

Body Mass Index and Type 2 Collagen Turnover in Individuals After Anterior Cruciate Ligament Reconstruction

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Context: Individuals with an anterior cruciate ligament reconstruction (ACLR) are at an increased risk of developing posttraumatic osteoarthritis. How osteoarthritis risk factors, such as increased body mass index (BMI), may influence early changes in joint tissue metabolism is unknown.

Objective: To determine the association between BMI and type 2 cartilage turnover in individuals with an ACLR.

Design: Cross-sectional study.

Setting: Research laboratory.

Patients or Other Participants: Forty-five individuals (31 women, 14 men) with unilateral ACLR at least 6 months earlier who were cleared for unrestricted physical activity.

Main Outcome Measure(s): Body mass index (kg/m^2) and type 2 collagen turnover were the primary outcomes. Body mass index was calculated from objectively measured height and mass. Serum was obtained to measure type 2 collagen turnover, quantified as the ratio of degradation (collagen type 2 cleavage product [C2C]) to synthesis (collagen type 2 C-propeptide [CP2]; C2C:CP2). Covariate measures were physical activity level

before ACLR (Tegner score) and current level of disability (International Knee Documentation Committee Index score). Associations of primary outcomes were analyzed for the group as a whole and then separately for males and females.

Results: Overall, greater BMI was associated with greater C2C:CP2 ($r = 0.32$, $P = .030$). After controlling for covariates (Tegner and International Knee Documentation Committee Index scores), we identified a similar association between BMI and C2C:CP2 (partial $r = 0.42$, $P = .009$). Among women, greater BMI was associated with greater C2C:CP2 before ($r = 0.47$, $P = .008$) and after (partial $r = 0.50$, $P = .008$) controlling for covariates. No such association occurred in men.

Conclusions: Greater BMI may influence greater type 2 collagen turnover in those with ACLR. Individuals, especially women, who maintain or reduce BMI may be less likely to demonstrate greater type 2 collagen turnover ratios after ACLR.

Key Words: collagen type 2 C-propeptide, collagen type 2 cleavage product, osteoarthritis

Key Points

- Greater body mass index was positively associated with greater type 2 collagen turnover in individuals after anterior cruciate ligament reconstruction (ACLR), with a moderate association identified in women.
- Education regarding the potential significance of a healthy body mass index for the purpose of maintaining optimal long-term joint health after ACLR is important.
- Body composition may be an important factor to consider in recovery from ACLR and efforts to prevent posttraumatic knee osteoarthritis.

Approximately 250 000 anterior cruciate ligament (ACL) injuries are sustained each year.¹ Individuals who have sustained an ACL injury and undergone ACL reconstruction (ACLR) are at an increased risk for developing posttraumatic knee osteoarthritis (PTOA).² The consensus from the literature is that obesity is one of the most predictive risk factors in the development of idiopathic knee osteoarthritis (OA) phenotypes (pooled odds ratio [OR] = 2.63, 95% confidence interval [CI] = 2.28, 3.05).³ The odds of undergoing a total knee arthroplasty are higher in obese men and women compared with those who are overweight or of normal weight.⁴ For this reason, decreasing excess body weight is considered an essential factor in an effective idiopathic OA treatment

strategy,⁵ yet little is known about how greater body mass affects the onset and progression of PTOA phenotypes in humans.

Individuals who sustain ACL injuries are typically young and physically active,⁶ but only 63% returned to the same level of physical activity after ACLR.⁷ Additionally, those who sustained a knee injury were at a higher risk for weight gain after knee injury.⁸ Increased nonlean body mass may result in aberrant mechanical loading of tissues within the injured knee,⁹ which may hasten the progression of knee-joint tissue breakdown and lead to early onset of PTOA.¹⁰ Additionally, chondrocyte damage after ACL injury or ACLR may change the mechanotransduction of signals from activities of daily living, thereby influencing the

expression of different cellular processes that may further affect knee-joint tissue metabolism adversely.¹¹ Body mass index (BMI; body mass [kg]/height² [m]) may directly influence the movement biomechanics that are associated with PTOA onset. That is, a higher BMI may be associated with higher rates of loading during walking gait,¹² which may adversely affect proteoglycan breakdown and type 2 collagen turnover within the cartilage. Biomechanical changes influenced by BMI may affect joint metabolism in multiple ways that could affect the eventual development of osteoarthritic changes in knee-joint tissues.

Previous authors¹³ demonstrated a higher prevalence of hand OA in those with higher BMI, suggesting that nonweight-bearing joints were affected by increased adiposity. An increase in nonlean body mass also increased concentrations of circulating adipocytokines, which may influence generalized long-term joint inflammation.¹⁴ Increased pro-inflammatory cytokines have been reported within weeks after ACL injury and ACLR, which may affect long-term healing of the knee-joint tissues. Prolonged expression of pro-inflammatory cytokines may upregulate degenerative cartilage enzymes, which leads to increased type 2 collagen breakdown. Type 2 collagen turnover after ACL injury and ACLR¹⁵ was hypothesized to be an important marker of cartilage metabolism that may indicate changes in cartilage health. Serum markers of type 2 collagen breakdown or turnover were higher in individuals after ACL injury or ACLR versus healthy controls and related to lower extremity joint loading in those who underwent ACLR.¹⁵ Unfortunately, whether BMI is related to type 2 collagen turnover in patients after ACLR remains unknown.

Therefore, the primary purpose of our study was to determine the association between BMI and serum markers of type 2 collagen turnover assessed with markers of degradation (collagen type 2 cleavage product [C2C]) and synthesis (collagen type 2 C-propeptide [CP2]) in individuals with unilateral ACLR. Sex was also a factor leading to increased risk of ACL injury¹⁶ and of biological importance for predicting certain aspects of BMI, yet the association between BMI and type 2 collagen turnover has not been evaluated in males versus females. Consequently, we secondarily investigated the influence of sex on the association between BMI and type 2 collagen turnover. We hypothesized that individuals with higher BMI would demonstrate greater type 2 collagen turnover (C2C:CP2) and that sex would not influence associations between type 2 collagen turnover and BMI. Identifying an association between BMI and type 2 collagen turnover in individuals after ACLR would be important for better understanding the pathogenesis for PTOA after ACLR.

METHODS

We conducted a descriptive cross-sectional laboratory experiment that involved objectively assessing BMI and collecting serum on the same day within a 30-minute period. The Institutional Review Board at the University of North Carolina at Chapel Hill approved all investigational methods and recruitment techniques for the current study and protecting the rights of all participants. All participants completed a written informed consent before data collection.

Participants

We studied individuals with primary unilateral ACLR in this sample of convenience. Participants had undergone ACLR a minimum of 6 months before data collection. All participants had received approval from a physician for unrestricted physical activity, and all reported performing a minimum of 20 minutes of moderate physical activity 3 times per week. We excluded individuals with any history of lower extremity orthopaedic surgery other than ACLR, bilateral ACLR, multiligament reconstruction to the ACLR knee, ACLR revision surgery, diagnosed knee OA or current self-reported OA symptoms (eg, pain, swelling, stiffness), balance or neuromuscular disorder, or an orthopaedic injury to either limb during the previous 6 months.

Procedures

All participants were asked to self-report age, sex, ACL graft type, whether concomitant meniscectomy or meniscal repair was performed with ACLR, months since ACLR, and physical activity level using the Tegner Activity Scale¹⁷ (indicating the level before ACL injury and after ACLR at the time of testing). Participants were asked to mark *unknown* for any demographic question they were unsure how to answer. Study personnel subsequently contacted participants with regard to any *unknown* selection to determine the appropriate answer.¹⁸ All participants completed the subjective section of the International Knee Documentation Committee (IKDC) Index¹⁹ to determine self-reported disability. Height and weight were measured with each participant in uniform apparel minus shoes. Next, participants sat quietly completing paperwork for a minimum of 20 minutes before blood collection.

Body Mass Index

Trained research personnel measured each person's height and weight using a calibrated stadiometer (Perspective Enterprises, Portage, MI) and scale (Detecto, Webb City, MO), respectively. Participants wore uniform tight-fitting Spandex (DuPont, Wilmington, DE) apparel for these measurements. Body mass index (kg/m²) was calculated from the recorded measures.

Collagen Type 2 Cleavage Product and Collagen Type 2 C-Propeptide Measurement and Analysis

Five milliliters of blood were collected via a 21-gauge needle from the antecubital fossa via syringe. The blood was immediately transferred to a serum separation tube, put on ice to clot, and then centrifuged at 4°C at 3000g for 10 minutes. The serum was pipetted equally into four 2.0-mL cryovials and frozen in a -80°C ultra-freezer for batch analysis. Serum for type 2 collagen breakdown (C2C; IBEX Technologies, Inc, Montreal, QC, Canada) and collagen synthesis (CP2; IBEX Technologies, Inc) was assessed via commercially available specific enzyme-linked immunosorbent assays. Specific assay detection sensitivities were as follows: C2C = 1.0 ng/mL, CP2 = 1.6 ng/mL. The investigator performing the assays was blinded to the BMI outcome. Assays were performed in triplicate to determine standards and in duplicate for unknowns, which demonstrated intra-assay variability <10% in our labora-

Table. Demographics, Outcome Variables, Potential Covariates^a

Characteristic	Value
Female/male, No.	31/14
Age, y	21.8 ± 2.9
Height, m	1.69 ± 0.11
Mass, kg	74.1 ± 18.4
Body mass index, kg/m ²	25.6 ± 4.2
C2C : CP2	0.13 ± 0.05
ACL graft type, No. (%)	
Patellar tendon	32 (71.1)
Hamstrings tendon	12 (26.7)
Cadaver tendon	1 (2.2)
History of concomitant meniscal surgery during ACLR? No.	
Yes	19
No	21
Unknown	5
No. months post-ACLR	48.3 ± 38.2
Tegner Physical Activity score	
Pre-ACL injury	8.82 ± 1.14, 43
Post-ACL injury	7.05 ± 1.86, 43
International Knee Documentation Committee Index, %	87.13 ± 9.71

Abbreviations: ACL, anterior cruciate ligament; ACLR, anterior cruciate ligament reconstruction; C2C, collagen type 2 cleavage product; CP2, collagen type 2 C-propeptide.

^a Values are mean ± SD, unless otherwise indicated.

tory. Serum concentrations of C2C and CP2 were assessed individually, and the C2C : CP2 ratio was used to evaluate the amount of collagen breakdown relative to synthesis, which we defined as *type 2 collagen turnover*.

Multiple assay kits from different manufacturers' production batches and lots were used for each collagen marker. Production batches elicited measures found in the literature and in accordance with assay specifics for standard curves and quality control. Nonetheless, between-batches variance (inter-assay coefficient of variance) is a significant confounder to biomarker data interpretation.^{20,21} To account for this possibility, we concurrently assayed select participant samples ($n = 7$) within all collagen markers in the different production batches of the biomarkers. We developed a regression equation to convert all batch 1 values to batch 2 value levels, and these values were used in all subsequent statistical comparisons. This procedure was based on recommendations in the literature for dealing with batch variance.^{20,22}

Statistical Analysis

Primary analyses consisted of individual bivariate, 2-tailed, Pearson product moment correlations between BMI and serum concentrations of C2C:CP2. We conducted secondary analyses to investigate associations between potential confounders significantly associated with the primary variables (IKDC, pre-Tegner score); significant values underwent a tertiary analysis. We used partial correlations to account for the effect of the significant confounding variables on the association between BMI and serum concentrations of C2C:CP2. All analyses were repeated with women and men assessed separately. Association levels for the current study were defined as *negligible* (0.0–0.29), *low* (0.3–0.49), *moderate* (0.5–0.69), *high* (0.7–0.89), and *very high* (0.9–1.0).²³ Additionally, we

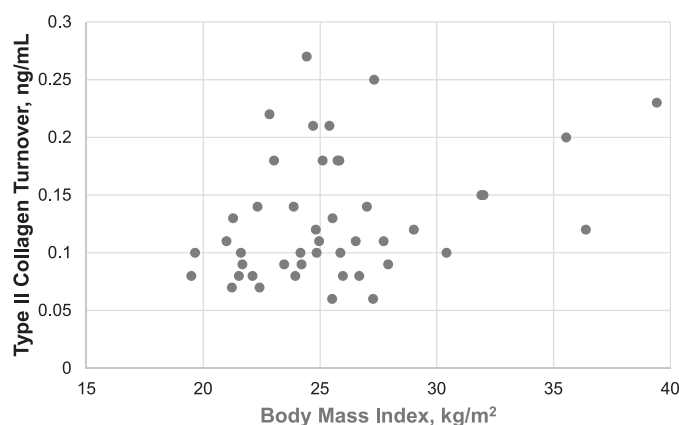


Figure 1. Association between body mass index and serum concentrations (collagen type 2 cleavage product: collagen type 2 C-propeptide). Greater body mass index status demonstrated an association with greater type 2 collagen turnover after controlling for International Knee Documentation Committee Index and preinjury Tegner Activity Level scores (partial $r_{35} = 0.42$, $P = .009$).

calculated 95% CIs for significant associations to provide a more thorough description of their variability and magnitude. The significance level was set a priori at $P \leq .05$ for all assessments conducted using SPSS (version 19; IBM Corp, Armonk, NY).

RESULTS

The Tegner Activity Scale and IKDC Index score data were incomplete for 5 participants; therefore, we conducted secondary sex analyses of 28 female and 12 male participants. Participant demographics, outcome variables, and potential covariates can be found in the Table.

Overall, greater BMI was associated with greater collagen turnover ($n = 45$, $r = 0.324$, 95% CI = 0.04, 0.56; $P = .03$) and lesser IKDC Index ($n = 43$, $r = -0.34$, 95% CI = -0.04 , 0.67, $P = .026$). Greater collagen turnover was associated with greater preinjury Tegner activity level scores ($n = 39$, $r = 0.364$, 95% CI = 0.05, 0.61; $P = .023$). After controlling for preinjury Tegner Activity Level score and IKDC with a partial correlation, greater BMI maintained a low association with a greater C2C:CP2 ratio (partial $r_{35} = 0.42$, 95% CI = 0.10, 0.66; $P = .009$; Figure 1).

Sex Analyses

Women. Greater BMI was associated with greater collagen turnover ($n = 31$, $r = 0.47$, 95% CI = 0.14, 0.71; $P = .008$). Additionally, greater BMI was associated with a lesser IKDC Index ($r = -0.385$, 95% CI = -0.67 , 0.01; $P = .032$), while greater collagen turnover trended toward an association with greater preinjury Tegner Physical Activity score ($r = 0.36$, 95% CI = -0.04 , 0.66; $P = .061$). After controlling for IKDC score with a partial correlation, greater BMI was moderately associated with greater collagen turnover in the women of our cohort (partial $r_{25} = 0.50$, 95% CI = 0.23, 0.70; $P = .008$; Figure 2).

Men. We found a negligible and nonsignificant association between greater BMI and greater collagen turnover in men ($n = 14$, $r = 0.075$, $P = .8$; Figure 2).

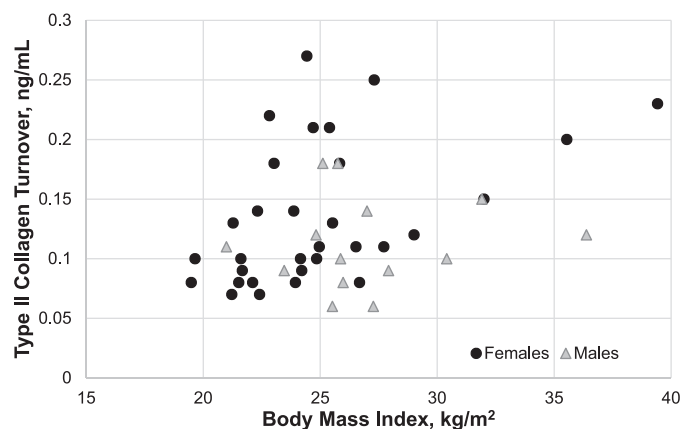


Figure 2. Associations of body mass index and serum concentrations (collagen type 2 cleavage product:collagen type 2 C-propeptide) between women (circles) and men (triangles). After controlling for International Knee Documentation Committee Index score, greater body mass index was moderately associated with greater collagen turnover in women (partial $r_{25} = 0.50$, $P = .008$). For men, we found a negligible and nonsignificant association between greater body mass index and greater collagen turnover ($r = 0.075$, $P = .8$).

DISCUSSION

Our primary finding was that greater BMI was associated with greater collagen turnover in individuals after ACLR. Furthermore, women demonstrated a stronger association between greater BMI and greater type 2 collagen turnover than men and women combined; the association in men alone was negligible and nonstatistically significant. Therefore, the moderate association between greater BMI and greater collagen turnover in the entire cohort may have been influenced by the association between these 2 variables in the women, who made up the majority of the cohort (68.8%). Associations between BMI and the C2C:CP2 ratio remained significant after accounting for the IKDC Index and preinjury Tegner scores, suggesting a unique association of BMI with collagen turnover, regardless of perceived disability or preinjury activity level. Our results indicate that BMI may also be associated with early changes in cartilage metabolism that may eventually affect cartilage breakdown in those with ACLR.

Individuals who have sustained an ACL injury are known to be at greater risk for knee OA, regardless of whether they undergo ACLR or remain ACL deficient.²⁴ For example, Struwer et al²⁵ reported that approximately 20% and 6% of individuals demonstrated moderate to severe (Kellgren-Lawrence grades 2 or 4) radiographic evidence of OA, respectively, only 10 years after ACLR.²⁵ The exact mechanism responsible for the elevated risk of early-onset knee PTOA OA and progression is not entirely clear, although a combination of biomechanical,²⁶ mechanical,²⁷ and metabolic²⁸ factors is likely. Body mass index is a recognized modifiable risk factor for idiopathic knee OA onset and progression.²⁹ The majority of individuals with idiopathic OA phenotypes are over 45 years of age and may be classified as overweight or obese (ie, having increased BMI), possibly increasing their risk of OA development.³⁰ Excessive nonlean body mass, consisting of a high proportion of adipose tissue, is common in overweight and obese individuals.³¹ Extra adiposity leads to increased mechanical stress on the lower extremity joints, which is

hypothesized to contribute to the development and progression of knee OA.⁸ In addition to the mechanical stress that greater nonlean mass imposes on the lower extremity joints, adipose tissue is metabolically active, which can affect cartilage degradation.³² Pro-inflammatory cytokines are involved in the regulation of the enzymes responsible for cartilage degradation (metalloproteinases).³⁰ Additionally, adipokines (adipose-specific pro-inflammatory cytokines) induce systemic low-grade inflammation, which may increase the breakdown of joint tissues.³⁰ Adipokines are also produced and released by osteoblasts and chondrocytes, thereby potentially increasing inflammation at the knee joint.³² Several specific adipokines (leptin and adiponectin) are highly associated with the degradation of cartilage.³³ Therefore, greater adiposity and subsequently a high BMI may have simultaneous biomechanical and biochemical influences on cartilage degradation, which may hasten the progression of PTOA. Although we focused on markers of collagen turnover in this initial study, future work may evaluate the effects of adipokines and inflammation as possible mechanisms influencing the association between BMI and collagen turnover in individuals with ACLR.

Sex and BMI

The association between greater BMI and a greater C2C:CP2 ratio among women was stronger than among the entire mixed-sex cohort or men alone. Body mass indexes of women and men were not different ($T\text{-score}_{47} = -1.741$, $P = .088$). It is possible that the lean-to-nonlean mass ratio was responsible for the moderate association in women, whereas the same association was not present in men. As a simple index of mass to height (kg/m^2), BMI is unable to discriminate between lean and nonlean mass, though it is associated with more direct measures of body fat (ie, skinfold, dual-energy X-ray absorptiometry [DXA]).³³ It may be important to maintain a certain ratio of lean to nonlean mass to prevent the development of knee OA. Females tend to have higher circulating levels of adipokines compared with males, who have been noted to have greater degradation of cartilage.³⁴ Therefore, females with a greater BMI, composed primarily of a higher percentage of adipose tissue, may signal more deleterious metabolic changes that negatively affect joint tissue health than their male counterparts with similar BMIs. However, our male cohort was relatively small ($n = 14$). Future studies with more male participants should be conducted to confirm this finding.

Understanding the true effect of nonlean mass on changes in cartilage metabolism after ACLR is vital. Given the potential importance of the muscle-to-fat mass composition, DXA may be a better tool for assessing body composition than BMI. Dual-energy X-ray absorptiometry would provide specific quantities of lean versus nonlean mass, allowing the investigation of specific tissue associations with cartilage homeostasis. Regrettably, we did not measure body composition. Yet as a post hoc analysis, we applied the Boer estimation of lean body mass formula³⁵ to our data. Women had less muscle mass as a percentage of body mass compared with men ($70.2\% \pm 6.9\%$ versus $74.4\% \pm 4.4\%$; $P = .036$); hence, the women had a higher overall adipose content than the men. We can only

speculate that the estimated differences in muscle mass may have affected the metabolic environment at the joint (inducing elevated cytokines in females³²), resulting in the stronger association in women compared with men for greater BMI and greater C2C : CP2 ratio. Future researchers should investigate the direct effect of lean versus nonlean body composition on joint metabolism.

Treatment Implications

Body mass index has been suggested as a strong predictor for radiographic knee OA³⁶ and, as a modifiable marker of incident OA, it provides a prophylactic target for decreasing the risk of PTOA onset in individuals after ACLR. Maintenance of lean body mass or the reduction of nonlean mass is a standard recommendation for those with idiopathic knee OA and those at risk for developing idiopathic knee OA phenotypes for the purpose of decreasing disability and lowering the risk of OA onset, respectively.³⁷ Our findings further support the association of a higher BMI with greater type 2 collagen turnover after ACLR, which may indicate an increased risk for PTOA onset. Maintaining a healthy body mass may be especially important for females with ACLR, given the stronger association between greater BMI and greater C2C : CP2 ratio we found in women. Body mass index is a modifiable factor associated with PTOA risk; therefore, educating patients about their BMI status as well as maintaining a healthy BMI should be part of the standard of care for individuals undergoing ACLR.

Limitations

This study had several limitations that may be important to consider. The sample contained nearly twice as many women ($n = 31$) as men ($n = 14$), yet this disparity may reflect the sex distribution of ACL injury and ACLR in the general population.¹ We did not have complete information regarding the type and severity of concomitant tissues affected at the time of ACL injury, as we relied on self-reported injury and surgery (concomitant injury and graft type) history. We included individuals with and those without a history of self-reported concomitant meniscal injury at the time of ACL injury. Future investigators should evaluate how a history of a concomitant meniscal injury, meniscal surgery, or ACLR graft type influences associations between BMI and collagen breakdown. Our participants' medical histories may not have captured previous upper extremity or joint or cartilage injuries that may have affected serum measures. The cross-sectional design of our study influenced the length of time between ACLR and testing in our participants (range = 9–163 months); however, the time from injury was not associated with either primary variable (BMI: $r = -0.22$, C2C : CP2: $r = -0.09$; $P > .05$). Ideally, participants rest for at least 30 minutes before blood is drawn. Logistically, this study had a 20-minute minimum rest. Finally, BMI is not a direct measure of body composition and does not discriminate between lean and nonlean mass. Even so, BMI is used routinely and extensively in research and clinical settings as a cost-effective indicator of body composition and body weight appropriateness. Future authors should include a direct measure of body composition to determine if an association between lean versus nonlean mass exists and

differs from the associations identified between BMI and collagen turnover after ACLR.

CONCLUSIONS

After ACLR, greater BMI was associated with greater type 2 collagen turnover. Women displayed a moderate association, whereas men demonstrated a negligible and nonsignificant negligible association. As a modifiable risk factor, BMI status should be monitored early after ACL injury. Education regarding the potential value of a healthy BMI for the purpose of maintaining optimal long-term joint health after ACLR is important. Body composition may be a necessary factor to consider in recovery from ACLR and efforts to prevent PTOA development. Future investigators should incorporate a direct measure of body composition (ie, DXA) to determine if lean versus nonlean mass is associated with joint metabolism after ACLR.

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