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The obesity paradox and orthopedic surgery

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Abstract

The Obesity Paradox describes the counterintuitive finding that although obesity contributes to the development of chronic conditions such as chronic kidney disease and cardiovascular disease, obesity seems to improve mortality in patients with these diseases. This paradox has also been sited in the critical care literature in regard to acute kidney injury, obesity and mortality. This study's objective is to examine the impact of obesity and post-surgical acute kidney injury on hospital length of stay and 2-year mortality after orthopedic surgery.

We reviewed the electronic medical records of all adult elective orthopedic surgery patients over 2 years in a large academic hospital. The 1783 patients who met inclusion criteria were divided into obese (body mass index, BMI ≥ 30, n = 1123) and non-obese groups (BMI < 30, n = 660). Demographics, medications, comorbidities, and perioperative variables were included in multivariable logistic regression analyses with acute kidney injury, length of hospital stay, and two-year mortality as primary outcomes. Outcomes were analyzed for the entire group, the obese cohort and the non-obese cohort.

Acute kidney injury developed in 5% of the post-surgical orthopedic patients. Obesity increased the likelihood of developing acute kidney injury post orthopedic surgery (odds ratio [OR] = 1.82; 95% Confidence interval [CI] 1.05–3.15, $P = .034$). Acute kidney injury increased length of stay by 1.3 days and increased the odds of two-year mortality (OR = 2.08; 95% CI 1.03–4.22, $P = .041$). However, obese patients had a decreased likelihood of two-year mortality (OR = 0.53; 95% CI 0.33–0.84, $P = .009$).

In adult orthopedic surgery patients, obesity increased the risk of acute kidney injury. Patients who developed an acute kidney injury had longer hospital stays and higher two-year mortality. Paradoxically, obesity decreased two-year mortality.

Abbreviations: AKI = acute kidney injury, BMI = body mass index, CKD = chronic kidney disease, GFR = glomerular filtration rate, LOS = length of hospital stay.

Keywords: acute kidney injury, mortality, obesity paradox, orthopedic surgery

1. Introduction

Obesity is defined as a body mass index (BMI) ≥ 30.[1] Obesity is a known risk factor for the development of cardiovascular disease, hypertension, type 2 diabetes mellitus and chronic kidney disease (CKD).[2] However, paradoxically, obesity confers a survival advantage in patients with these same chronic diseases.[3,4,5]

This obesity paradox has also been associated with acute kidney injury (AKI) in the critical care setting. Although obesity is associated with a higher incidence and severity of AKI in critical care, obesity is associated with improved in-hospital mortality in those patients requiring renal replacement therapy.[6,7,8]

Obesity has been shown to be an independent risk factor for postoperative AKI.[9] Acute kidney injury occurs in 3% to 21% of orthopedic surgeries. Higher BMI and certain comorbidities such as age, male sex, heart failure, diabetes, hypertension, and CKD have been associated with AKI after orthopedic surgery.[10,11] However, obesity has rarely been included in the surgical risk scores for AKI.[11,12,13] Our aim was to evaluate whether obesity is a risk factor for AKI in orthopedic surgery. In addition, we aimed to evaluate the effects that AKI and obesity have on short-term length of hospital stay (LOS) and long-term two-year mortality.

2. Methods

2.1. Study design and population

This study was approved by the Penn State College of Medicine institutional review board. As a single institutional observational cohort research study, 2224 elective orthopedic surgery patients were identified during a two-year period. Charts and operating room records were reviewed in the 1783 patients who met inclusion criteria: ≥18 years old, surgeries performed under general anesthesia, documented height and weight, comorbid-

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ities, medications, and pre and post-operative serum creatinine and hematocrit.

2.2. Data collection

The following variables were collected: demographics - age, gender, body mass index; co-morbidities - diabetes mellitus, heart failure, coronary artery disease, hypertension, CKD; medications -angiotensin converting enzyme inhibitors, angiotensin receptor blockers, non-steroidal anti-inflammatory drugs, beta-blockers, calcium channel blockers, diuretics; intraoperative factors - procedure, anesthetic agents, estimated blood loss, vasopressor use (ephedrine, epinephrine, phenylephrine), fluid quantities, and pre- and post-operative changes in hematocrit and creatinine.

2.3. Outcomes

Our first outcome was postoperative AKI, defined per the KDIGO guidelines as an increase in serum creatinine ≥ 0.3 mg/dL or an increase of $\geq 50\%$ from preoperative creatinine[14] within 72 hours following surgery. Our second outcome was length of hospital stay adjusted for the variables collected. Our third outcome was the adjusted two-year mortality, which was determined by chart review 2 years following the index orthopedic operation and collaborated with the social security death index.

First using bivariate comparisons with the variables and outcomes, followed by multivariable logistic regression, each outcome was analyzed for the total group, an obese cohort with BMI≥ 30 and a non-obese cohort with BMI < 30. Obesity was defined by the Centers for Disease Control and Prevention (CDC).[15]

2.4. Statistical analysis

Using frequencies and percentages or means, medians, and standard deviations, all variables were summarized before analysis. The distributions of continuous variables were assessed for normality using histograms, normal probability plots, and box plots. Because BMI failed the linearity in the logit assumption of logistic regression based on the Box-Tidwell test, BMI could not be used as a continuous predictor so we defined obesity by the CDC definition of a BMI ≥ 30 kg/m^2. To determine what factors were associated with the outcomes of AKI or mortality, and to quantify with odds ratios the magnitude and direction of any significant associations, logistic regression was applied. To determine the factors associated with length of stay, quantile regression of the median was employed. The magnitude and direction of any significant relationships were quantified with model estimates of the difference between group medians or increase in median length of stay. The bivariate analyses results allowed us to create a multivariable model for each outcome. Obesity, as the primary predictor, was adjusted for other statistically and clinically significant variables. For AKI, the model included obesity and was adjusted for age, gender, angiotensin converting enzyme inhibitor and angiotensin receptor blocker medications, diabetes, heart disease (coronary artery disease and/or congestive heart failure), hypertension, vasopressors, and spine surgery. For mortality and length of stay, the model included both obesity and AKI and was adjusted for age, gender, diabetes, heart disease, hypertension and chronic kidney

disease. A model with an interaction term between AKI and obesity was tested first, but the interaction between was not significant to either model. The predictors were tested for multicollinearity using variance inflation factor (VIF) statistics, before fitting the models. Goodness of fit for the logistic regression models was assessed using the Deviance, Pearson, and Hosmer and Lemeshow goodness-of-fit tests while Q-Q plots were used for the quantile regression models. SAS version 9.4 (SAS Institute, Cary, NC) was used for all analyzes.

3. Results

3.1. Demographics

With a mean age of 61.0 years old, 58% were female, 94% Caucasian, 37% were non-obese with a mean BMI of 25.6 kg/m^2, 63% were obese with a mean BMI of 37.5 kg/m^2. Obese patients had more comorbidities and took more medications. Only 1.0% of patients were underweight (BMI < 18.5), 11.8% were normal weight ($18.5 < $ BMI < 25), 23.9% were overweight ($25 \leq $ BMI < 30), and 63.3% were obese (BMI ≥ 30) (Table 1).

Table 1

Patient variables: total patients, non-obese patients, obese patients.

Variable	Total (N=1783)	Non-obese - BMI < 30 (N=654)	Obese– BMI ≥ 30 (N=1129)
Age (yr)	61.0 ± 13.6	63.1 ± 15.8	59.8 ± 12.1
Gender			
Female	58.5%	59.6%	57.8%
Male	41.5%	50.4%	52.2%
BMI (kg/m^2)	33.2 ± 7.7	25.6 ± 3.1	37.5 ± 6.1
Hypertension	61.6%	52.0%	67.1%
Diabetes mellitus	20.7%	11.9%	25.8%
Heart disease (CHF and/or CAD)	16.7%	17.3%	16.3%
GFR	85.4 ± 26.6	87.0 ± 28.1	84.4 ± 25.6
Chronic kidney Disease (GFR < 60)	15.0%	13.9%	15.6%
B-blockers	30.9%	25.0%	34.3%
Calcium channel blockers	17.3%	16.1%	18.1%
Diuretic	33.2%	24.5%	38.3%
NSAID	47.2%	46.9%	47.4%
ACEI and/or ARB	39.4%	30.2%	44.7%
Crystalloid (mL)	2285.0 (1400.0)	2246.5 (1350.0)	2300.0 (1400.0)
Estimated blood loss (mL)	200.0 (250.0)	200.0 (230.0)	200.0 (200.0)
Vaso-pressors Intraoperative	62.3%	66.9%	59.6%
Preoperative Hematocrit	39.7 ± 4.3	39.0 ± 4.4	40.1 ± 4.1
Postoperative Hematocrit	32.3 ± 4.6	31.2 ± 4.5	32.9 ± 4.5
Change in Hematocrit	−7.5 ± 4.0	−7.9 ± 4.4	−7.2 ± 3.8
Spine	9.5%	10.9%	8.7%
Total hip Arthroplasty	30.3%	43.0%	23.0%
Total knee arthroplasty	47.6%	31.0%	57.2%
Miscellaneous	12.6%	14.1%	11.1%
acute kidney injury (AKI)	5.1%	3.2%	6.1%
Length of hospital stay	3.0 (2.0)	3.0 (2.4)	3.0 (1.8)
2 yr mortality	5.2%	7.5%	3.9%

* Mean ± SD or Median (IQR) or %.
ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BMI = body mass index, GFR = glomerular filtration rate, NSAID = non-steroidal anti-inflammatory drug.
[27]Hennrikus MT. 2020.

Table 2

Multivariable model: acute kidney injury adjusted for covariates.

Variable	Odds ratio	95% Confidence interval	P value
Obesity	1.82	1.05–3.15	.034
ACEI/ARB	1.68	1.00–2.84	.052
Age (per 5 yr)	1.06	0.96–1.18	.260
Sex (Male vs Female)	1.57	0.99–2.50	.057
Diabetes	0.94	0.57–1.57	.824
Heart disease	2.41	1.47–3.95	<.001
Hypertension	2.09	1.04–4.18	.038
CKD	2.93	1.76–4.88	<.001
Pressors Intraoperative	1.40	0.83–2.35	.206
Spinal surgery	2.65	1.45–4.84	.002

*Odds ratios and p-values from multivariable binomial logistic regression model.
ACEI = angiotensin converting enzyme inhibitors, ARB = angiotensin receptor blocker, CKD = chronic kidney disease.

3.2. Acute kidney injury outcome

We found a 5% (90/1783 patients) incidence of post-operative AKI in our orthopedic patients. In the AKI group, the average preoperative glomerular filtration rate (GFR) was 79 mL/min/1.73 m^2 and the average post-operative GFR was 46 mL/min/1.73 m^2. The average change in serum creatinine level was 0.7 mg/dL. None of our patients required dialysis.

A 5 unit increase in BMI, increased the odds of AKI by 1.43 (CI 1.26–1.62, $P < .0001$). In the multivariable logistic regression analysis, obesity, HTN, heart disease, spine surgery and CKD were significant risk factors for post-operative AKI. The odds ratios are detailed in Table 2.

3.3. Length of hospital stay outcome

Based on the adjusted multivariable model for LOS, AKI resulted in the greatest increase in LOS (1.32 days, $P = .001$). Age, diabetes mellitus, heart disease and CKD were also associated with a greater LOS. See Table 3 for the median differences in LOS adjusted for covariates.

3.4. Mortality outcome

AKI, age, diabetes mellitus, and CKD were statistically significant factors increasing the odds of two-year mortality. In the entire cohort, AKI increased the odds of two-year mortality by 108% (OR = 2.08, 95% CI 1.03–4.22, $P = .041$). However, obesity decreased the odds of two-year mortality by 47% (OR = 0.53,

Table 3

Multivariable model: length of stay adjusted for covariates.

Variable	Median difference	95% Confidence interval	P value
AKI	1.32	0.51–2.12	.001
Obesity	−0.07	−0.20–0.05	.239
Age (per 5 yr)	0.01	0.002–0.02	.008
Sex (Female vs Male)	0.14	−0.004–0.29	.057
Diabetes	0.28	0.10–0.47	.003
Heart disease	0.32	0.08–0.55	.008
Hypertension	−0.05	−0.18–0.07	.411
CKD	0.58	0.21–0.94	.002

*Median difference estimates and P values from multivariable quantile regression of the median model
AKI = acute kidney injury, CKD = chronic kidney disease

Table 4

Multivariable model: two-year mortality adjusted for covariates.

Variable	Odds ratio	95% Confidence interval	P value
AKI	2.08	1.03–4.22	.041
Obesity	0.53	0.33–0.84	.009
Age (per 5 yr)	1.36	1.22–1.51	<.001
Sex (Male vs Female)	1.38	0.88–2.17	.167
Diabetes	2.65	1.61–4.36	<.001
Heart disease	1.28	0.77–2.12	.343
Hypertension	0.70	0.43–1.14	.150
CKD	1.88	1.14–3.11	.014

Odds ratios and P values from multivariable binomial logistic regression model.
AKI = acute kidney injury, CKD = chronic kidney disease.

95% CI 0.33–0.85, $P = .009$). See Table 4 for two-year mortalities adjusted for covariates.

4. Discussion

After analyzing our data, we did not find that AKI nor obesity were associated with any significant short-term in-hospital mortality. Compared to the other comorbidities that were associated with increased LOS (diabetes, heart disease, hypertension and CKD), AKI resulted in the greatest LOS, with an increase of 1.3 days. None of our patients required renal replacement therapy and no patient's GFR dropped below a stage 3, moderate kidney disease (GFR = 30–59 mL/min/1.73 m^2). In 96% of the AKI patients, the discharge creatinine had returned to baseline or better. However, even mild, reversible AKI has been associated with progression to CKD and mortality.[16,17] Our data also revealed an increased 2-year mortality in patients who had reversible postoperative AKI.

Obesity has been found to be an independent risk factor for AKI in both cardiac surgery and non-cardiac surgery.[18,19] Our findings also demonstrate that obesity contributes to post-operative AKI in orthopedic surgery. Attention needs to be given to perioperative fluid resuscitation, nephrotoxic agents and hypotensive episodes in these patients. Obesity is a confusing confounder posing contradictory medical outcomes. We found that obesity increased the odds of postoperative AKI by 82%; AKI increased the odds of two-year mortality by 108%; but paradoxically, obesity decreased the odds of two-year mortality by 46%. These findings are in alignment with the "*obesity paradox:*" even though obesity seems to contribute to AKI and AKI increases mortality, obesity appears protective of mortality.

The "obesity paradox" is the finding that obesity, which is a risk for developing chronic diseases such as CKD, heart disease, and diabetes mellitus, "counter-intuitively," is protective of mortality in those same chronic conditions.[3,4,5] The critical care literature has also noted the "obesity paradox" associated with AKI. Authors have reported that obesity is an independent risk factor for severe AKI in critically ill surgical and medical patients. However, even though obesity increases the incidence of severe AKI, obesity then has a protective affect on mortality in critically ill patients who develop AKI.[20–23] One explanation for the "obesity paradox" considers AKI an accelerated catabolic condition where adipose tissue can supply the needed energy.[24] Another explanation suggests that the chronic inflammation of obesity pre-conditions the body against acute excessive inflammation.[25]

However, are we looking at the "obesity paradox" from the wrong angle? Perhaps it is not obesity, which confers protection

from mortality; perhaps it is the development of disease (AKI, CKD, heart disease, or diabetes mellitus), unrelated to obesity that confers the greatest risk to mortality. For example, a normal weight individual who develops AKI or chronic conditions such as CKD, heart disease, or DM may have a graver underlying etiology for their disease such as an underlying defect in their immune or cardiovascular-renal system than individuals with obesity-related-disease. We expect obese patients to be at risk for these conditions, but we do not expect normal weight individuals to spontaneously develop these diseases. Ninety seven percent of our non-obese cohort was normal weight and overweight. Only 3% were underweight. Should we be extra vigilant with non-obese patients who develop acute and chronic disease?

We believe that the clinical implication of our findings is that perioperative management should not stop at hospital discharge. Developing AKI postoperatively is a poor prognostic marker. Postoperative AKI, especially in non-obese patients portends worse long-term mortality outcomes, even when the AKI is reversible. All patients who develop postoperative AKI should continue to undergo long-term surveillance for progressive systemic disease.

Limitations of our study include our inability to document the cause of death in our patients or document their renal function 2 years after their surgery. We know that patients who develop AKI are at greater risk of developing CKD,[26] but we do not know if CKD contributed to mortality in our patients. In addition, this was a single centered study, limited to elective orthopedic surgeries with a limited number of patients.

In conclusion, we found that obesity is a risk factor for AKI following orthopedic surgery. AKI increased LOS and increased the odds of 2-year mortality. However, paradoxically, obesity decreased two-year mortality. Either obesity confers a survival benefit or the development of disease, such as AKI, in non-obese patients is a sign of underlying pathology that confers a survival disadvantage.

Author contributions

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