Research Protocol

DOI: 10.7860/JCDR/2026/87539.24164

Physiotherapy Section

Methodological Framework for Predictive Modelling using Metabolic, Mechanical and Radiographic Parameters in Knee Osteoarthritis Diagnosis: A Research Protocol for Cross-sectional Study

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ABSTRACT

Introduction: Osteoarthritis (OA) is a very common chronic musculoskeletal disorder, which is often diagnosed with the help of clinical and radiographic techniques; nevertheless, these traditional methods might not be capable of detecting the disease during its initial stages or explaining the underlying molecular pathogenesis.

Need of the study: Knee OA is a multifactorial disease driven by metabolic, biomechanical and structural factors, yet diagnosis relies on late radiographic changes after irreversible damage. Current predictive models incorporate isolated radiographic features and clinical data, but omit integrated biomarkers or biomechanical factors. A unified model that integrates these domains is essential for proactive diagnosis and personalised OA management.

Aim: To develop and validate a predictive model based on metabolic and mechanical markers for knee OA and evaluate its concurrent validity with radiographic grading.

Materials and Methods: A cross-sectional study will be conducted at the Outpatient Department of Maharishi Markandeshwar Super Speciality Hospital, Haryana, India, from September 2025 to September 2027. Adults aged 45-70 years with symptomatic unilateral or bilateral knee OA confirmed by radiographic evaluation will be recruited using purposive sampling. Metabolic markers {lipid profile and glycated Haemoglobin (HbA1c)}, mechanical parameters (tibial torsion and Q-angle) and radiographic severity, based on the Kellgren-Lawrence (KL) grading system, will be assessed using standardised measurement procedures. Pearson's correlation coefficient (r) or Spearman (ρ) will be used to determine the relationship between various variables. Step-wise multiple regression will be used to determine the most significant predictors of the clinical outcome. A p-value of <0.05 is considered statistically significant.

Keywords: Biomarkers, Disease progression, Joint disease, Prognosis, Risk assessment

INTRODUCTION

The Osteoarthritis (OA) is a chronic musculoskeletal disorder and there has been a significant change in comprehension of OA [1]. Previously, OA was viewed as a cartilage disease [2]. OA has become a complicated and debilitating abnormality that impacts the whole joint with the involvement of the subchondral bone and synovium [3]. As per the World Health Organisation (WHO) Global Burden of Disease Study 2010, hip and knee OA ranks 11th in disability causes. The global age-standardised prevalence of knee OA was 3.8%, and hip OA was 0.85%. Prevalence was higher in females than males [4]. Such an increase in prevalence is expected to put a considerable burden on the healthcare systems and increase the need for both therapeutic interventions and joint replacement procedures.

The OA has a multifactorial aetiology that includes metabolic disturbances, mechanical overload and radiological changes, which lead to the development and progression of the disease [5]. Early diagnosis is often overlooked because, in general clinical practice, early functional or biochemical changes are not prioritised relative to structural degeneration [6]. A clear prediction of the disease course is necessary to diagnose and manage the disease early.

The rapid progress in the sphere of biomarkers, biomechanics and imaging technologies provides new opportunities to develop more predictable models [7-9]. The metabolic indicators (e.g., adipokines and inflammatory cytokines) may provide insight into the systemic effects associated with OA, while biomechanical measurements can help identify changes in joint loading patterns [10]. Radiographic procedures also provide an elaborate assessment of structural joint alteration. A combination of all these modalities with predictive modelling, including statistical and machine-learning methods, could lead to a more accurate and clinically relevant knee OA prediction model [11].

Although numerous studies have explored the risk factors for knee OA, a unified model that simultaneously incorporates metabolic, mechanical and radiographic domains has yet to be established. The creation of an inclusive model would help to identify those at increased risk as early as possible, thus allowing prompt intervention and improving the overall quality of life.

Primary Objective

- To find the correlation between metabolic and mechanical markers and radiographic grading of KOA.
- To do regression analysis of metabolic and mechanical markers at different stages of KOA.

Secondary objective: To determine the concurrent validity of the prediction model with radiographic grading of KOA.

Null hypothesis: Higher metabolic parameters and poor mechanical markers are not significantly correlated with the presence and severity of knee OA as evident on radiographs.

Alternate hypothesis: Higher metabolic parameters and poor mechanical markers are significantly correlated with the presence and severity of knee OA as evident on radiographs.

REVIEW OF LITERATURE

Increasingly, knee OA is recognised as a multifactorial condition with a metabolic, biomechanical and structural aetiology. These relationships have now been quantified and are important for disease prediction and progression [11].

To study the causal relationship between glycated Haemoglobin (HbA1c) and knee OA, Chen L et al., applied the Mendelian randomisation approach. Results from the study indicated that genetically determined higher HbA1C levels were found significantly associated with an increased risk of knee OA {Odds Ratio (OR)=1.561, 95% Confidence Interval (CI): 1.110-2.197; p=0.011}, suggesting that chronic hyperglycaemia may be involved in the pathogenesis of OA [10].

Following this, Tsukada A et al., carried out a cross-sectional study of 156 patients with knee OA (HbA1c ≥6.5%, n=28; <6.5%, n=128; matched n=27/group), with both the unmatched and matched high HbA1c groups showing significantly higher levels of mast cell markers than the matched low HbA1c group {before: Tryptase Beta 2 (TPSB2): p=0.004; Carboxypeptidase A3 (CPA3): p=0.010; after: TPSB2: p=0.005; CPA3: p=0.014}. Further, the expression of PAX Interacting Protein 1 (PAXIP1) (p=0.009) and ARG1 (p=0.021) was significantly higher in mast cell-enriched fractions among participants with high HbA1c levels, suggesting that poor glycaemic control is associated with increased inflammatory activity in knee OA [11].

Guo B et al., built several machine learning models that included lipid metabolism-related biomarkers to predict the risk of knee pain. The three best models performing the stacked ensemble (AUC=0.85), GBM (AUC=0.83) and random forest (AUC=0.826) had good discriminative power. The Lipid Accumulation Product (LAP), Triglyceride-Glucose (TyG) index, TyG-Body Mass Index (BMI), and Low-Density Lipoprotein Cholesterol (LDL-C) were consistently identified as features associated with knee pain outcomes by feature importance and SHapley Additive exPlanations (SHAP) analyses, indicating that metabolic dysregulation plays a critical role in knee pain outcomes [12].

The recent study by Ashmeik W et al., investigated whether there is a relationship between metabolic markers and changes in knee structure measured by Magnetic Resonance Imaging (MRI) in individuals who had early OA. The study demonstrated that higher fasting glucose (β=1.31; 95% CI: 0.57-2.05; p=0.002; adjusted R^2=0.43) and HbA1c (β=0.90; 95% CI: 0.07-1.73; p=0.04; adjusted R^2=0.18) were significantly associated with increased meniscal degeneration. Additionally, elevated total cholesterol (β=0.94; 95% CI: 0.01-1.86; p=0.048; adjusted R^2=0.15) and non High-Density Lipoprotein Cholesterol (HDL-C) cholesterol (β=1.05; 95% CI: 0.14-1.96; p=0.03; adjusted R^2=0.20) were significantly associated with greater cartilage degeneration. The authors found that glycaemic and lipid abnormalities might be associated with early structural changes in knee OA [13].

Abdullah SS et al., studied the association of Q angle, Joint Space Width (JSW) and progression of knee OA in patients over 50 years of age, using both weight-bearing and non weight-bearing radiographs. This study showed that the Q angle was in the range of 8.72° to 14.58° (WB) and 10.13° to 14.92° (NWB) and these were significantly related to the severity of OA. In particular, a Q angle < 11.72° and a medial JSW < 3.725 mm were found to be strongly associated with rapid progression of knee varus OA (p<0.001). The results indicate that decreased Q angle is associated with disease progression and is a clinically significant finding for the severity of knee OA [14].

To assess alterations of 3D lower limb alignment in knee OA with and without weight-bearing, Kaneda K et al., conducted a Computed Tomography (CT) study. A total of 45 knees from 25 patients (mean age 69.9 ± 8.9 years) were included in the study and showed that weight-bearing caused a significant increase in knee flexion (up to 4.08 ± 4.36°), varus alignment (up to 3.03 ± 2.16°) and tibial internal rotation (up to 3.88 ± 2.00°). There was a significant difference between K-L grades 1 and 2 (p=0.008), grades 1 and 3 (p<0.001) and grades 1 and 4 (p<0.001). The results indicate that elevated IR under WB loading is related to knee OA progression and could be a key indicator to detect and stratify the severity of disease [15].

Overall, current evidence suggests that HbA1c, lipid profile, Q-angle and tibial torsion are important independent predictors of knee OA. However, studies that combine these variables into a single predictive model are limited. Hence, this research paper seeks to fill this gap by comparing metabolic, mechanical and radiographic markers in combination and hence provide a valuable and clinically meaningful predictive model of knee OA. Thus, this study aims to develop and validate a predictive model based on metabolic and mechanical markers for knee OA and evaluate its concurrent validity with radiographic grading.

MATERIALS AND METHODS

The cross-sectional study will be conducted at the Outpatient Department of Maharishi Markandeshwar Super-Speciality Hospital, Haryana, India, from September 2025 to September 2027. Ethical clearance was obtained from the Institutional Ethics Committee (IEC-3436). The trial has been registered in Clinical Trials Registry–India (Registration no: CTRI/2025/09/094402). All the patients will be informed about the study procedures and written informed consent will be obtained before enrolment.

Inclusion criteria: Participants aged between 45 and 70 years, including both males and females, with symptomatic knee OA confirmed radiographically using the KL classification system [9] will be included in the study. Individuals presenting with either unilateral or bilateral knee OA will be considered eligible.

Exclusion criteria: Participants will be excluded if they have a history of osteoporosis, rheumatoid arthritis, gout or any other inflammatory or autoimmune joint disease; a history of total knee replacement or any prior knee surgery; any fixed deformity of the lower limb or spine; or regular use of corticosteroids or other medications that may influence joint or metabolic status. Individuals who are unwilling to provide informed consent will also be excluded from the study.

Sample size calculation: The sample size was determined using the Riley's formula [16].

$$n = \frac{p}{(SVH - 1)\ln\left(1 - \frac{R^2_{CS\_adj}}{SVH}\right)}$$

where 'n' is the number of participants, p is predictor parameters {10 predictors including HbA1c, Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, tibial torsion, Q-angle, BMI, age and gender}, and SVH global shrinkage factor (0.90) was assumed to minimise overfitting. R2 adjusted value (0.20) from a previous study of KOA with metabolic markers [13]. So, the minimum sample size is calculated by using the above-mentioned formula.

The minimum sample size is N= 400.

A total of 400 participants with symptomatic knee OA will be recruited via purposive sampling from the outpatient department. Participants will then be stratified by radiographic severity using the KL grading system (Grades I-IV) exclusively for analytical comparisons of metabolic and biomechanical parameters across disease stages.

Study Procedure

In the first evaluation, demographic data such as age, sex, weight, height, limb length and waist circumference will be recorded. Standardised clinical procedures will be used to measure mechanical markers (tibial torsion and Q-angle). A radiographic evaluation of

the knee joint will be done based on plain X-ray and results will be categorised based on the KL grading system. Laboratory analysis will be performed to obtain metabolic indicators (a complete lipid profile: total cholesterol, LDL, triglycerides) and the level of HbA1c. The primary researcher will record all measurements with the help of standardised protocols to guarantee uniformity and reduce the impact of measurement bias.

Outcome Measures

Primary outcomes: Radiographic images will be obtained using standard positioning guidelines and a radiologist will grade them according to the KL classification system [9]. Standard anteroposterior weight-bearing radiographs of the knee joint will be obtained and evaluated by a radiologist. The KL system grades knee OA based on osteophyte formation, joint space narrowing, subchondral sclerosis and bony deformity, spanning Grade I (doubtful changes) to Grade IV (severe OA). KL grading will be the dependent outcome variable in the regression analysis.

Secondary outcomes:

- Metabolic variables will also comprise a lipid profile, including the evaluation of total cholesterol, low-density lipoprotein cholesterol high-density lipoprotein cholesterol and triglycerides; the mentioned variables will help to evaluate lipid metabolism and cardiovascular risk. HbA1C will also be analysed to assess the levels of glycaemic control and reference ranges will be used to determine normal, pre-diabetes or diabetic conditions.
- Mechanical measures will be measured and these are tibial torsion measured through Thigh-Foot Angle measurement and Q-angle measurement using a universal goniometer (Baseline® HiRes™ 360° International Standards of Measurement (ISOM) Goniometer, Model 12-1000HR, 12-inch length, Fabrication Enterprises Inc., USA) when the subject is in a standard standing position. The goniometer will be checked for zero error and calibrated before data collection as per the manufacturer's recommendations to ensure measurement accuracy. Q-angle will be measured using a universal goniometer, with normal ranges of 14°-17° in males and 17°-20° in females [17]. Tibial torsion will be assessed via the thigh-foot angle method, where positive values denote external rotation; normal adult values range from +10° to +20° external rotation, with deviations deemed abnormal and potentially disruptive to knee biomechanics [18].

STATISTICAL ANALYSIS

Statistical analysis will be conducted using IBM Statistical Package for the Social Sciences (SPSS) Statistics version 32.0. Normality will be evaluated using Kolmogorov-Smirnov tests as appropriate. Correlations will employ Pearson's coefficient for normal data and Spearman's rank for non normal or ordinal variables, including KL grades. Logistic and linear regression models will be used to describe the associations of predictors with outcomes. Logistic regression models will be used for the KL grading system. A linear regression model will be used for continuous data. The univariate model will initially be used to describe the association of each biomarker with the outcome without adjusting for demographic characteristics. A multivariable model will be used to evaluate the association of all included biomarkers with outcomes, adjusting for age and gender. Area Under the Curve (AUC) and Receiver Operating Characteristic (ROC) curves will be generated to assess the discriminative ability of a combination of biomarkers on the prediction of outcomes. A value of $p<0.05$ will be considered statistically significant.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Feb 04, 2026
- Manual Googling: Jul 06, 2026
- iThenticate Software: Jul 08, 2026 (1%)

ETYMOLOGY: Author Origin

EMENDATIONS: 9

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Jan 20, 2026**
Date of Peer Review: **Feb 12, 2026**
Date of Acceptance: **Jul 10, 2026**
Date of Publishing: **Aug 01, 2026**