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Original Article

Systemic Inflammatory Biomarkers and Insulin Resistance in Primary Knee Osteoarthritis: A Hospital-Based Case–Control Study

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ABSTRACT

Background: Knee osteoarthritis (KOA) is increasingly regarded not as a purely mechanical degenerative disorder but as a systemic metabolic–inflammatory condition. The extent to which circulating inflammatory mediators and insulin resistance coexist in established KOA, and whether they track with symptom severity, remains incompletely defined in Indian populations. **Objectives**: To compare serum interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), high-sensitivity C-reactive protein (hs-CRP), fasting plasma glucose (FPG), fasting serum insulin and the homeostatic model assessment of insulin resistance (HOMA-IR) between patients with primary KOA and age- and sex-matched healthy controls, and to examine the relationship of these variables with adiposity and clinical severity. **Methods**: A hospital-based analytical case–control study was conducted at a tertiary care teaching hospital in central India over 24 months. Sixty patients aged 40–65 years with primary KOA diagnosed by American College of Rheumatology criteria and Kellgren–Lawrence (K–L) grade II–IV radiographic change, and 60 age- and sex-matched apparently healthy controls, were recruited consecutively. IL-6 and TNF-α were measured by sandwich ELISA, hs-CRP by particleenhanced immunoturbidimetry, FPG by the glucose oxidase–peroxidase method and fasting insulin by chemiluminescent immunoassay; HOMA-IR was derived. Pain was assessed by visual analogue scale (VAS) and function by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Groups were compared by independent Student's t-test and chi-square test; associations were assessed by Pearson correlation. **Results**: Cases and controls were comparable for age (57.69 ± 7.73 vs 57.20 ± 8.23 years; $p = 0.739$) and sex distribution ($p = 0.46$), while body mass index (BMI) was higher in cases (29.22 ± 3.48 vs 25.01 ± 2.63 kg/m^2; $p < 0.001$). All three inflammatory markers were significantly elevated in KOA: IL-6 15.13 ± 5.47 vs 6.47 ± 2.00 pg/mL, TNF-α 53.95 ± 13.69 vs 30.85 ± 9.80 pg/mL and hs-CRP 4.75 ± 1.51 vs 1.79 ± 0.60 mg/L (all $p < 0.001$). Metabolic indices were likewise higher in cases: FPG 102.94 ± 12.14 vs 91.96 ± 8.69 mg/dL, fasting insulin 12.42 ± 3.54 vs 8.54 ± 2.04 µIU/mL and HOMA-IR 3.15 ± 0.97 vs 1.94 ± 0.48 (all $p < 0.001$). Within the KOA group, none of the inflammatory markers or HOMA-IR correlated significantly with VAS or WOMAC scores (all $p > 0.05$). BMI correlated positively with HOMA-IR ($r = 0.305$; $p = 0.018$) and, unexpectedly, inversely with TNF-α ($r = −0.386$;

p = 0.002). **Conclusion**: Patients with primary KOA showed substantially higher systemic inflammatory activity and insulin resistance than matched controls, yet these abnormalities were unrelated to each other and to symptom severity. In established disease, low-grade inflammation and insulin resistance appear to operate as parallel rather than tightly coupled processes, and circulating cytokine levels are unlikely to serve as surrogates for clinical severity.

Keywords: Knee osteoarthritis; Interleukin-6; Tumour necrosis factor-alpha; C-reactive protein; Insulin resistance; HOMA-IR.

INTRODUCTION

Osteoarthritis is the most prevalent chronic joint disorder worldwide and a leading contributor to years lived with disability, affecting more than half a billion people, with the knee the most commonly involved joint [1,2]. In India, community-based surveys report prevalence estimates in the range of 22–39%, and knee involvement predominates [3,4]. The burden is expected to grow with population ageing, rising obesity and increasingly sedentary patterns of living. For much of the twentieth century, osteoarthritis was conceptualised as the inevitable mechanical consequence of ageing cartilage. That view has been substantially revised. Contemporary evidence positions osteoarthritis as a whole-joint disease in which synovial inflammation, subchondral bone remodelling and altered chondrocyte metabolism are early rather than terminal events [5,6]. Chondrocytes, synovial fibroblasts and infiltrating macrophages generate interleukin-1β, IL-6 and TNF-α, which suppress matrix synthesis, induce matrix metalloproteinases and aggrecanases, and sustain a catabolic joint environment [7,8]. Importantly, this inflammatory activity is not confined to the joint: circulating IL-6 and CRP are modestly but consistently raised in knee osteoarthritis and have been reported to predict radiographic progression [9,10,11]. A parallel line of enquiry has linked osteoarthritis to metabolic dysfunction. The proposed metabolic phenotype of osteoarthritis is characterised by central obesity, dyslipidaemia, insulin resistance and low-grade systemic inflammation, and epidemiological studies indicate that metabolic syndrome and type 2 diabetes increase osteoarthritis risk independently of mechanical loading [12,13,14]. Mechanistically, insulin resistance and inflammation are plausibly reciprocal: adipose tissue is an endocrine source of IL-6 and TNF-α, both of which impair insulin signalling, while hyperinsulinaemia in turn promotes an inflammatory chondrocyte phenotype [15,16,17]. Despite this conceptual convergence, most studies have examined inflammatory markers or metabolic indices in isolation, and relatively few have assessed both simultaneously in the same cohort with concurrent measurement of pain and function. Data from Indian populations are particularly sparse, even though diet, body composition and the well-documented ethnic predisposition to insulin resistance at lower body mass index may alter the strength of these associations [4,18]. The present study was therefore designed to quantify circulating IL-6, TNF-α and hs-CRP alongside fasting glucose, fasting insulin and HOMA-IR in patients with primary knee osteoarthritis and matched healthy controls, and to determine whether these variables relate to adiposity and to clinically assessed disease severity.

MATERIALS AND METHODS

Study design and setting

This hospital-based analytical case–control study was conducted over 24 months in the Department of Biochemistry in collaboration with the Department of Orthopaedics at Index Medical College Hospital and Research Centre, Indore, Madhya Pradesh, a tertiary care teaching hospital.

Participants

Cases were adults aged 40–65 years with primary knee osteoarthritis diagnosed by consultant orthopaedic surgeons using the American College of Rheumatology clinical criteria [19] and confirmed radiographically as Kellgren–Lawrence grade II, III or IV in one or both knees [20]. Controls were apparently healthy adults of the same age range, individually matched to cases for sex and for age within ±5 years, recruited from hospital staff, patient attendants and individuals attending for routine health examination, and drawn from the same geographical region. Controls had no clinical or radiological evidence of knee osteoarthritis and no history of inflammatory joint disease, diabetes mellitus or other chronic systemic illness. Participants were excluded if they had secondary osteoarthritis attributable to trauma, congenital deformity, infection or inflammatory arthropathy; rheumatoid arthritis, gout or ankylosing spondylitis; previous knee arthroplasty or major knee surgery; acute infection or febrile illness within the preceding four weeks; chronic liver or kidney disease; malignancy; autoimmune disease; type 1 or uncontrolled type 2 diabetes mellitus; thyroid dysfunction; chronic cardiovascular disease with active inflammation; current corticosteroid, immunosuppressive or disease-modifying antirheumatic therapy; regular antioxidant supplementation in the preceding three months; or pregnancy or lactation.

Sample size and sampling

Sample size was estimated a priori using G*Power version 3.1.9.7 (Heinrich Heine University, Düsseldorf, Germany) for the comparison of two independent means, assuming an effect size (Cohen's d) of 0.60, a two-tailed alpha of 0.05, power

of 80% and an allocation ratio of 1:1. This yielded a minimum of 45 participants per group. Given the number of biochemical variables to be analysed and the planned correlation analyses, the target was increased to 60 per group, giving 120 participants in total. Consecutive sampling was used: all eligible patients attending the orthopaedics outpatient department during the study period were screened, and for each enrolled case a matched control was recruited, until the target was reached.

Clinical and radiological assessment

Demographic details, medical history, drug history and lifestyle characteristics were recorded on a pre-validated case record form. Height, weight, waist and hip circumference, pulse and blood pressure were measured using standard techniques, and body mass index was calculated as weight in kilograms divided by height in metres squared. Pain intensity was recorded on a 10-cm visual analogue scale. Functional status was assessed using the 24-item Western Ontario and McMaster Universities Osteoarthritis Index covering pain, stiffness and physical function, with higher scores indicating greater impairment [21]. Standing anteroposterior and lateral radiographs of both knees were graded by an experienced radiologist blinded to laboratory results.

Sample collection and biochemical analysis

After an overnight fast of 8–12 hours, 10 mL of venous blood was drawn between 08:00 and 10:00 h to limit circadian variation. Blood was distributed into a plain clot activator tube (5 mL) for serum IL-6, TNF-α and hs-CRP, a sodium fluoride tube (2 mL) for plasma glucose and a potassium EDTA tube (3 mL) as required. Samples in plain tubes were allowed to clot for 30 minutes and centrifuged at 3000 rpm for 10–15 minutes within one hour of collection. Serum was aliquoted into sterile cryovials and stored at −80 °C until analysis; repeated freeze– thaw cycles were avoided. Haemolysed, lipaemic, clotted or insufficient samples were rejected. Serum IL-6 and TNF-α were measured by commercially available sandwich enzyme-linked immunosorbent assay kits according to the manufacturer's instructions, with absorbance read at 450 nm on an ELISA microplate reader and concentrations derived from a standard calibration curve; results were expressed in pg/mL. Samples were analysed in batches to minimise inter-assay variation. High-sensitivity CRP was measured by particle-enhanced immunoturbidimetric assay on a fully automated clinical chemistry analyser and expressed in mg/L. Fasting plasma glucose was determined by the glucose oxidase–peroxidase method [22] and fasting serum insulin by chemiluminescent immunoassay on an automated analyser.

Internal and external quality control procedures were followed throughout.
Insulin resistance was estimated using the homeostatic model assessment [23]:
HOMA-IR = [fasting insulin (μIU/mL) × fasting plasma glucose (mg/dL)] ÷ 405

Statistical analysis

Data were compiled in a spreadsheet and analysed using [insert software and version]. Continuous variables are presented as mean ± standard deviation and categorical variables as frequencies and percentages. Normality was assessed before parametric testing. Continuous variables were compared between groups using the independent Student's t-test and categorical variables using the chi-square test. Associations between biochemical variables, body mass index and clinical severity scores within the case group were examined using Pearson's correlation coefficient, interpreted as very weak (0.00–0.19), weak (0.20–0.39), moderate (0.40–0.59), strong (0.60–0.79) or very strong (0.80–1.00). A two-tailed p value below 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

A total of 120 participants were analysed, comprising 60 patients with knee osteoarthritis and 60 matched controls. The two groups were well matched for age and sex, confirming the adequacy of the matching procedure, but cases were significantly heavier, with a mean body mass index in the overweight-to-obese range compared with the normal range in controls (Table 1). Among the cases, K–L grade III was the commonest radiographic stage (43.3%), followed by grade IV (31.7%) and grade II (25.0%). Mean VAS score indicated moderate to severe pain and mean WOMAC score indicated substantial functional limitation.

Table 1. Demographic and clinical characteristics of cases and controls

Variable	Cases (n = 60)	Controls (n = 60)	p value
Age (years), mean ± SD	57.69 ± 7.73	57.20 ± 8.23	0.739
Male, n (%)	25 (41.7)	29 (48.3)	0.46
Variable	**Cases (n = 60)**	**Controls (n = 60)**	**p value**
Female, n (%)	35 (58.3)	31 (51.7)	—
BMI (kg/m²), mean ± SD	29.22 ± 3.48	25.01 ± 2.63	<0.001

K–L grade II, n (%)	15 (25.0)	—	—
K–L grade III, n (%)	26 (43.3)	—	—
K–L grade IV, n (%)	19 (31.7)	—	—
VAS score, mean ± SD	6.41 ± 1.36	—	—
WOMAC score, mean ± SD	56.45 ± 15.02	—	—

BMI, body mass index; K–L, Kellgren–Lawrence; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; SD, standard deviation. Age and BMI compared by independent Student's t-test; sex distribution by chi-square test.

Inflammatory biomarkers

All three circulating inflammatory markers were markedly higher in patients with knee osteoarthritis than in controls (Table 2). Mean serum IL-6 was more than twofold higher, TNFα approximately 75% higher and hs-CRP more than 2.5-fold higher in cases, with all comparisons highly significant.

Table 2. Comparison of inflammatory biomarkers between cases and controls

Biomarker	Cases (n = 60)	Controls (n = 60)	p value
IL-6 (pg/mL)	15.13 ± 5.47	6.47 ± 2.00	<0.001
TNF-α (pg/mL)	53.95 ± 13.69	30.85 ± 9.80	<0.001
hs-CRP (mg/L)	4.75 ± 1.51	1.79 ± 0.60	<0.001

Values are mean ± standard deviation. IL-6, interleukin-6; TNF-α, tumour necrosis factoralpha; hs-CRP, high-sensitivity C-reactive protein. Independent Student's t-test.

Glycaemic and insulin resistance indices

Fasting plasma glucose, fasting serum insulin and HOMA-IR were all significantly higher in the osteoarthritis group (Table 3). Notably, the mean HOMA-IR among cases exceeded the value conventionally taken to indicate moderate insulin resistance, whereas the control mean lay within the insulin-sensitive range, despite the exclusion of participants with known or uncontrolled diabetes from both groups.

Table 3. Comparison of glycaemic and insulin resistance indices between cases and controls

Parameter	Cases (n = 60)	Controls (n = 60)	p value
Fasting plasma glucose (mg/dL)	102.94 ± 12.14	91.96 ± 8.69	<0.001
Fasting serum insulin (µIU/mL)	12.42 ± 3.54	8.54 ± 2.04	<0.001
HOMA-IR	3.15 ± 0.97	1.94 ± 0.48	<0.001

Values are mean ± standard deviation. HOMA-IR, homeostatic model assessment of insulin resistance. Independent Student's t-test.

Association with clinical severity

Within the osteoarthritis group, correlation analysis showed no statistically significant association between any inflammatory biomarker and either VAS or WOMAC score, and HOMA-IR was likewise unrelated to both severity measures (Table 4). All correlation coefficients were of very weak magnitude and the direction of association was inconsistent.

Table 4. Correlation of inflammatory biomarkers and HOMA-IR with clinical severity scores in patients with knee osteoarthritis (n = 60)

Variable	VAS (r)	p value	WOMAC (r)	p value
IL-6	0.038	0.771	0.126	0.336
TNF-α	−0.088	0.502	−0.035	0.791
hs-CRP	−0.146	0.267	0.115	0.380
HOMA-IR	0.091	0.488	−0.090	0.493

Pearson's correlation coefficient. Abbreviations as in Tables 1–3.

Association with adiposity

Body mass index correlated positively and significantly with HOMA-IR, consistent with adiposity-driven insulin resistance (Table 5). Unexpectedly, body mass index showed a moderate inverse correlation with serum TNF-α, whereas its associations with IL-6 and hsCRP were very weak and non-significant.

Table 5. Correlation of body mass index with inflammatory and metabolic variables in patients with knee osteoarthritis (n = 60)

Variable	Pearson's r	p value
IL-6	−0.050	0.706
TNF-α	−0.386	0.002
hs-CRP	−0.085	0.519
HOMA-IR	0.305	0.018

Pearson's correlation coefficient. Abbreviations as in Tables 1–3.

DISCUSSION

This study produced two findings that sit somewhat uneasily together. Patients with primary knee osteoarthritis showed unambiguous elevation of all three circulating inflammatory markers and clear evidence of insulin resistance relative to carefully matched healthy controls. Yet within the disease group, neither the inflammatory markers nor HOMA-IR showed any meaningful relationship with pain or functional disability, and the inflammatory markers were not associated with each other's presumed metabolic driver. The between-group signal was therefore strong, while the within-group signal was essentially absent.

The magnitude of the inflammatory elevation is consistent with the accumulated literature. Stannus and colleagues reported that circulating IL-6 and TNF-α were associated with radiographic knee osteoarthritis and cartilage loss in older adults [24], and the Chingford cohort identified serum IL-6 as a significant predictor of incident radiographic knee osteoarthritis [9]. Attur and co-workers demonstrated increased inflammatory gene expression in peripheral blood leucocytes of patients with symptomatic knee osteoarthritis [11], and Spector and colleagues showed that even modest increases in CRP are present early in the disease and predict progression [10]. Reports from Indian settings have similarly documented raised IL-6 and CRP in radiographic knee osteoarthritis [25]. The present data extend these observations by demonstrating that all three markers are concurrently raised in the same cohort under standardised assay conditions.

The metabolic findings are equally consistent with the metabolic-phenotype hypothesis. Fasting insulin and HOMA-IR were substantially higher in cases even though individuals with known or uncontrolled diabetes were excluded, indicating that insulin resistance in this population is subclinical rather than a reflection of overt dysglycaemia. This mirrors reports that metabolic syndrome and diabetes independently predict osteoarthritis severity and progression [12,13,26,27] and supports the view that impaired insulin signalling contributes to a catabolic chondrocyte phenotype rather than merely accompanying obesity [14,17].

The absence of correlation with clinical severity deserves careful interpretation rather than dismissal. Pain and disability in osteoarthritis are only loosely coupled to structural and biochemical disease activity; central sensitisation, psychological factors, muscle strength, comorbidity and coping strategies all contribute substantially to symptom burden. A serum cytokine concentration measured at a single time point captures a systemic average that may bear little relation to the local synovial environment driving nociception. It is also plausible that the cohort, restricted to K–L grade II–IV disease, was too narrow in biological range for a severity gradient to emerge, and that inflammatory markers discriminate disease presence better than disease intensity. Similar dissociation has been noted previously, with systemic markers showing only modest relationships with symptom scores despite robust case–control differences [9,24].

The inverse correlation between body mass index and serum TNF-α runs counter to the expectation that adipose tissue drives circulating TNF-α, and it should be reported with candour rather than explained away. Several considerations are relevant. Circulating TNF-α is largely a paracrine cytokine with a short half-life, and plasma concentrations correlate poorly with adipose tissue expression; assay platforms differ substantially in their measurement of low range TNF-α; and in a sample of 60 a moderate coefficient can arise from a small number of influential observations. The concurrent positive correlation between body mass index and HOMA-IR in the same participants indicates that the anthropometric data behave as expected against a well-validated metabolic index. This finding is best regarded as hypothesis-generating and requires replication with a larger sample and preferably a high-sensitivity TNF-α platform before any biological interpretation is advanced.

Taken together, the results support a model in which systemic inflammation and insulin resistance are both features of established knee osteoarthritis but function as parallel rather than tightly coupled pathways at this stage of disease. If

inflammation and insulin resistance were reciprocally reinforcing in the manner suggested by mechanistic work [15,16], a correlation between the cytokines and HOMA-IR would be expected within the case group; none was observed. One interpretation is that the reciprocal relationship operates predominantly during disease initiation, and that by the time radiographically established osteoarthritis is present, both abnormalities have plateaued and their coupling is no longer detectable cross-sectionally.
Longitudinal designs are needed to test this.

Strengths and limitations
Strengths include individual matching of controls for age and sex, exclusion of conditions known to confound inflammatory and metabolic measurements, standardised pre-analytical handling with batched cytokine assays, use of validated clinical instruments, and the simultaneous measurement of inflammatory and metabolic domains in a single Indian cohort — a population under-represented in this literature.

Several limitations temper the conclusions. The design was cross-sectional and hospital-based at a single tertiary centre, so temporal and causal inferences cannot be drawn and the sample may over-represent advanced disease. The sample size, while adequate for group comparison, gives limited precision for correlation estimates; with 60 participants the study had roughly 80% power to detect correlations of about 0.35 or greater, so weaker but genuine associations may have been missed. Only circulating markers were measured; synovial fluid concentrations may reflect joint-level activity more faithfully. Other relevant mediators — IL-1β, matrix metalloproteinases, leptin, adiponectin and cartilage oligomeric matrix protein — were not assessed for reasons of cost. Waist–hip ratio and physical activity were recorded but not modelled, and residual confounding by adiposity distribution and activity level cannot be excluded. Finally, the analyses were unadjusted; multivariable modelling of the metabolic outcomes would strengthen inference in future work.

CONCLUSION
Patients with primary knee osteoarthritis demonstrated significantly higher circulating IL-6, TNF-α and hs-CRP, together with higher fasting glucose, fasting insulin and HOMA-IR, than age- and sex-matched healthy controls. These abnormalities were, however, unrelated to pain and functional disability and unrelated to one another within the disease group. The findings reinforce the characterisation of knee osteoarthritis as a systemic inflammatory and metabolic disorder while cautioning against the use of circulating cytokine concentrations as surrogate markers of clinical severity. Prospective studies incorporating synovial fluid sampling and repeated measurement are required to establish whether inflammatory and metabolic pathways converge earlier in the disease course.

REFERENCES

1. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet. 2019;393(10182):1745–59.
2. GBD 2019 Osteoarthritis Collaborators. Global, regional, and national burden of osteoarthritis and years lived with disability. Ann Rheum Dis. 2020;79:819–28.
3. Pal CP, Singh P, Chaturvedi S, Pruthi KK, Vij A. Epidemiology of knee osteoarthritis in India and related factors. Indian J Orthop. 2016;50(5):518–22.
4. Sharma MK, Swami HM, Bhatia V, Verma A, Bhatia SPS, Kaur G. An epidemiological study of correlates of osteoarthritis in geriatric population of UT Chandigarh. Indian J Community Med. 2007;32(1):77–8.
5. Robinson WH, Lepus CM, Wang Q, Raghu H, Mao R, Lindstrom TM, et al. Low-grade inflammation as a key mediator of the pathogenesis of osteoarthritis. Nat Rev Rheumatol. 2016;12(10):580–92.
6. Scanzello CR, Goldring SR. The role of synovitis in osteoarthritis pathogenesis. Bone. 2012;51(2):249–57.
7. Kapoor M, Martel-Pelletier J, Lajeunesse D, Pelletier JP, Fahmi H. Role of proinflammatory cytokines in the pathophysiology of osteoarthritis. Nat Rev Rheumatol. 2011;7(1):33–42.
8. Goldring MB, Otero M. Inflammation in osteoarthritis. Curr Opin Rheumatol. 2011;23(5):471–8.
9. Livshits G, Zhai G, Hart DJ, Kato BS, Wang H, Williams FMK, et al. Interleukin-6 is a significant predictor of radiographic knee osteoarthritis: the Chingford Study. Arthritis Rheum. 2009;60(7):2037–45.
10. Spector TD, Hart DJ, Nandra D, Doyle DV, Mackillop N, Gallimore JR, et al. Low-level increases in serum C-reactive protein are present in early osteoarthritis of the knee and predict progressive disease. Arthritis Rheum. 1997;40(4):723–7.
11. Attur M, Krasnokutsky S, Statnikov A, Samuels J, Li Z, Friese O, et al. Low-grade inflammation in symptomatic knee osteoarthritis. Osteoarthritis Cartilage. 2015;23(7):1013–21.
12. Yoshimura N, Muraki S, Oka H, Tanaka S, Kawaguchi H, Nakamura K, et al. Accumulation of metabolic risk factors and the incidence of knee osteoarthritis. Arthritis Res Ther. 2012;14(4):R185.

13. Schett G, Kleyer A, Perricone C, Sahinbegovic E, Iagnocco A, Zwerina J, et al. Diabetes is an independent predictor for severe osteoarthritis. Diabetes Care. 2013;36(2):403–9.
14. Courties A, Sellam J. Osteoarthritis and type 2 diabetes mellitus: what are the links? Diabetes Res Clin Pract. 2016;122:198–206.
15. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444(7121):860–7.
16. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest. 2006;116(7):1793–801.
17. Berenbaum F. Diabetes-induced osteoarthritis: from a new paradigm to a new phenotype. Diabetes Metab. 2011;37(2):85–91.
18. Yusuf E. Metabolic factors in osteoarthritis: obese people do not walk on their hands. Arthritis Res Ther. 2012;14(4):123.
19. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Arthritis Rheum. 1986;29(8):1039–49. 20. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis. 1957;16(4):494–502.
21. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC. J Rheumatol. 1988;15(12):1833–40.
22. Trinder P. Determination of blood glucose using an oxidase-peroxidase system with a noncarcinogenic chromogen. J Clin Pathol. 1969;22(2):158–61.
23. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412–19.
24. Stannus O, Jones G, Cicuttini F, Parameswaran V, Quinn S, Burgess J, et al. Circulating levels of IL-6 and TNF-α are associated with knee radiographic osteoarthritis and knee cartilage loss in older adults. Osteoarthritis Cartilage. 2010;18(11):1441–7.
25. Malathi R, Kothari S, Chattopadhyay A, Agrawal PK, Banerjee U, Sahu RK. Raised serum IL-6 and CRP in radiographic knee osteoarthritis in Eastern India. J Med Sci Clin Res. 2017;5(5):21687–92.
26. Puenpatom RA, Victor TW. Increased prevalence of metabolic syndrome in individuals with osteoarthritis: an analysis of NHANES III data. Postgrad Med. 2009;121(6):9–20.
27. Courties A, Berenbaum F, Sellam J. The phenotypic approach to osteoarthritis: a look at metabolic syndrome-associated osteoarthritis. Joint Bone Spine. 2019;86(6):725–30.
28. Berenbaum F, Eymard F, Houard X. Osteoarthritis, inflammation and obesity. Curr Opin Rheumatol. 2013;25(1):114–8.
29. Pepys MB, Hirschfield GM. C-reactive protein: a critical update. J Clin Invest. 2003;111(12):1805–12.
30. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol. 2014;6(10):a016295.

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Data Availability: Data supporting the findings of this study are available from the corresponding author upon reasonable request.