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Fat mass, but not fat-free mass, predicts increased foot pain with obesity, independent of bariatric surgery

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Highlights

- Compared to a waiting-list control, bariatric surgery is associated with a significant reduction in foot pain
- Higher baseline fat mass was significantly associated with higher foot pain at 6-month follow-up
- Higher baseline fat-free mass was associated with lower foot pain at 6-month follow-up
- The change in adipokines may explain the change in foot pain following bariatric surgery

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Study conception and design: Walsh, Quinn, Evans, Yaxley, Chisholm, Kow, Shanahan

Participant recruitment: Walsh, Chisholm, Kow

Acquisition of data: Walsh, Evans

Analysis and interpretation of data: Walsh, Quinn, Yaxley, Shanahan

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Short title: Fat mass is predictive of foot pain following bariatric surgery.

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Abstract

Background: Foot pain is a common manifestation of obesity.

Objective: To determine; i) if bariatric surgery is associated with a reduction in foot pain and; ii) if body mass index (BMI) or body composition predict a change in foot pain.

Setting: University Hospital.

Methods: Participants with foot pain awaiting bariatric surgery were recruited for this prospective study. Multivariable linear regression was used to determine predictors of change in foot pain between baseline and six-month follow-up using body composition (fat mass index (FMI) and fat-free mass index (FFMI)) or BMI, adjusting for, depression, age, gender and group (surgery versus control).

Results: Forty-five participants (38 female), mean±SD age of 45.7±9.4years, were recruited for this study. Twenty-nine participants mean±SD BMI of 44.8±7.0kg underwent bariatric surgery, while 16 participants mean±SD BMI of 47.9±5.2kg were on the waiting-list (control). One participant was lost to follow-up. The treatment group lost a mean of 24.3kg (95% CI 21.1 to 27.5), while the control group gained 1.2kg (95% CI -2.5 to 4.9), respectively. In multivariable analysis, bariatric surgery was significantly associated with reduced foot pain at six-month follow-up -32.6 points (95% CI -43.8 to -21.4, p<0.001), while FMI was significantly associated with increased pain at follow-up 1.5 points (95% CI 0.2 to 2.8, p=0.027), after controlling for FFMI, age, gender and depression.

Conclusions: Bariatric surgery was significantly associated with reduced foot pain. Higher baseline FMI, but not FFMI or BMI, was predictive of increased foot pain at follow-up. Foot pain may be mediated by metabolic, rather than mechanical, factors in bariatric surgery candidates.

Keywords: Foot; pain; obesity; bariatric surgery

Background

Musculoskeletal pain is strongly associated with obesity [1]. Obesity increases the risk of lower-limb complaints such as osteoarthritis, and affects the speed of recovery following injury [2]. Increased body mass index (BMI) is strongly associated with foot pain [3], with increased body weight excessively loading pedal joints and tissues, thought to be the underlying mechanism. Indeed, obesity is associated with hindfoot stiffness, increased plantar pressure and pronated foot posture, which may increase the risk of pain [4]. Whilst much attention is directed toward the effect of excessive mechanical loading, foot pain associated with obesity may also be due to metabolic dysfunction related to excessive fat. Further exploration of the relationship between obesity and foot pain is important as it may better inform more targeted management strategies.

Studies investigating the effect of body composition on musculoskeletal pain in the low-back [5], knee [6] and foot [7,8] are associated with fat mass, but not fat-free mass.

These findings propose that the type of tissue present may be more important than the weight of the tissue. Furthermore, obesity has been associated with hand osteoarthritis [9,10], which as a non-weight bearing structure, suggests that the effect of obesity may extend beyond excessive mechanical loading. There is evidence that cytokines from adipose tissue, adipokines, may be upregulated with obesity with strong associations between adipose tissue and serum adipokines [11].

Leptin, a proinflammatory adipokine, chiefly secreted by subcutaneous adipose tissue, has been found to be a mediator between body weight and knee osteoarthritis [12] and is associated with generalised musculoskeletal pain in women [13]. Furthermore, higher serum leptin predicts a slower recovery from upper extremity soft tissue disorders [14]. Articular chondrocytes express receptors for leptin [15], providing a direct pathway for adipose tissue to interact with joint cartilage, beyond mechanical loading. This suggests that the link between obesity and joint pain may be mediated locally via the effects of systemic adiposity.

Despite the strong association between obesity and foot pain, there is a paucity of literature investigating the effectiveness of weight loss on reducing symptoms. Indeed, the effectiveness of bariatric surgery on the morbidly obese, a group plagued with foot pain, has been largely unexplored. Moreover, whether there are predictors or correlates for a change in foot pain, to suggest a possible underlying mechanism whether that be mechanical or metabolic are also undetermined.

This study aims to investigate whether; i) bariatric surgery is associated with a reduction in foot pain, ii) if baseline body mass index (BMI), body composition or a change in adipokines predict change in foot pain following bariatric surgery.

Materials and Methods

Participants

This project was a prospective observational study conducted between January 2015 and June 2017. A convenience sample of people with foot pain was recruited from the surgical waiting lists at two tertiary hospitals in Adelaide, South Australia. The treatment group was recruited for baseline measures immediately prior to bariatric surgery and re-evaluated again six-months post-operatively and underwent either a Roux-en-Y gastric bypass, a sleeve gastrectomy or a laparoscopic adjustable gastric band. The control group was recruited from the same waiting lists as the treatment group, but these patients were not scheduled to have surgery within six-months. Participants in the control group were re-evaluated at six-month follow-up. Ethics approval has been given for this project by Southern Adelaide Clinical Human Research Ethics Committee (Project ID 211.14).

Inclusion and exclusion criteria

People on the waiting list for bariatric surgery were eligible for inclusion if they were aged ≥18 years and had reported foot pain for ≥3 months of ≥30mm on a visual analogue scale, as this has been shown to represent moderate (or greater) pain [16]. People were excluded if they had; a systemic inflammatory condition, clinically significant peripheral neuropathy, known infectious disease, cancer, previous bariatric or foot surgery, were non-ambulatory or were pregnant.

Anthropometric data

Age, body weight, height, and waist and hip circumference were recorded at the time of the body composition assessment. Body weight and height was measured to the nearest 0.1kg and 0.1cm, respectively using an electronic stadiometer (with shoes, socks, and bulky clothing removed) (Seca 284, Germany). From these data, BMI (weight(kg)/height(m^2)) was calculated [17]. Waist and hip circumference were measured using a flexible steel measuring tape (Lufkin, US) in duplicate to the nearest 0.1cm and the mean score was recorded.

Foot pain

Foot pain and disability was assessed with the Manchester-Oxford Foot Questionnaire (MOXFQ) [18]. The MOXFQ is a reliable and valid 16-item questionnaire that comprises three separate underlying dimensions: walking/standing problems (seven items), foot pain (five items), and social interaction (four items) [19]. Item responses are each scored from 0-4, with 4 representing the most severe state. The scale score representing each dimension was produced by summing the responses of each item within that dimension. This produces raw scale scores, which were then transformed to a scale from 0–100 (100 most severe). The foot pain domain was used for this study, it has been previously recommended for measuring relief of pain [19].

Body composition

Participants underwent a dual-energy X-ray absorptiometry (DXA*)* scan, with the Lunar Prodigy Advance (GE Healthcare, WI, USA), at baseline and at six-months follow-up. The DXA was used to assess body composition; total fat mass (FM), total lean mass and total bone mineral content (BMC). Lean mass and BMC were combined to give fat-free mass (FFM). Fat mass and FFM were normalised for height by calculating fat mass index (FMI) (total body fat(kg)/height(m)^2) and fat-free mass index (FFMI) (FFM/height(m)^2) [20].

Adipokines

Fasting blood samples were collected and centrifuged, and aliquots of serum were stored at -80^{o}C until the final analysis. Serum concentrations of leptin, adiponectin and resistin were measured with the Millipore human adipokine kits on the MAGPIX machine and analysed with xPONENT software (Luminex Corporation, TX, USA). Samples were prepared at appropriate dilutions and assessed according to the manufacturer's instructions. Internal control samples supplied by the manufacturer were tested and duplicate analyses were used to ensure quality control.

Depressive symptoms

Given the bidirectional association of depression and pain [21], depression was measured. The Center for Epidemiologic Studies Depression scale (CES-D) consists of 20-items designed to assess depressive symptoms [22]. All items are graded via four-point Likert scale, which are later graded between 0–3. A score of ≥16 has been shown to be sensitive to detect depressive symptoms [23] and this was used define depression in this cohort.

Data analysis

All data distributions were checked for normality via the inspection of histograms and the Shapiro-Wilks test prior to interferential statistical analysis. Differences between treatment and control groups at baseline were assessed using chi-squared tests for categorical data and t-tests or Mann-Whitney *U* tests for continuous data that is normally or non-normally distributed, respectively. Given the low numbers and the fact that BMI is the sum of FMI and FFMI, two multivariable linear regressions were used to assess differences between baseline and follow-up. The dependent variable was foot pain at follow-up. The independent variables were foot pain at baseline, age, gender, group, depression and either BMI (model 1) or FMI and FFMI (model 2). We also used partial correlation, to investigate whether change in foot pain was associated with change in leptin, adiponectin or resistin. Standard homoscedasticity and normality checks of residuals were carried out to ensure model validation (using

Stata's hettest and swilk commands). These models were also adjusted for age, gender, group, depression, FMI and FFMI. In all analyses, a p-value (two-sided) less than 0.05 was deemed to be statistically significant. Results are reported with 95% confidence intervals (95% CI). All data analyses were performed with SPSS V24 (IBM SPSS Statistics, New York) and Stata V14.2 (StataCorp LP, College Station, Texas).

Sample size

The primary outcome measure was the change in foot pain following bariatric surgery. Given we did not expect to see a significant change in foot pain in the control group [24,25], the sample size was based on a mean±standard deviation (SD) of change in foot pain within the treatment group of 13±25.1 based on previous studies [19,26]. A conservative sample size calculation required 34 participants in the treatment group to provide 80% power, assuming a Type I error of 5%.

Results

Participant baseline characteristics

Baseline characteristics are described in Table 1. There were 45 participants (38 women), with a mean±SD age of 45.7±9.4 years, recruited for this study. Twenty-nine participants were in the treatment group and 16 were in the control group. All participants underwent baseline measures, one participant (from the treatment group) was lost to follow-up. The baseline mean±SD BMI for the treatment and control group was 44.8±7.0 and 47.9±5.2 kg, respectively. Fat-free mass index was significantly different between groups, with a mean±SD in the treatment group of 21.4±3.2 versus 23.0±2.3 in the control group, p=0.041. Otherwise there were no statistically significant between-group differences in baseline characteristics. There were 13, 11, and 5 participants who underwent Roux-en-Y gastric bypass, sleeve gastrectomy or laparoscopic adjustable gastric band, respectively.

Multivariable linear regression

After adjusting for age, gender and depression, bariatric surgery was a significant predictor of change in foot pain, β=-30.7 (95% CI -41.9 to -19.5, $p<0.001$), Table 2. Body mass index was not a significant predictor of a change in foot pain with β=0.5 (95% CI -0.3 to 1.4, p=0.213). Using a similar model, but substituting FMI and FFMI for BMI, bariatric surgery and FMI were significant predictors of a change in foot pain, β=-32.6 (95% CI -43.8 to -21.4, $p<0.001$) and FMI β=1.5 (95% CI 0.2 to 2.8, p=0.027), respectively. The relationship between FFMI and a change in foot pain was not statistically significant, β=-1.4 (95% CI -3.4 to 0.5, p=0.145), and was divergent from FMI, Table 3. There was no evidence of model violation in either model: Table 2 – swilk p=0.74, hettest p=0.40; and Table 3 – swilk p=0.21, hettest p=0.93. The within-group change in baseline variables can be found in Supplementary File 1.

Partial correlation of adipokines with change in pain

Change in foot pain was not significantly correlated with change in leptin or adiponectin, when adjusted for the same confounders in Table 3. On the other hand, change in pain and change in resistin were negatively correlated (ρ=-0.42, p=0.024) when adjusted for the other confounders in Table 3.

Discussion

This study found clinically significant improvements in foot pain following bariatric surgery. Bariatric surgery rendered a marked decrease in foot pain severity between baseline and follow-up, while increased baseline FMI, but not FFMI or BMI, yielded increased foot pain at follow-up, after controlling for age, gender and depression.

The findings of this study are concordant with previous work investigating body composition predicting foot pain. A study evaluating incident foot pain in an overweight cohort [27] found that increased FMI, but not FFMI, predicts pain while a large community cohort study found that increased FMI was associated with a six per cent increase in future foot pain over four years [7]. Our study is the first to measure the change in foot pain severity in relation to body composition, rather than incident foot pain, and additionally our study adjusts for the affect of bariatric surgery. We found that fat mass, not fat-free mass (which had a negative correlation with foot pain severity), may potentially be the main perpetrator linking obesity and pain and does suggest that excessive mechanical loading may not be the exclusive interface between obesity and foot pain. The findings also suggest that details on body composition may be more clinically important than the BMI and that body fat may have affects on the musculoskeletal system that are not resolved with the reduction of in body weight e.g. degenerative joint or soft tissue changes.

Elevated BMI has been found to be a predictor of future foot pain over a two-year period in a community cohort [28] and indeed was a predictor of foot joint pain in a study of women over a five-year period [29]. The findings of our study, however, suggest that using the BMI alone may underestimate the impact of adiposity and it may not be a good predictor of future prognosis for bariatric cohorts with foot pain. Moreover, there is evidence that examining fat mass alone may underestimate the effect of this tissue, a recent study of women with foot pain found the ratio of visceral to subcutaneous abdominal fat was associated with foot pain, suggesting that not only the amount of fat, but its location could impact on pain [30].

The challenge for addressing musculoskeletal pain in those undergoing bariatric surgery is that whilst weight loss reduces fat mass [31] and improves psychological health [32], this group often remains obese (BMI ≥30 kg/m^2) and will continue to be at risk of generalised musculoskeletal pain. Complete resolution of pain may be unlikely following bariatric surgery, however, it is clearly associated with a reduced severity of foot pain in the short-term for this cohort. Whether the relief of pain persists beyond this time is unknown, but data from a large cohort study investigating hip and knee pain suggests that the reduction in pain severity may be sustained [33].

Our study has some limitations. Firstly, the observational design means this was not a true waiting-list control trial, which would have made for a stronger study design and future trials may also focus on the change in foot pain by comparing bariatric procedures head-to-head. Secondly, our small sample size prohibited a large multivariable regression model, but the effect of bariatric surgery on foot pain is so large that the addition of the other variables is unlikely to change the statistical significance of this predictor. There may have been type II errors in the models e.g. FFMI, and a larger sample may have found a statistically significant association. Thirdly, given the sample size we were also not able to include the adipokines in the multivariable models. The partial correlation analysis, that found a significant inverse relationship between resistin and pain, suggests resistin may play a mediation role between body fat with pain. A previous study suggested that resistin may have anti-inflammatory effects by activating transforming growth factor beta (TGF-β) [14], a molecule involved in tendon healing, but larger samples are required to sufficiently explore this relationship. Finally, the six-month follow up is a relatively short-term period and the results may not be representative of changes that occur over a longer period.

Our study has a number of strengths. It is the first study to examine if body composition predicts change in foot pain in bariatric participants, and the first to provide detailed, validated examination of foot pain, longitudinally in a bariatric cohort. The examination of FMI and FFMI and the inverse relationship they have with foot pain is novel and does question the usefulness of BMI in predicting a change in foot pain in bariatric populations. The analysis of serum adipokines in relation to foot pain is also novel.

Conclusions

Bariatric surgery is significantly associated with a reduction in foot pain. Body fat, but not body weight, is an independent predictor of increased foot pain at six-months follow up in a bariatric cohort. Serum adipokines are associated with foot pain, whereas BMI is not, thus the mechanisms underlying foot pain in bariatric cohorts may be more related to metabolic activity rather than mechanical overload.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Conflict of interest:

TPW: Declares no conflict of interest

SJQ: Declares no conflict of interest

AME: Declares no conflict of interest

AY: Declares no conflict of interest

JAC: Declares no conflict of interest

LK: Declares no conflict of interest

EMS: Declares no conflict of interest

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Table 1: Baseline characteristics of the treatment and control groups[a] (values are mean (SD) unless otherwise indicated)

	Treatment group (n = 29)	Control group (n = 16)	*P* value
Age, years	45.1 (9.0)	45.3 (10.4)	0.958
Gender, no. of women (%)	25 (86.2)	13 (81.3)	0.661
Height, m	1.7 (0.1)	1.7 (0.1)	0.906
Weight, kg	123.9 (19.4)	132.4 (15.5)	0.140
Waist circumference, cm	127.4 (11.7)	134.0 (13.2)	0.094
Hip circumference, cm	139.2 (13.2)	141.9 (13.8)	0.527
BMI, kg / m^2	44.8 (7.0)	47.9 (5.2)	0.120
FMI, kg / m^2	23.4 (5.7)	24.6 (4.1)	0.497
FFMI, kg / m^2	21.3 (3.2)	23.4 (3.0)	0.041
FMI / FFMI ratio	1.1 (0.2)	1.1 (0.2)	0.533
Adiponectin, μg / ml, median (IQR)[b]	12.5 (17.1)	8.5 (20.0)	0.445
Leptin, ng / ml, median (IQR)[b]	41.8 (26.8)	56.3 (32.7)	0.150
Resistin, ng / ml, median (IQR)[b]	31.9 (25.3)	29.0 (16.0)	0.471
Depressive symptoms, n (%)[c]	15 (51.7)	10 (62.5)	0.486
MOXFQ pain domain score	54.1 (16.2)	63.4 (17.5)	0.080

[a] *P* calculated for differences between the treatment and control groups analysed with the independent samples t-test

[b] *P* calculated for differences between the treatment and control groups analysed with the Mann-Whitney *U* test

[c] *P* calculated for differences between the treatment and control groups analysed with the chi-squared test

Abbreviations: *SD* standard deviation, *m* metres, m^2 metres squared, *kg* kilogram, *μg* microgram, *ng* nanogram, *ml* millilitre, *cm* centimetre, *MOXFQ* Manchester-Oxford Foot Questionnaire, *IQR* Interquartile range

Table 2: Multivariable relationship between baseline predictors for change in foot pain between baseline and follow-up, with BMI as a predictor

	β-coefficients (95% CI)	*P* value
Age	0.1 (-0.6 to 0.9)	0.677
Bariatric surgery	-30.7 (-41.9 to -19.5)	< 0.001
BMI	0.5 (-0.3 to 1.4)	0.213
Depression	7.2 (-4.3 to 18.7)	0.214
Gender (female)	10.7 (-5.4 to 26.8)	0.186

Abbreviations: *CI* confidence interval, *BMI* body mass index

Table 3: Multivariable relationship between baseline predictors for change in foot pain between baseline and follow-up, with FMI and FFMI as predictors

	β-coefficients (95% CI)	*P* value
Age	0.3 (-0.5 to 1.0)	0.480
Bariatric surgery	-32.6 (-43.8 to -21.4)	< 0.001
Depression	3.6 (-8.5 to 15.6)	0.553
FMI	1.5 (0.2 to 2.8)	0.027
FFMI	-1.4 (-3.4 to 0.5)	0.145
Gender (female)	4.8 (-13.0 to 22.5)	0.588

Abbreviations: *CI* confidence interval, *FMI* fat mass index, *FFMI* fat-free mass index