, the research management - together with the rest of the research team -, the analysis of results, the writing of the final report and the dissemination of findings. Having a PPI co-applicant will guarantee the public perspective is present in all stages of research and internal discussions. An external, independent member of the public will be involved in deciding the future of the research progress as a member of the study steering committee.

Finally, the local-regional bariatric support group has contributed to the current application with their feedback on the research topic, outputs and methodology, and it will be involved in the research again when preliminary results are available in order to plan the final analysis. The group holds monthly meetings with about 25 patients, carers, family members, and friends.

With these three elements (an internal co-applicant, an external public representative and a support group) we expect to have different contributions to the study covering a wide range of interests. The PI and the rest of the research team will make sure that PPI representatives involved on this project have enough support to understand and contribute to the project, organising the appropriate training when necessary. The patient and patient support group will receive training from and support by the research team as well as the Research Design Services PPI representative/s.

Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication

Our study results will be reported at national and international scientific meetings. We will also present our findings to the lay audience in coordination with our patient representative co-applicant.

We will liaise with relevant patient groups and charities (local-regional bariatric support group, National Osteoporosis Society). Our results will inform local organisation of care for patients undergoing bariatric surgery for obesity in our trust. Patient information leaflets will be designed to inform on our study findings under the supervision of our patient representative co-applicant.

In addition, we will organise talks in local schools to discuss bone health in obesity, and will involve NDORMS (Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences) and the Press Office at the University of Oxford to reach a wider audience once findings are made public.

Limitations of the study design, data sources, and analytic methods

The proposed study is observational in nature, and hence cannot address causality but rather describe associations. Advanced methods (SCCS) will be used to minimise confounding.

Fractures have been previously validated in CPRD with high accuracy [Van Staa TP, et al. J Bone Miner Res. 2000;15(6):993-1000].

Since CPRD-HES linkage is only available in English hospitals, the prediction tool will only have been validated for this region and may not be generalizable to the wider population. Further research may be needed in different datasets to validate the prediction tool for other regions and countries. Furthermore, since patients may choose to undergo bariatric surgery at a private hospital there may be missing surgeries in HES captured through CPRD. However, this is unlikely to significantly affect the overall result, only restrict the sample size.

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