Associations between obesity and rotator cuff tears, and the mediating role of inflammation: Findings from the UK Biobank and clinical cohort

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INTRODUCTION: Rotator cuff tears (RCTs) represent a prevalent musculoskeletal condition and are one of the primary contributors to shoulder pain and functional impairment. Observational studies have established a significant association between obesity and RCTs, which may be linked to the pro-inflammatory state associated with obesity. However, the underlying biological mechanisms remain unclear.

METHODS: This research encompassed 499,942 participants from the UK Biobank, consisting of 5,531 RCTs and 494,411 controls (**UK Biobank cohort**). Obesity was evaluated by waist-to-hip ratio adjusted for BMI (WHRadjBMI), and RCTs were discovered using ICD-10 codes. Logistic regression was conducted to assess the relationship between WHRadjBMI and the risk of RCTs. Moreover, plasma proteome data were acquired for all subjects, from which 91 inflammation-associated proteins were chosen for subsequent investigation. Multivariable linear regression was employed to study the correlation between WHRadjBMI and protein levels, while logistic regression was utilized to examine the link between WHRadjBMI-associated proteins and RCT status. Proteins exhibiting variable effects among models, including CX3CL1 and CCL28, underwent stratified analysis to further investigate their correlation with RCTs. Additionally, Mendelian randomization and mediation analysis were also employed to investigate the genetic relationship among the three. Demographical and clinical information and peripheral blood samples from 68 RCT patients (**clinical validation cohort**) were collected to validate the correlation between obesity, CX3CL1 levels, and the features of RCTs (acute vs. chronic and small vs. medium tears). Circulating levels of CX3CL1 protein were measured via enzyme-linked immunosorbent assay (ELISA).

RESULTS: The univariate model developed in the **UK Biobank cohort** revealed that WHRadjBMI was significantly associated with the occurrence of RCTs [P = 1.14E-06, OR (95% CI) = 1.068(1.040, 1.097)]. In the multivariate model that further incorporated variables such as age, gender, smoking, alcohol intake, MDI and ethnicity, WHRadjBMI remained an independent influencing factor for RCTs [P = 9.69E-05, OR (95% CI) = 1.057(1.028-1.087)]. Proteomic analyses identified 59 inflammation-related proteins significantly associated with WHRadjBMI, of which 16 were further associated with RCTs. Most proteins (14/16) showed consistent directional effects across models; however, CX3CL1 and CCL28 exhibited opposing trends. Stratified analyses showed that CX3CL1 demonstrated a non-linear, bidirectional association with RCT risk: moderate expression was protective [P = 0.351, OR (95% CI) = 0.892 (0.701-1.134)], whereas high expression was associated with increased risk [P = 0.132, OR (95% CI) = 0.851 (0.691-1.052)] **(Figure 1A)**. No significant associations were observed for CCL28 **(Figure 1B)**. Subsequent Mendelian randomization analysis indicated that only CX3CL1 demonstrated genetic causal relationships with both WHRadjBMI [P = 0.028, OR (95% CI) = 0.870(0.790,0.959)] and RCTs [P = 0.014, OR (95% CI) =0.923 (0.862, 0.984)]. In other words, CX3CL1 mediated the causal relationship between WHRadjBMI and RCT, and the mediation analysis suggested that the mediation ratio of CX3CL1 was 8.8% (P = 0.036). In the **clinical validation cohort**, those with obesity had a higher prevalence of medium-sized tears (87.5%) compared to overweight (38.2%) and normal BMI (55.6%) groups (P = 0.0048). CX3CL1 levels were inversely correlated with BMI (R = − 0.26, P = 0.034) **(Figure 2A)**. However, CX3CL1 expression did not significantly differ by tear size **(Figure 2B)** or severity **(Figure 2C)**.

DISCUSSION: This study aimed to investigate the causal relationship between central obesity and RCTs, and to explore the potential inflammatory mechanisms involved. Using a large prospective cohort from the UK Biobank, we identified WHRadjBMI as an independent risk factor for RCTs. Proteomic and genetic analyses further implicated CX3CL1 as a potential mediator in this association. Stratified and clinical analyses suggested a non-linear, dose-dependent relationship between CX3CL1 expression and RCT risk. These findings provide new insights into the metabolic-inflammatory pathways underlying tendon degeneration. Existing evidence suggests that in obese individuals, adipose tissue functions as an active endocrine organ, releasing several adipokines such as adiponectin, leptin, resistin, and visfatin, which may lead to systemic metabolic dysregulation. Resistin has been demonstrated to elevate levels of critical inflammatory mediators, such as IL-1β, TNF-α, and CX3CL1, in human articular chondrocytes[1]. These inflammatory cascades may disrupt tendon homeostasis by facilitating extracellular matrix degradation and triggering tenocyte apoptosis[2,3]. As the sole member of the CX3C chemokine subclass, CX3CL1regulates the recruitment and colonization of leukocytes in adipose tissue inflammation[4]. CX3CL1 also enhances the phagocytic functions of macrophages[5]. Given that tendon micro-ruptures are associated with cell death which necessitates debris clearance, CX3CL1 likely functions as a 'find-me' signal for macrophages migrating from the bloodstream, subsequently contributing to the inflammation observed in RCTs[6]. However, these mechanisms require further experimental investigation to be fully understood.

SIGNIFICANCE/CLINICAL RELEVANCE: This study suggests that obesity may adversely affect RCTs through mediation by inflammatory responses. These findings offer new insights into the mechanisms underlying RCTs, indicating that effective weight management could help identify at-risk populations and contribute to the prevention and treatment of RCTs.

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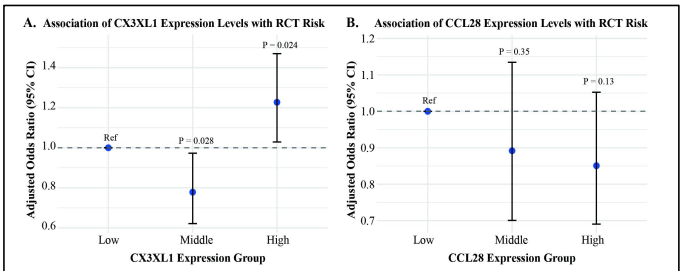

Figure 1. Clinical and causal associations between WHRadjBMI, inflammatory proteins, and RCTs. (A) Stratified expression analysis of CX3CL1, showing a bidirectional association with RCT risk across different expression tertiles. (B) Stratified expression analysis of CCL28, with no significant association between its expression levels and RCT risk across tertiles. Ref, reference; OR, odd ratio; CI, confidence interval.

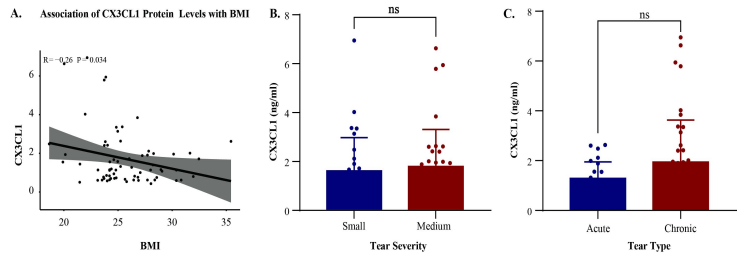

Figure 2. Clinical Validation between obesity, CX3CL1 levels, and RCT characteristics. (A) Correlation analysis of BMI with CX3CL1 protein levels, showing a significant inverse relationship. (B-C) Comparison of CX3CL1 protein levels, suggesting there was no significant difference across tear severity and type groups. ns, no significant