Case Report

Serum and Urinary CTX Levels as Biomarkers of Osteoarthritis: A Narrative Review

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ABSTRACT

Background: Osteoarthritis (OA) is a leading progressive and disabling degenerative disorder of synovial joints, resulting in damage to cartilage tissue, characterized by pain, stiff joints, and immobility of the limb. Standard X-ray technique for detecting premature cartilage abnormality or for serial assessment is insufficiently responsive. The development of biochemical markers of cartilage turnover (particularly C-terminal crosslinked telopeptide of type II collagen [CTX-II]) to monitor cartilage catabolism and its activity as biochemical biomarkers has stimulated interest in their use for investigation. This narrative review was done to analyze existing information with the aim of finding out the status of CTX-II as a predictive, prognostic, or outcome measure of OA in either serum or urine. **Materials and Methods:** A narrative review was carried out using published literature searched electronically and in published databases, original research papers, longitudinal studies, cross-sectionals, case-controls, intervention studies, animal studies, systematic reviews and meta-analyses between the years 2001 and 2025 evaluating serum/and or urinary CTX-II for OA. 22 studies that met the aims were searched and included. **Results:** Collectively, the reviewed articles reported a significantly higher serum or urinary CTX-II concentration in OA compared to healthy individuals. This high CTX-II concentration was strongly correlated with radiographic severity, magnetic resonance imaging (MRI) -proven articular cartilage damage, reduced joint space, severity of pain, and limitation of function and/or activity. Longitudinal studies have shown that a greater concentration of basal CTX-II was associated with development of future loss of cartilage and progression of the disease. Finally, changes in the CTX-II concentration also correlated with the biologic response of pharmacologic or intra-articular therapy, which supports that this analyte could be used to monitor outcome. **Conclusion:** Both the serum and the urine CTX-II showed significant correlations with structural damage, disease severity and progression, and treatment response and can be valuable for the earliest diagnosis, prediction of outcome and management of OA but require further standardization and studies at a large scale.

Key words: Osteoarthritis, Biomarkers, Cartilage, Disease Progression.

One of the most common types of musculoskeletal diseases is osteoarthritis (OA), representing one of the major causes of pain and disability around the globe. OA typically consists of gradual breakdown of articular cartilage, subchondral bone remodeling, and inflammatory synovium leading to loss of joint function. Radiography, although commonly employed for this purpose, reveals late-stage structural alterations and is not effective in assessing cartilage damage and progression of the disease so far [1]. Thus, great effort was focused on discovering biological biomarkers of cartilage metabolism, which may be used as valid surrogates for monitoring disease progression and severity.

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Type II collagen peptides (especially C-terminal crosslinked telopeptide of type II collagen [CTX-II]) are the primary components of the articular cartilage structural matrix. It can be released into the serum during cartilage degeneration, which is then cleared by the kidney into urine. The assay of serum CTX-II and urinary CTX-II will serve as biochemical correlates of the rate of articular cartilage degradation. Several studies reported increased levels of serum and urine CTX-II compared with controls in patients with knee OA and found it to be correlated with degree of radiological damage, magnetic resonance imaging (MRI) appearance of cartilage loss, and progression over time [1-5]. This current narrative review was aimed at determining how serum and urine CTX-II levels perform in the role of biomarkers for the diagnosis, stage, disease progression, and monitoring of treatment for OA.

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MATERIALS AND METHODS

Literature search strategy

A wide literature search was undertaken in PubMed, Scopus, Google Scholar, and print journals which were available through local and online journal databases searched from January 2001 until July 2025 inclusive. Keywords and combinations included were the term knee osteo¬¬arthritis, OA (and/or osteo¬¬arthritis), cartilage cross-linked telopeptide type II, CTX-II, (serum/urine) CTX-II, biomarkers, cartilage degradation, cartilage turnover.

Study selection

A literature search identified about 70 articles. Titles and abstracts were initially examined to identify papers with relevance, followed by full-text review. In total, 22 articles examining CTX-II in serum and/or urine that had been evaluated in an OA context were selected for inclusion.

Inclusion criteria

Studies were included if they had evaluated serum and/or urinary CTX-II in subjects with OA; determined the potential diagnostic, prognostic, and disease monitoring value of CTX-II and showed a relationship of CTX-II with radiographic, MRI findings, clinical severity, progression of disease, or treatment effect. Only original research articles, animal studies, meta-analyses, and systematic reviews in the English language were included.

Exclusion criteria

The studies that did not estimate any measure of CTX-II; or did not examine OA-related illnesses were excluded. Conference abstracts, letters to the editor, editorials, or replications; and those without the minimum level of outcome-and design–methods data that would fulfil the needs of this overview were not included for this review.

Data synthesis

Included studies were narratively assessed and summarized on study design, study population, CTX-II specimen (serum vs. Urine), main conclusions, and clinical implications. The heterogeneous study designs, outcome measures, and assessment methods of biomarkers precluded a quantitative meta-analysis.

TABLE 1: Review of literature

SLO	Author (Year)	Study Design	Sample Size	Population	Biomarker Assessed	Outcome Measures	Key Findings	Conclusion
1.	Garnero et al. (2001) [1]	Cross-sectional comparative study	67 knee OA patients + 67 healthy controls	Adults with primary knee OA (mean age ~64 yrs) and age-matched controls	uCTX-II (along with COMP, Glc-Gal-PYD, PIIINP, HA, etc.)	WOMAC index (pain, stiffness, function), radiographic JSA (joint space area) and minimal JSW (joint space width)	OA patients had higher levels of uCTX-II. The JSA and minimal JSW showed a strong negative correlation with uCTX-II levels. The multivariate analysis showed that uCTX-II was the most accurate predictor of radiographic joint damage.	uCTX-II serves as an indicator of cartilage destruction which helps to determine the level of knee OA structural damage through its relationship with radiographic joint deterioration.
2.	Dam et al. (2009) [2]	Prospective longitudinal study (21-month follow-up)	158 subjects (with and without radiographic knee OA(ROA)	Adults with and without knee ROA	uCTX-II	MRI-based cartilage volume loss, KL grading, joint space width	Baseline uCTX-II was higher in subjects with knee ROA and predicted longitudinal cartilage loss on MRI. uCTX-II strongly predicted cartilage volume loss.	Elevated baseline uCTX-II was but was less effective than MRI at detecting changes.
3.	Wang et al. (2014) [3]	Prospective cohort study	140	Middle-aged women (40–67 yrs) without clinical knee disease	uCTX-II	MRI cartilage defects, bone marrow lesions, tibial bone area	Higher uCTX-II levels predicted cartilage defects, tibial bone expansion, and bone marrow lesions. There was no significant prediction accuracy for the next 2 years.	Higher levels of uCTX-II showed early structural damage which progressed to permanent knee damage. years2

4.	Zohiery et al. (2014) [4]	Case-control study	70 (50 OA patients, 20 controls)	Adults with knee OA and healthy controls	Serum and synovial CTX-II	Ultrasound findings, X-ray grading, WOMAC, VAS, Lequesne index.	Serum and synovial CTX-II levels were significantly elevated in OA patients, who showed a direct relationship between ESR and CRP together with OA severity assessment and Lequesne index measurement.	The CTX-II biomarker serves as an effective diagnostic tool which assesses the severity of knee OA while ultrasound technology enhances clinical assessment of effusion, Baker's cyst and synovitis.
5.	Abdel Ghany et al. (2016) [5]	Case–control cross-sectional study	60 (40 OA patients, 20 controls)	Postmenopausal women with symptomatic knee OA and healthy controls	uCTX-II	WOMAC index, KL grading	OA patients exhibit elevated levels of uCTX-II. CTX-II levels and WOMAC scores have a positive relationship. No significant relationship between CTX-II levels and the degree of radiographic severity.	The uCTX-II test showed early signs of cartilage degradation in OA but did not show the degree of the condition.
6.	Bai & Li (2016) [6]	Experimental longitudinal animal study	36 rabbits	OA-induced and sham-operated rabbits	Serum CTX-II and COMP	Mankin score, histopathology	OA rabbits showed significantly elevated levels of COMP and CTX-II compared with healthy rabbits. They also showed significant correlations with histology.	Simultaneously combining the CTX-II and COMP helped early diagnosis and determining stages of OA.
7.	Bihlet et al. (2019) [7]	Post hoc cross-sectional analysis of RCTs	1241	Patients with painful radiographic knee OA	uCTX-II, CTX-I, Osteocalcin	KL grading, WOMAC index, BMI, gender	uCTX-II resulted in two distinct outcomes, through its relationship with weight-bearing pain and radiographic severity. Women had higher levels of uCTX-II than men.	uCTX-II is a strong biomarker for both structural damage and pain severity in knee OA, displaying different results between male and female patients.
8.	Sofat et al. (2019) [8]	Cross-sectional case–control study	130	Advanced OA, mild OA, and healthy controls	uCTX-II	MRI (MOAKS), WOMAC, VAS, PPT	CTX-II levels showed a direct relationship with the MRI results, which detected cartilage damage, bone marrow lesions, synovitis, and pain scores.	CTX-II, together with MRI, represents a valuable method in assessing the severity and progression of disease in painful knee OA.
9.	Hao et al. (2019) [9]	Systematic review and meta-analysis	53 studies (OA patients and controls)	Patients with knee and hip OA and healthy controls	Serum COMP, uCTX-II, Serum/Synovial MMP-3	The SMD (standardized mean difference)	uCTX-II demonstrated moderate diagnostic effectiveness for knee OA, but it had high diagnostic effectiveness for hip OA. COMP and CTX-II showed better results in male subjects.	Serum COMP and uCTX-II are reliable biomarkers in the diagnosis of knee and hip OA.
10.	Wang et al. (2019) [10]	Prospective observational	140 (90 OA patients, 50	Patients with knee OA (K-L grades I–IV) and	Serum CTX-II and YKL-40	WOMAC score, KL grade, treatment	The OA patients showed higher serum CTX-II and YKL-40 levels, which increased with K-L grade.	The combination of serum CTX-II and YKL-40 serves as

		and treatment-evaluation study	controls)	healthy elderly controls		response (3, 6, 9 weeks)	The combination of CTX-II and YKL-40 achieved high diagnostic accuracy. There was a significant decrease in the levels following the treatment.	strong biomarkers which help in early diagnosis of OA, determine its severity and track treatment results.
11.	Henroti n et al. (2019) [11]	Open-label, prospective, multicentre pilot study	46 patients	Patients with symptomatic knee OA receiving intra-articular hyaluronic acid derivative (HYMOVIS)	Serum Coll2–1, Coll2–1NO2, CTX-II, PIIANP, CS-846, COMP, MMP-3, MPO, IL-6	Change in cartilage biomarkers, MRI cartilage volume/thickness, KOOS score, WORMS effusion score.	The ratios ofvColl2–1/PIIANP and CTX-II/PIIANP declined, indicating that cartilage catabolism had decreased with treatment.	HYMOVIS has potential to improve pain and function in OA.
12.	Arunruk thavon et al. (2020) [12]	Prospective cross-sectional diagnostic study.	129 participants (78 knee OA, 51 healthy controls)	Patients aged >40 years with knee OA; controls without clinical or radiographic knee OA	uCTX-II	uCTX-II levels (ELISA), KL grade, WOMAC index, effect of age and gender	The knee OA patients exhibited significantly higher urinary CTX-II levels than the control. uCTX-II maintained a separate link to radiographic severity while age, gender and WOMAC index showed no significant impact.	uCTX-II is a diagnostic tool which measures disease severity in knee OA and offers potential benefits for tracking disease progression.
13.	Cheng et al. (2020) [13]	Systematic review & meta-analysis (13 observational studies)	2,856 participants (1,341 knee OA; 1,515 controls)	Adults with radiological/clinical knee OA and healthy controls (European, Asian, African populations)	uCTX-II	SMD of uCTX-II between OA and controls; subgroup analyses by KL grade, gender, ethnicity, and study size	uCTX-II levels showed significant elevation in knee OA patients compared to control groups. Severe OA patients (KL 3-4) showed elevated levels which exceeded those found in KL 2 patients. The study results showed superior outcomes for female participants and European test subjects.	uCTX-II serves as a non-invasive Biomarker that successfully differentiates between knee OA patients and healthy individuals while demonstrating the severity of advanced OA.
14.	García-Alvarado et al. (2020) [14]	Cross-sectional descriptive study	155 women with knee OA	Mestizo women with radiographically confirmed knee OA from northeastern Mexico (median age 49 years; mean BMI 29.1 kg/m²)	Urinary C-terminal telopeptide of type II collagen (uCTX-II), adjusted for creatinine	Radiographic grading (Kellgren–Lawrence), WOMAC pain scale, BMI; uCTX-II measured by competitive ELISA	uCTX-II levels showed an increase according to OA severity. The study found that higher uCTX-II levels resulted in greater WOMAC pain scores and higher BMI measurements. The research found a significant link between uCTX-II levels and obesity.	The study found that uCTX-II levels showed a direct relationship with both radiographic grade and pain intensity in women who had knee OA, which established uCTX-II as an effective non-invasive biomarker that indicates cartilage breakdown and disease progression.
15.	Shen et al. (2020) [15]	Experimental longitudinal	60 SD rats (30 OA model,	Male Sprague–Dawley rats with OA induced by	Serum CTX-II and C2C	Macroscopic cartilage score, Mankin histological	The levels of serum CTX-II and C2C started to rise after week 2 in OA rats and continued to increase	Combined early detection of serum CTX-II and C2C

		animal study (ACLT-induced OA rat model with ROC analysis)	30 sham controls)	anterior cruciate ligament transection; evaluated at 0, 2, 4, 6, 8, and 10 weeks	(measured by ELISA)	score, serum CTX-II & C2C levels, ROC–AUC for CTX-II, C2C and combined biomarkers	throughout the study period. The two markers demonstrated a strong positive relationship, with CTX-II and C2C showed a strong relationship. The ROC analysis revealed better diagnostic accuracy with the use of combined biomarkers.	provides higher diagnostic accuracy than either marker alone and shows strong correlation with cartilage degeneration, supporting their potential value for evaluation and early diagnosis of osteoarthritis.
16.	Bay-Jensen et al. (2022) [16]	Narrative review	Not applicable (review of multiple clinical and preclinical studies)	Patients with OA across multiple cohorts (various ages, sexes, and ethnicities summarized from published literature)	Type II collagen markers (uCTX-II, C2C, Coll2-1, Coll2-1NO2, PRO-C2, PIIANP, T2CM) and aggrecan markers (ARGS, AGNx-1/NITEGE, AGNx-2/FFGV, CS846)	Association of biomarkers with radiographic severity, progression, prognosis, pharmacodynamics, and cartilage turnover; evaluation of degradation vs formation markers	The test results for uCTX-II show constant elevation in patients with OA as the levels of this biomarker increase with the advancement of the disease. The PRO-C2 and PIIANP tests measure cartilage development, while low PRO-C2 levels indicate an increased chance of radiographic disease progression. The compounds Coll2-1NO2, CS846, and COMP together with uCTX-II demonstrate independent links to the OA disease severity observed through radiographic assessment. The markers ARGS and NITEGE, which measure aggrecan degradation, serve as indicators for ADAMTS activity and the process of cartilage remodeling. The combination of different biomarker methods better explains how cartilage undergoes destruction and regeneration, yet only a few markers can distinguish between different OA endotypes.	The biomarkers - Type II collagen and Aggrecan present substantial evidence about cartilage deterioration and development, which enables medical professionals to assess disease progression and treatment effects. The current medical field lacks any biomarkers that can be used for routine laboratory testing, and there are no validated biomarkers that exist for identifying endotypes of OA.
17	Ishijima et al. (2022) [17]	Multi-center randomized controlled trial (predefined biomarker sub-analysis)	200 knee OA patients randomized; uCTX-II analyzed in 126 patients (IA-HA n=68, NSAID n=58)	Adults with symptomatic knee OA (KL grades 1–3)	uCTX-II, creatinine-corrected (ELISA)	Change in uCTX-II levels, % change from baseline; JKOM score; pain VAS; radiographic severity (K–L grade)	uCTX-II levels showed significant increases after IA-HA treatment, which decreased following NSAID treatment. Baseline uCTX-II levels showed positive correlation with radiographic severity but showed no relationship to pain or JKOM scores. The study found different biomarker responses, which were observed despite patients showing	uCTX-II serves as a measurement for cartilage breakdown while showing distinct biological reactions to both IA-HA and NSAID treatment, which establishes its effectiveness as a biomarker to study OA treatment mechanisms and

							identical symptom improvement.	their specific responses in different patient populations.
18.	Rethinam Meenakshisundaram et al. (2024) [18]	Case–control study	80 participants (40 cases, 40 controls)	Adults aged 20–50 years; cases with history of knee trauma in past 10–12 weeks and controls without knee trauma	Serum IL-6, Serum TGF-β1, Urinary CTX-II	VAS score, WOMAC index, KL grading, ELISA-uCTX-II estimation	The study found that cases had elevated serum IL-6, TGF-β1, and uCTX-II levels when compared to the control group, with a significant difference that reached the level of statistical significance ($p<0.05$). The study discovered that IL-6 levels showed a relationship with age and WOMAC score and uCTX-II while TGF-β1 showed a relationship with VAS score.	The study shows that L-6 functions as a potential biomarker that can detect post-traumatic knee OA at an early stage. The combined analysis of IL-6, TGF-β1, and uCTX-II enables detection of the disease before any visible radiographic alterations occur.
19.	Nongmaithem et al. (2024) [19]	Descriptive cross-sectional study	102 patients	Patients with primary knee OA (mean age 62.3 years)	uCTX-II	VAS, WOMAC, KL grading	uCTX-II levels showed a positive relationship with both pain measured by VAS and functional disability assessed by WOMAC. Higher levels of the biomarker coincided with more severe symptoms.	uCTX-II serves as a valuable non-invasive biomarker that indicates cartilage turnover, pain and functional disabilities in knee OA.
20.	Shin et al. (2024) [20]	Prospective case–control study	40 OA patients + 15 controls	Patients with severe knee OA undergoing TKA (Total knee arthroplasty)/UKA (unicompartmental knee arthroplasty) and healthy controls	Plasma and urinary inflammatory markers including (p)CCL11, pCXCL16, pIL-8, pIL-15, pHA, (u)CCL2, uCCL11, uCCL19, uCXCL16, uIL-1β, uIL-6, uIL-8, uIL-12p70, uIL-15, uIL-33, uMMP-3, uHA, uCTX-II, and uCOMP	Cytokine levels, ROC analysis, correlation with synovial fluid markers	Increased levels of plasma and urinary biomarkers especially pCCL11 and pIL-15 and uCCL11 and uCCL19 and uHA and uCTX-II showed a relationship with synovial fluid markers.	The plasma and urinary biomarkers especially pCCL11 and pIL-15 and uCCL11 and uCCL19 and uHA and uCTX-II could be used as non-invasive indicators to measure synovial inflammation which occurs in advanced knee OA cases.

21.	Singh S et al. (2025) [21]	Case–control study (Level III evidence)	160 participants (80 Knee OA cases, 80 controls)	Adults with primary knee OA graded by Kellgren–Lawrence system and healthy adults without knee joint complaints	Serum C-terminal cross-linked telopeptide of type II collagen (sCTX-II)	KL grading, WOMAC score, ROC curve analysis, ELISA-based serum CTX-II estimation	The serum CTX-II levels in Knee OA cases showed a significant increase compared to control group levels. The levels showed an upward trend according to the increasing severity of KL. The ROC analysis showed high diagnostic accuracy because it used established cut-off values to detect early disease.	Serum CTX-II is a strong biomarker for diagnosis of knee osteoarthritis in early stages, strongly correlating with disease severity.
22.	Ghatge et al. (2025) [22]	Case–control study	50 OA patients, 50 controls	Maharashtrian population with primary knee OA	uCTX-II	KL grading, ELISA	uCTX-II levels showed a significant increase in OA patients. The uCTX-II levels showed higher measurements for early-stage knee OA patients who had Grades 1 & 2 than for patients with advanced Grades 3 & 4 stages.	uCTX-II serves as an indicator of cartilage destruction which helps to determine the level of knee OA structural damage through its relationship with radiographic joint deterioration.

OA:Osteoarthiritis, Uctx-II C-termminal cross-linked telopeptide of type II collagan, Sctx-II: Serum C –terminal cross linked telopeptide of type II collagan, Western Ontario and McMaster Universities multifunction index, KL grading: Kellgren-Lawrence greding, VAS – Visual

DISCUSSION

This narrative review indicates a positive role of serum and uCTX-II for diagnosis and monitoring of OA. The vast majority of studies show that CTX-II is significantly higher in patients with OA than in those without the disease, as CTX-II measurements correlate with various structural measures in OA, i.e., radiographic changes, MRI-based measures of cartilage, pain, as well as function of the knee, and progression of OA. Longitudinal studies suggest that patients with high initial CTX-II values can predict future cartilage loss; furthermore, it has been found that treatment and changes in CTX-II level are reflected in relation to an interventional approach to treatment of OA. Several existing systematic reviews and meta-analyses have also indicated that uCTX-II performed with moderate to good accuracy for diagnosis, correlates well with structural joint damage and reflects disease progression [9,13]. Many recent reviews have highlighted the utility of CTX-II when analyzed together with radiological data and biochemical markers, and not as a stand-alone. Several cohort studies also suggested better accuracy in diagnosis and prognostic value when CTX-II was assessed in a Multimarker approach combined with, COMP, YKL-40, C2C, and inflammatory cytokines. [5,10,15,18,20].

Thus, CTX-II correlated well with joint structural damage, and it did correlate with clinical symptoms. The pain and clinical symptomatology are dependent on multiple factors beyond cartilage destruction [3,12].Although the available data are promising, all included studies are cross-sectional or short-term longitudinal studies. Therefore, no conclusions can be made about long-term predictive value and causality of CTX-II. The heterogeneity across studies, about study populations, assays, sample type, units of measurement, as well as standardization on the treatment of elevated creatinine values of creatinine correction, has resulted in the absence of a straightforward comparison between studies, and standardized reference intervals cannot be applied for most groups. Most studies have investigated cartilage of the knee rather than that of other joints; limited data exist concerning the early or pre-radiological stages of the disease and concerning ethnic and other minority groups. Multi-center prospective studies with standardized CTX-II test and reporting measures are needed to assess this test for routine clinical practice. Studies examining combined multimarker panels (with CTX-II), imaging modalities, and other biological parameters are required to improve early and pre-radiological diagnosis, staging, progression, and monitoring of treatment.

CONCLUSION

Serum and uCTX-II represent potential valid biomarkers of cartilage degradation for OA, which are significant predictors and markers for the progression, severity, and response to treatment of knee OA. Their clinical usefulness, though established as feasible for the future, requires more validation through large, prospective studies.

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