Original Research Article

Type I Collagen Cross-linked C-Telopeptide (CTX-I): A diagnostic tool for primary knee osteoarthritis

Sudhir Singh[1*], Lal Shrikant Kaushik[2], Chetan Verma[3]

[1]Professor, [2,3]Resident, Department of Orthopaedics, Teerthankar Mahaveer Medical College & Research Centre, Moradabad, Uttar Pradesh, INDIA.
Email: susi59@live.in

Abstract

Aims: The aim of this study was to find the efficacy of Type I Collagen cross-linked C- Telopeptide (CTX-I) as a biomarker in differentiating a case of primary knee osteoarthritis (KOA) with the normal knee joint and its ability to discriminate between radiological severity grades as determined by K-L grading. **Methodology:** Adults having no complaints attributable to knee joints were taken as Controls (50 subjects) and those having symptoms and signs pertaining to primary KOA were taken as Cases (100 subjects). WOMAC Score was recorded and weight bearing standing radiography of the knee joint was done. Blood samples were analyzed for sCTX-I level. **Results:** Our results showed that sCTX-I was significantly higher in cases than in controls (4.59±1.69 ng/ml vs 0.35±0.14 ng/ml, p<0.001) and was higher in K-L grade II than in K-L grade I (4.60 ± 1.71 vs 3.13 ± 2.35 ng/ml. p=0.03). sCTX-I independently co-related positively with WOMAC score (r=0.20) (*p*=0.04), with KL grade (r=0.23) (*p*=0.01) and with Age (r=0.04) (*p*=0.01). The receiver operative curve (ROC) analysis suggested a "Cut-off" value of sCTX-I as 0.91ng/ml (Sensitivity 100%; Specificity100%; Accuracy100%; p=0.001) between normal persons and persons having knee osteoarthritis and a "Cut-off" value of sCTX-I as 2.26 ng/ml (Sensitivity 88%; Specificity 63%; Accuracy 70.8%; p=0.03) between K-L grade I (At Risk group) and K-L grade II (mild) case of KOA. **Conclusion:** We observed that sCTX-I biomarker is able to distinguish between normal adult person and a case of OA; and between "At Risk" (K-L grade I) and mild OA case (K-L grade II).
Key Words: CTX-I, KOA, Osteoarthritis, Biomarker, K-L grading.

[*]**Address for Correspondence:**
Dr Sudhir Singh, Professor, Department of Orthopaedics, Teerthankar Mahaveer Medical College & Research Centre, Moradabad, Uttar Pradesh, INDIA.
Email: susi59@live.in
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INTRODUCTION

Osteoarthritis of the knee (OA) is a chronic, progressive degenerative disease that presents as pain, swelling, stiffness and deformity in the joint.[1] Overall prevalence of knee OA in India was found to be 28.7%.[2] It is also recognized that the cartilage itself is not capable of producing inflammation or pain. The element of pain is derived from changes in the non-cartilaginous structures like synovium, subchondral bone, ligaments, and surrounding muscles.[3] Historically, primary knee osteoarthritis (KOA) is diagnosed clinically by occurrence of pain and swelling in knee joint, bony crepitus, and bony deformity.[4] Later radiological criteria were added to aid diagnosis and staging of the disease severity.[5] WOMAC Score is widely accepted and practiced method to measure disability and pain in knee osteoarthritis.[6] Radiology can help in diagnosing at an early stage (K-L II) when the disease has yet not produced overt clinical signs and symptoms. Yet, most people with KOA seek medical help very late in the disease process when it is past the stage at which pharmacological or surgical treatments will slow or reverse the progression. The ability to diagnose the disease

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in molecular stage or Pre-radiological stage (K-L grade I) can open the door for more successful interventions. We chose to study the serum level of CTX-I, a degradation product of type 1 bone collagen in serum in patients diagnosed with KOA.

AIMS AND OBJECTIVES: The aim of this study is study the assess the level of Serum CTX-I in patients having primary knee osteoarthritis and in normal adults. Efficacy of this biomarker in predicting the presence or absence of KOA and its ability to predict the severity and progression of disease.

MATERIAL AND METHOD

1 Cases and controls

The study was designed as a prospective case-control study with level III evidence and included 150 subjects (100 cases and 50 controls). Cases included all those patients who had reported to our out-patient department with complaints of primary knee osteoarthritis. Control subjects were those persons who did not have any complaint pertaining to knee joint. Subjects were excluded if they had a) any other pathology effecting knee joint, b) Secondary osteoarthritis, c) pregnant or lactating females, d) any renal, hepatic disease, rheumatoid arthritis, uncontrolled diabetes, bleeding disorder or malignancy, e) were on treatment of osteoarthritis, f) drug abuse. All subjects were explained about the purpose and relevance of the study those who volunteered were included in the study after signing the patient information sheet and the consent form. The study proposal was approved by research committee and Institutional ethics committee and was done in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments (2013) or comparable ethical standards.

2 Self-assessment questionnaires and imaging

All subjects were asked to fill up WOMAC score sheet and weight bearing antero-posterior knee radiographs were taken. WOMAC score was calculated and K-L grading of all subject was done and recorded. Disease severity was graded as per K-L grading system. and the Case group was subdivided as Pre-radiological or "At Risk grade" (K-L grade I), mild grade (K-L Grade II), moderate grade (K-L grade III) and severe grade (K-L grade IV) of the disease. Control Group comprised of individuals with normal healthy knee joints and were labeled as K-L grade 0. This grading system defines radiographic OA in 5 categories. Radiographs scored as grade 0 (normal) showed no radiographic features of OA; K-L grade I (questionable) included a minute radiographic osteophyte of doubtful pathologic significance. Radiographs showing an osteophyte but no joint space narrowing were assigned a K-L grade II (mild); moderate diminution of joint space was graded K-L III (moderate); and K-L grade IV (severe) was defined by severe joint space narrowing with subchondral bone sclerosis.[7]

3 Sample collection and Analysis

Five ml. of venous blood was drawn from the antecubital vein between 12pm-2pm after a rest of 30 minutes. Whole blood was collected between 12pm-2pm after a pre informed fasting of 6-8 hours in untreated test tube (anti-coagulant free tubes). Collected blood was incubated undisturbed at room temperature for 20 minutes. Blood sample was centrifuged at 3,000 rpm for 10 minutes at 4°celsius. Immediately aliquot supernatant (serum) was stored in plain vials at -20°celsius. Stored serum was tested for serum levels of Carboxy terminal telopeptide (*s*CTX-I) by enzyme linked immuno-sorbent assay ELISA technique for *s*CTX-I levels. The data was analyzed by SPSS (Statistical Package for Social Sciences) Version 25.0 Statistical Analysis Software and ROC Curve.

RESULTS

1 Demographic profile

Present study included 100 Cases (M 36, F 64; mean age 53.91±10.36) and 50 Controls (M 34, F 16; mean age 33.80±9.48), a total of 150 subjects. Subjects in Control group were significantly younger than subjects of Case group (p=0.001). In Case group WOMAC Score (49.97±17.98) was significantly higher than in Controls (11.24±06.07) (p<0.001). (Table 1)

Table 1: WOMAC score (%) and sCTX-I (ng/ml) between Cases and Controls

	Controls (n-=50)		Cases (100)		Significance
	Min. -Max.	Mean ± SD	Min. -Max.	Mean ± SD	
WOMAC Score (%)	0.0 – 24.0	11.24 ± 6.07	6.25 ± 87.50	49.97 ± 17.98	t= 14.78 *p*= 0.001
sCTX-I level (ng/ml)	0.14 ± 0.81	0.35 ± 0.14	01.02 ± 8.52	04.59 ± 1.69	t= 17.66 *p*= 0.001

(*p*<0.05), a- not computed, #-Computed between 3 categories)

Among 100 cases there were 8 subjects with of KL grade I, 50 cases with KL grade II, 33 cases with KL grade III and 9 cases with KL grade IV KOA in Case group while Controls were recorded as KL grade 0. (Table 3)

2 Levels of biomarker

Analysis of our results showed that in Case group the mean sCTX-I level (4.59±1.69 ng/ml) was significantly higher than in Control group (0.35±0.14 ng/ml) (p=0.001) (Table 1). Variation of sCTX-I level in different age was studied. The level of sCTX-I rises with increasing age in cases as well as controls. But the difference in sCTX-I level with higher age group was significant (p=0.001). In Controls, although the level of sCTX-I was higher as the age increases but this difference was not significant (p=0.48) (Table 2).

Table 2: sCTX-1 levels (ng/ml) in different age groups in Cases and Controls

Age in years	Case (n=100)			Controls (n=50)			test and *p* value
	n	Mean	SD	N	Mean	SD	
<50	34	5.76	2.1	45	0.32	0.09	t=10.97
50-59	31	4.57	0.92	3	0.70	0.11	*p*=0.001
60-69	27	5.29	1.36	2	0.55	0.33	
>70	8	5.62	1.54	0	0	0	
Significance	F=14.34, *p*=0.001			F=1.04, *p*=0.48#			

sCTX-I level increases with increasing K-L grade (F= 2.98, p=0.03) (Table 3). sCTX-I level differs significantly between K-L grade I and grade II (p=0.03). But the difference between K-L grade II and grade III (p=0.79); and between K-L grade III and grade IV(p=0.15) is not significant (Table 5).

3 Co-relation of biomarker with other parameter

One-way ANOVA was computed to find the association between K-L Grade with WOMAC score and sCTX-I level in Case group was done. Results showed that K-L Grading is significantly associated with WOMAC score (F=20.18, p=0,001) and with sCTX-I level (F= 2.98, *p*=0.03) (Table 3)

Table 3: Comparison of sCTX-1 level with WOMAC Score and KL Grade

K-L Grade	sCTX-1 Levels (ng/ml)				WOMAC Score (%)		
	N	Min	Max	Mean ± SD	Min	Max	Mean ± SD
0	50	0.14	0.81	0.35 ± 014	0.0	24.0	11.24 ± 6.07
I	8	1.12	7.54	3.13 ± 2.35	6.25	42.7	22.16±11.48
II	50	1.02	8.52	4.60 ± 1.71	15.6	83.3	45.93±13.48
III	33	1.19	8.52	4.69 ± 1.45	42.7	87.5	57.39±16.48
IV	9	3.78	7.45	5.45 ± 1.03	48.9	83.3	69.90±11.78
One-way ANOVA (Case group only)	F= 2.98, *p*= 0.03 Between KL grade I/II/III/IV				F= 20.18, *p*= 0.001 Between KL grade I/II/III/IV		

Pearson Correlation and coefficient (r) value was calculated. It showed moderate positive co-relation between Age with WOMAC Score (r=0.43) (*p*=0.001), Age with KL grade (r=0,40) (*p*=0.001) and Age with sCTX-1 level (r=0.40) (*p*=0.04). (Table 4) Pearson Correlation and coefficient (r) value was calculated for sCTX-I with WOMAC score/ KL grade and Age. It showed weak but positive co-relation with WOMAC Score (r=0.20) (*p*=0.04), KL grade (r=0.23) (*p*=0.01) and with Age (r=0.04) (*p*=0.01). (Table 4)

Table 4: Co-relation among Age, K-L grade, WOMAC Score and sCTX-I level

SN	Variable	Respondents Mean ± SD	Pearson Correlation Coefficient (r) value	p value
1	Age (years)	53.75 ± 10.60	0.40	0.001
	K-L Grade	2.43 ± 00.76		
2	Age (years)	53.75 ± 10.60	0.43	0.001
	WOMAC Score (%)	49.97 ± 17.98		
3	Age (years)	53.75 ± 10.60	0.40	0.01
	sCTX-1 levels(ng/ml)	04.59 ± 01.69		
4	sCTX-1 level (ng/ml)	04.59 ± 01.69	0.20	0.04
	WOMAC Score (%)	49.97 ± 17.98		
5	sCTX-1 level(ng/ml)	04.59 ± 01.69	0.23	0.01
	K-L Grade	02.43 ± 00.76		

4 Diagnostic potential of biomarker

The receiver operative curve (ROC) analysis was done. A "Cut-off" value of sCTX-I as 0.91ng/ml (Sensitivity 100%; Specificity100%; Accuracy100%) between control group and Case group. (Table 6). Similarly, "Cut-off" point as 2.26ng/ml (Sensitivity 88%; Specific 63%; Accuracy 70.8%) between K-L grade I and K-L grade II; "Cut-off" point as 5.12ng/ml (Sensitivity 42.4%; Specificity 56%; Accuracy 48.8%) between K-L grade II and K-L grade III; "Cut-off" point

of 4.99 ng/ml (Sensitivity 77.8%; Specificity 57.6%; Accuracy 70.0%) and in between K-L grade III and K-L grade IV KOA is suggested (p>0.05). (Table 5)

Table 5: Cut-off values of sCTX-1 levels in various K-L grades

Area Under Curve Test Result Variable(s): sCTX-I level(ng/ml)										
	Area	Std. Error[a]	Asymptotic Sig.b (p-value)	Asymptotic 95% Confidence Interval		Cut-off value	Sensitivity	Specificity	Accuracy	*P* - value
				Lower Bound	Upper Bound					
Control vs Case	1.00	0.001	0.001	1.000	1.00	0.91	100%	100%	100%	P=0.02
KL I vs KL II	0.708	0.001	0.05	1.000	1.00	2.26	88%	63%	70.8%	P=0.03
KL II vs KL III	0.484	0.06	0.80	0.358	0.611	5.12	42.4%	56%	48.8%	P>0.05
KL III vs KL IV	0.700	0.09	0.06	0.518	0.883	4.99	77.8%	57.6%	70.0%	P>0.05

A. Under the nonparametric assumption. b. Null hypothesis: true area = 0.5

DISCUSSION

Osteoarthritis is becoming more prevalent due to the rising life expectancy, sedentary life style and increasing obesity in India. The diagnosis is not difficult to diagnose clinically when the disease has reached mild (K-L grade II), moderate (K-L grade III) and severe stage (K-L grade IV). But the challenge is to diagnose the condition at questionable stage (K-L grade I) as patient does not have any clinical sign and symptoms at this stage. But this has been made possible with radiographic staging which has helped clinicians to diagnose KOA at questionable stage of the disease. Though the radiography is an accepted standard investigation yet, it lacks sensitivity and provides historical account of the joint damage which has already taken place.[8-10] The need of the hour is to find a laboratory biomarker which can act as an adjunct to imaging in detecting the disease in the molecular stage/ pre-radiological grade when joint damage is not evident on radiographs. Several studies conducted in past suggested the importance of serum CTX-I as it may prove to be a promising diagnostic and prognostic marker in serum for diagnosis of KOA [11-15]. This inspired us to study association of serum CTX-I levels with knee OA. We collected blood sample between 12pm-2pm after a pre informed fasting of 6-8 hours as an effect of feeding on serum levels of CTX-1 has been reported in the literature, though the exact cause is unknown.[16] Our study included 150 subjects, out of which 100 subjects (66.67%) of the subjects were in the Case Group of primary knee osteoarthritis, whereas 50 subjects (33.33%) were in the Control Group (persons who had no arthritis associations of joints). Age profile study shows that the majority of the subjects 66 (66%) in case group were more than 50 years of age. This is in conformity with the results reported by Cornozier (2004) who had reported patients 57% belonged from the age group > 50 years of age.[17] The gender differences in our study shows that in the Case group majority of the participants were females (64%) but in Control group majority of participants were males (68%). But this difference in male: female proportion in Control and Case group was similar (p=0.36). Kerkhof (2010) reported male preponderance in his study but no such significant differences between the genders was noted by Teirlinck (2019).[18,19] Knee osteoarthritis patients have significantly higher values of WOMAC score than in Controls (*p*=0.001) (Table 1) and this validates the efficacy of WOMAC score as an effective tool to differentiate between a KOA case and a normal heathy joint. Both, the efficacy of WOMAC score as a clinical disability and functionality index and K-L grade as radiological tool is closely correlates with clinical severity and progression of disease has been reported by many researchers in the past.[20- 23] Analysis shows that mean CTX-I level in KOA patient was almost 12 times higher than in Controls (p=0.001) (Table 2). Mean CTX-I level was significantly higher in males than females in cases (p=0.03), but not in the Controls (p=0.85).

Analysis also showed increase in level of sCTX-I with increasing disease severity as indicated by K-L grade (F=2.98, *p*=0.03) (Table 3). Though the *s*CTX-I levels increases with increasing disease severity from K-L grade I to K-L grade IV but this difference was statistically significant between K-L grade 0 and I (p=0.03); and between K-L grade I and K-L grade II (p=0.03) only. The difference in sCTX values between K-L grade II and K-L grade III; between KL grade III and K-L grade IV was not significant (*p*>0.05). This indicates that increased joint destruction in KOA patients is related to increased sCTX-I level and is in conformity with the results reported earlier by Garnero P (2001) who had stated that all bone turnover markers (including serum CTX-I, and urinary CTX-I were lower in Controls than in Cases).[15] Similar results have been reported earlier as well.[12] Hence it cannot be used as a reference biomarker tool to differentiate between various grades of knee osteoarthritis. It is well accepted that osteoarthritis is a disease of aging joints. Our study has reinforced it demonstrating significant co-relation between age, WOMAC score, K-L grade and sCTX-I level (Table 4). Age has moderate positive co-relation with WOMAC score (r=0.43, p=0.001) K-L grade (r=0.40, p=0.001) and

sCTX-I (r=0.40, p=0.01) (Table 4). sCTX level also shows independent weak positive and significant co-relation with WOMAC (r=0.020, p=0.04) and K-L grade (r=0.023, p=0.01). (Table 4) Such a co-relation has also been reported by the other researchers.[12]

The receiver operative curve (ROC) analysis was done with the aim of predicting the efficacy of sCTX-I level as a diagnostic tool. It suggested a cut-off value of sCTX-I level as 0.91 ng/ml between normal knee joint with a diseased joint. This "cut-off" value is highly sensitive, specific and accurate (100%) to differentiate between primary KOA case from normal population. Between "At Risk" grade (K-L grade I) ROC analysis suggested the "Cut-off" value as 2.26ng/ml with sensitivity (88%), specificity (63 %) with an accuracy of 70.8%. (Table 5, Fig. 2). Our search of available English literature did not reveal any study which has suggested the "cut-off" values for sCTX-I levels in KOA though an earlier study has suggested a "Cut-off" value of Urinary CTX-I as >14.4ng/ml which was highly sensitive (96.0 %) and specific (74.0 %) with an accuracy of 91.1%.[12] Most of the studies have taken K-L grade II/ III/ IV as symptomatic knee and K-L grade 0 with or without K-L grade 1 as normal control group.[24-26] In our study the controls had no complaint of knee pain and radiographs showed no changes (K-L grade 0). Any subject with history of knee pain in last 3 months and doubtful radiographic changes was taken as K-L grade I. We have defined his group as "At Risk Stage" because even though they do have doubtful radiologic evidence or any clinical feature pertaining to KOA, yet they are most likely to develop KOA in coming years. ROC analysis also suggested a cut-off value of sCTX-I as 2.26ng/ml between "At Risk stage" (K-L grade I) and mild (KL grade II) which has high sensitivity (88%), moderately specificity (63%) and accuracy of 70.8% with statistically significant (p>0.03) discriminating power. (Table 5, Fig. 2)

Similarly, ROC analysis suggested a cut-off value of 5.12ng/ml and 4.99 ng/ml to differentiate between mild and moderate case and between moderate and severe case respectively but the sensitivity, specificity and accuracy is low and the discriminating ability of sCTX-I is not significant (p>0.05). Hence, sCTX-I failed as a tool to predict progression of disease severity in mild, moderate and severe grade of KOA. (Table 5, Fig. 2). None of the previous studies have attempted to evolve any such "cut-off" value of sCTX-I despite showing a significant difference between normal joint and a person with primary knee osteoarthritis (KOA) and between "at risk stage" and mild KOA. Thus in present study, we have attempted to stress the utility of *s*CTX-I level as a diagnostic test and found a robust efficacy of the test. Studies have stated that K-L grade I/ subthreshold population is in sizeable number in our society and this group has to be targeted.[2] Hence, developing new serological parameters which are non-invasive and cost effective is imperative so as to decrease the global burden of disease in future.

However, this study has two limitations. Firstly, the sample size of cases in K-L grade I being less is a major limitation of our study. Secondly the case and control groups were not age and gender matched. Since the study was time bound by the funding source and Corona pandemic forced the closure of normal hospital services leading to the limitations.

CONCLUSION

Based on the data analysis we can conclude that sCTX-I is a specific, sensitive and accurate biomarker tool with robust discriminating ability to differentiate between normal and osteoarthritic knee and between "At risk" (K-L grade I) and mild case of KOA (K-L grade II), but it fails to distinguish between subgroups of radiographic knee (K-L grade II, grade III and Grade IV) with accuracy and significance. To improve and validate the reliability of this tool, further larger metacentric trials studies are warranted.

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