Serum Level of Cartilage Oligomeric Matrix Protein as a Screening Modality for Osteoarthritis among Knee Joint Pain Patients

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Abstract: Objectives: This study aimed to evaluate the diagnostic yield of estimation of serum cartilage oligomeric matrix protein (COMP) as a screening tool for osteoarthritis (OA) among patients with knee joint pain.
Patients & Methods: The study included 140 female patients with knee pain and 20 volunteers to donate blood as a control group for laboratory findings. All patients underwent full history taking, clinical examination for evaluation of pain severity using a visual analogue scale (VAS) and extent of patient mobility using mobility score (MS) and had knee anteroposterior radiographs that were scored using the Kellgren-Lawrence scoring (K-L score) system. Patients were classified according to K-L scores into: group A: pain plus no radiographic findings (K-L score=1), group B: pain plus doubtful or minimal radiographic findings (K-L score=1) and group C: pain plus radiographically determined OA (K-L score≥2). Venous blood samples were obtained from all patients and controls for erythrocyte sedimentation rate (ESR) determination and ELISA estimation of serum COMP and high-sensitivity C-reactive protein (hsCRP) levels. Results: Group C patients had significantly higher pain scores and lower MS compared to groups A and B. Mean patients' serum COMP levels was significantly higher compared to control levels and in group C compared both to controls and to groups B and A levels with significantly higher levels in group B compared to controls and group A. However, serum COMP levels were non-significantly higher levels in group A compared to control levels. There was a positive significant correlation between serum COMP levels and body mass index (BMI), pain VAS score and radiological grade and a negative significant correlation with MS. ROC curve analysis revealed that elevated serum COMP is a sensitive predictor and high BMI is a specific predictor for the presence of OA. Serum COMP at 1097.5 ng/ml was the best cutoff point with high sensitivity (87.7%), positive predictive value (PPV, 92.6%) and accuracy (84.3%) for differentiation between patient with and without OA radiological manifestations and serum COMP at 1290 ng/ml showed 100% specificity and PPV and accuracy rate of 65.7% for diagnosis of the presence of radiological findings of OA. Conclusion: Estimation of serum COMP level could be considered as screening modality for patients with knee pain and using cutoff point of 1097.5 ng/ml helps to define patients free of OA and cutoff of 1290 ng/ml could define patients with OA.
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1. Introduction:

Arthritis is a chronic disease with a significant impact on the population. It damages the cartilage, synovium, and bone of the joints causing pain, impairment, and disability in patients. Current methods for diagnosis and monitoring the disease are only able to detect clinical manifestations of arthritis late in the process. However, with the recent onset of successful treatments for rheumatoid arthritis and osteoarthritis, it becomes important to identify prognostic factors that can predict the evolution of arthritis. This is especially critical in the early phases of disease so that these treatments can be started as soon as possible to slow down progression of the disease, [(1)].

A valuable approach to monitor arthritis would be by measuring biological markers of cartilage degradation and repair to reflect variations in joint remodeling. One such potential biological marker of arthritis is cartilage oligomeric matrix protein (COMP). In various studies, COMP has shown promise as a diagnostic and prognostic indicator and as a marker of the disease severity and the effect of treatment. This review highlights the progress in the utilization of COMP as a biomarker of arthritis, [(2)].

Articular cartilage is a multiphasic material with at least 2 major phases: a fluid phase composed of water and electrolytes, and a solid phase composed of chondrocytes located in lacunae together with matrix molecules that include collagen and

proteoglycans. The extracellular matrix of hyaline cartilage contains an elaborated collagen fibrillar network, which imparts its tensile strength and is essential for the mechanical stability and the proper function of the tissue, [3].

As articular cartilage degenerates in OA, so chondrocytes upregulate their biosynthetic activities, including type II collagen, as if to compensate for this damage. Only after secretion, as the molecules reach the extracellular space, the non-helical domains at the end; the procollagen type II amino-terminal propeptides and procollagen type II carboxy-terminal propeptides, are cleaved from the helical domain. The c-propeptide content and release from the cartilage is directly correlated with collagen synthesis, [4].

Cartilage oligomeric matrix protein is a member of the thrombospondin family of extracellular matrix proteins, [5]. COMP consists of five 87-kDa subunits held together by interchain disulfide bonds forming a 435-kDa pentameric protein. COMP is expressed in all types of cartilage, [6]. Immunohistological staining of articular cartilage has revealed a developmentally regulated localization of COMP to the chondrocyte territorial and interterritorial matrix, [7]. COMP binds in a zinc-dependent manner to collagen type I and type II and also to collagen type IX, [8]. COMP contains type 2 (epidermal growth factor-like) and type 3 (calmodulin-like) repeats in their central domains, [9]. It is becoming known that the mechanisms of cartilage matrix destruction such as roles of degradative enzymes and cytokines, so it is important to develop the reliable biomarkers to detect the early stage of cartilage destruction. The biomarker could be useful tool not only to understand the progression of joint destruction in osteoarthritis and rheumatoid arthritis but also to develop new treatment, [10]. Thus, the present study aimed to evaluate the diagnostic yield of estimation of serum COMP as a screening tool for OA among patients with knee joint pain.

2. Patients & Methods

The present study was based as screening study of patients attending the outpatient clinic of Rheumatology with knee joint pain. Only female patients were enrolled in the study to equalize the impact of gender on the serum level of COMP. Patients with history of knee trauma, rheumatoid arthritis, previous surgery at knee joint or previous treatment of osteoarthritis were excluded of the study. All patients underwent full history including duration of symptoms, mode of onset, precipitating and relieving factors and history of medical treatment. Patients' age, weight, height and body mass index (BMI) were determined.

Pain severity was assessed using a visual analogue scale (a 10 mm-scale, with "0" indicating no pain and "10" indicating worst pain ever), [11]. Local clinical examination was conducted for evaluation of the presence of swelling, stiffness, grinding or locking. The mobility score, which provides an estimate of the patient mobility ranging between being able to walk and undertake shopping unaided (score 9), through to being bedridden (score 0) was also estimated, [12].

Radiological examination to obtain anteroposterior radiographs of the knee in a weight-bearing extended position by using a standard radiographic technique and then radiographs were scored using the Kellgren-Lawrence scoring (K-L score) system, [13]: grade 0: normal knee, grade 1: doubtful and minimal OA of the knee, grade 2: mild OA of the knee, grade 3: moderate OA of the knee and grade 4: severe OA of the knee. The anteroposterior views characterize OA of the knee in the medial and lateral femorotibial compartments, with exclusion of the patellofemoral compartment. Patients were classified according to radiological findings into 3 supposed groups: group A: pain plus no radiographically determined OA (K-L score=0), group B: pain plus doubtful or minimal radiographically determined OA (K-L score=1) and group C: pain plus radiographically determined OA (K-L score≥2). Twenty healthy volunteers with no pain plus no radiographically determined OA of the knee and mobility score of 9 and accepted to give blood samples were included as control group for comparisons of laboratory findings.

Laboratory Investigation

All patients and controls gave fasting blood samples (1.6 ml blood for each 0.4 ml sodium citrate) for determination of ESR and another a 5-ml blood sample was collected in plain tube and allowed to clot and centrifuged at 3000 rpm for 10 minutes and serum was collected for ELISA estimation of:

1. Determination of serum hsCRP level using ELISA Kit (Phoenix Pharmaceuticals, Inc.). In the assay, 100 µl of each standard and samples were added into wells, covered and incubated for 2 hours at room temperature and then washed 4 times with wash solution. Then, 100 µl/well of anti-human CRP-HRP detection antibody were added, incubated for 2 hour at room temperature with gentle shaking and wash was repeated. TMB One-Step Substrate Reagent (100 µl/well) was added and wells are incubated for 25 minutes at room temperature. Reaction was terminated with 100 µl/well of stop solution and the degree of enzymatic turnover of the substrate is determined by dual wavelength absorbance

measurement at 450 nm immediately, [14].

2. Determination of serum COMP level using ELISA Kit (AnaMar Medical, Lund, Sweden). On the 1st day afternoon, serum sample was diluted 1/50 with dilution buffer and 75 µl of each standard and diluted samples were added into the pre-incubation plate (round bottom plate). Anti-COMP reagent (75 µl/well) was added, mixed on a shaker for 5 min and incubated overnight for about 15 hours at 4°C. On the 2nd day, 100 µl were transferred from the pre-incubation plate to the antigen coated plate and incubated at room temperature for 60 minutes. After wash for 3 times with wash solution, wells are emptied by trapping the strip on an absorbent tissue. Then, 100 µl/well of conjugate are added and wells are incubated for 60 minutes. After wash and drying, substrate reagent (100 µl/well) was added and wells are incubated for 50 minutes at room temperature. The degree of enzymatic turnover of the substrate is determined by dual wavelength absorbance measurement at 450 nm immediately, [15].

Statistical analysis

The obtained results were compared using Wilcoxon Rank test (Z-test) for unrelated data. The Receiver Operating Characteristic (ROC) curve was used to evaluate the predictability of serum COMP levels for the presence of OA and results were assured using the Regression multivariate analysis (Stepwise Method) to verify the diagnostic yield of combined measurements. The validity of multiple cutoff points to identify the valid cutoff points was assessed using the test validity characters including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy for various cutoff points. Statistical analysis was conducted using SPSS statistical program, (Version 10, 2002). P value <0.05 was considered statistically significant.

3. Results

The study included 140 female patients fulfilled the inclusion criteria. Radiological findings identified 26 patients with K-L score=0 (Group A), 52 patients had K-L score of 1 (Group B), 32 patients had K-L score of 2, 18 patients had K-L score of 3 and 12 patients had K-L score of 4; thus, group C included 62 patients. Patients included in groups B and C were significantly obese with significantly higher body weight and BMI compared both to controls and to patients included in group A with non-significantly higher body weight and BMI in group A compared to controls and in group C compared to group B, (Table 1). Patients included in group C had significantly higher pain scores and significantly lower mobility scores compared to groups A and B, with non-significant difference in favor of group A, (Table 2, Fig. 1).

All patients showed significantly higher ESR levels and serum hsCRP compared to controls with significantly higher levels in group C compared to both group A and B and a significantly higher levels in group B compared to group A, (Table 3, Fig. 2).

Mean serum COMP levels estimated in patients (1331.6±264.2; range: 890-1940 ng/ml) was significantly higher compared to levels estimated in control group. Moreover, mean COMP serum levels estimated in patients of group C were significantly higher compared both to control group and to groups B and A levels. Furthermore, mean COMP serum levels estimated in patients of group B were significantly higher compared to control group and group A levels with non-significantly higher levels in group A compared to control group, (Table 4, Fig. 3).

There was a positive significant correlation between serum COMP levels and BMI, ($r=0.246$, $p=0.040$), pain VAS score, ($r=0.521$, $p<0.001$) and radiological grade, ($r=0.778$, $p<0.001$) and a negative significant correlation ($r=-0.397$, $p=0.001$) with mobility score, (Table 5).

Evaluating the diagnostic predictability of serum COMP for the presence of OA, as judged by radiological finding, in patients with knee joint pain using ROC curve analysis versus clinical data revealed that elevated serum COMP is a sensitive and high BMI as specific predictors for the presence of OA with AUC=0.065 and 0.856, respectively, both AUC are significant ($p<0.001$) versus the null hypothesis. Knee joint mobility score was found to be specific predictor but with AUC=0.272 which despite being significant ($p=0.011$) versus the null hypothesis was less significant compared to BMI, (Fig. 4).

Verification of the obtained results for a cutoff point of serum COMP for identification of patients with OA among those who had knee joint pain, irrespective of the clinical data, defined serum COMP at 1097.5 ng/ml as the best cutoff point with high sensitivity (87.7%), positive predictive value (92.6%) and accuracy (84.3%) for differentiation between patient with and without radiological manifestations of OA. On contrary, serum COMP at 1290 ng/ml showed 100% specificity and positive predictive value and accuracy rate of 65.7% for diagnosis of the presence of radiological findings of OA, (Table 6).

Table (1): Patients' demographic data

	Control	Patients			
		Group A	Group B	Group C	Total
Number	20	26	52	62	140
Age (years)	42.5±5.4 (32-49)	44.3±4.1 (38-51)	46±4.1 (38-52)	47±5.3 (38-52)	45.4±5.3 (38-52)
Weight (Kg)	83.8±2.7 (79-89)	87±3.7* (80-93)	87.5±3.9* (80-93)	88±3.8* (79-95)	87.6±3.8* (79-95)
Height (cm)	162.6±5.4 (154-171)	165.5±2.8 (156-168)	162.5±3.8 (156-168)	160±4.3 (155-167)	162.9±4.3 (155-168)
BMI (kg/m^2)	31.8±2.3 (27.3-34.9)	31.8±1.6 (29-36.2)	33.1±1.9*† (29.8-36.2)	34.4±1.9*† (30.9-37.8)	33.1±2.9 (29-37.8)

Data are presented as mean±SD and ranges are in parenthesis
*: significant versus control group †: significant versus Group A

Table (2): Mean VAS pain and mobility scores among studied groups

	Group A	Group B	Group C
VAS Pain scores	3.9±1.4 (2-6)	5.1±1.6 (2-8)	6.2±1.3 (4-9)† ‡
Mobility score	7.1±1.7 (4-8)	6.1±0.8 (3-7)	4.9±1.1 (2-7)†‡

Data are presented as mean±SD and ranges are in parenthesis
†: significant versus Group A ‡: significant versus Group B

Table (3): Estimated ESR and serum hsCRP levels of patients categorized according to K-L scoring system compared to control levels

	Control	Group A	Group B	Group C
ESR	9.1±1.7	29.4±6.3*	34.8±8.5*†	43.1±12*†‡
Serum hsCRP (mg/l)	2.6±1.3	16.3±4.7	23.8±10*†	33.5±7.8*†‡

Data are presented as mean±SD and ranges are in parenthesis
*: significant versus control group †: significant versus Group A ‡: significant versus Group B

Table (4): Estimated serum COMP levels of patients categorized according to K-L scoring system compared to control levels

		Control	Group A	Group B	Group C
Mean±SD (ng/ml)		1015±161.6	1045.8±103.3	1250±155.8	1524±238.8
Range (ng/ml)		680-1260	890-1250	940-1520	1060-1940
Statistical analysis	Z		1.893	3.920	3.865
	p_1		>0.05	<0.001	<0.001
	Z			3.182	=3.183
	p_2			=0.001	=0.001
	Z				2.732
	p_3				=0.006

Data are presented as mean±SD and ranges are in parenthesis
p_1: significant versus control group p_2: significant versus group A p_3: significant versus group B

Table (5): Correlation coefficient between serum COMP levels and demographic and clinical data of studied patients

	"r"	p
Age	0.219	>0.05
Weight	0.164	>0.05
Height	0.169	>0.05
BMI	0.246	=0.040
VAS Pain scores	0.521	<0.001
Mobility score	-0.397	=0.001
Radiological K-L score	0.778	<0.001

Table (6): Test validity characters of estimation of serum COMP at 2 cutoff points

Cutoff point (ng/ml) Result	1065	1097.5	1290	1380	1480
True positive	54	50	33	26	18
True negative	6	9	13	13	13
False positive	7	4	0	0	0
False negative	3	7	24	31	39
Sensitivity	94.7%	87.7%	57.9%	45.6%	31.6%
Specificity	46.2%	69.2%	100%	100%	100%
PPV	88.5%	92.6%	100%	100%	100%
NPV	66.7%	56.3%	35.1%	29.5%	25%
Accuracy	85.7%	84.3%	65.7%	55.7%	44.3%

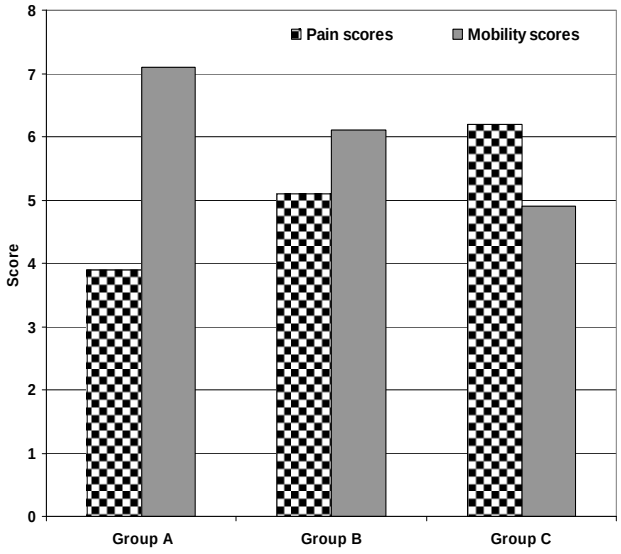

Fig. (1): Mean VAS pain and mobility scores reported in studied patients categorized according to K-L scoring system

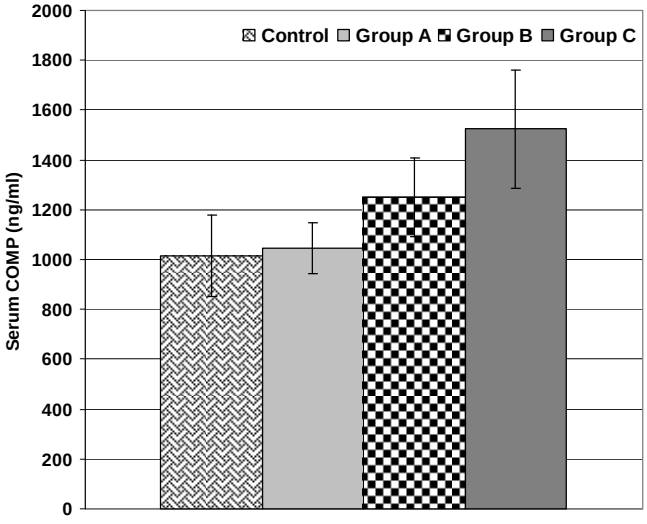

Fig. (3): Mean (±SD) of serum COMP estimated in studied patients categorized according to K-L scoring compared to control levels

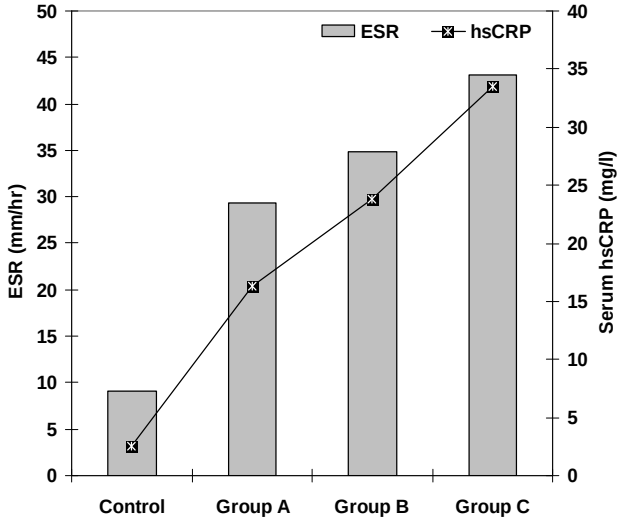

Fig. (2): Mean ESR and hsCRP estimated in studied patients categorized according to K-L scoring compared to control group

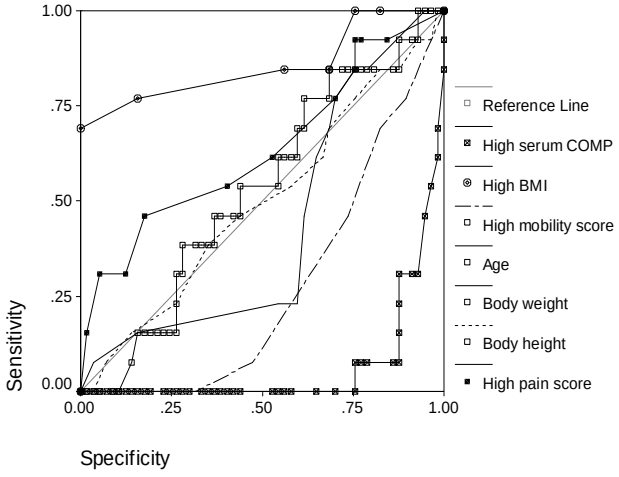

Fig. (4): ROC curve analysis for serum COMP versus demographic and clinical data for the prediction of the presence of OA in patients with knee joint pain

4. Discussion:

The detection of COMP in serum of studied population including patients and control indicated a fact that COMP, as a cartilage turnover marker is normally present in serum indicating continuous renewal of joint cartilage. This finding agreed with *Neidhart et al.,* [16] who found elevated serum COMP in seven of eight runners and during the run, the serum levels rose significantly, and gradually returned to baseline within 24 h. and attributed that elevated baseline levels of COMP might reflect increased joint matrix turnover due to prior extreme physical training, the reported significant increase during the run was possibly due to the severe physical strain on joint structures and concluded that serum COMP is a marker for distinct aspects of joint metabolism and/or damage in both disease and sport. Also, *Andersson et al.,* [17] reported that during normal daytime activities, serum COMP levels are constant and significantly decreased during the night indicating a rapid elimination of COMP once it has reached the circulation. Moreover, *Gordon et al.,* [18] tried to understand sources of variation in biomarkers for OA through evaluation of variation due to activity and food consumption and found all serum biomarkers increased after 1 h of non-exertional activity, but food consumption following activity was associated with a return of biomarker concentrations to baseline levels and demonstrated a positive association between the mean level of activity and serum COMP concentration.

Mean serum COMP levels estimated in patients was significantly ($P<0.05$) higher compared to levels estimated in control group and in patients with radiological evidence of OA compared both to control levels and to levels estimated in patients without radiological evidence of OA that were non-significantly higher compared to control levels. Moreover, there was a positive significant correlation between serum COMP levels and OA radiological severity and elevated serum COMP was found to be significant sensitive markers for differentiation between patients had or free of OA among patients had knee joint.

These results go in hand with the previously reported in literature concerning value of estimation of serum COMP in patients with OA; *Vilím et al.,* [19] found serum COMP positively correlated with knee joint space width both at baseline and after disease progression and knees that had progressed by two K-L grades were shown to have had significantly higher COMP levels at baseline and concluded that serum COMP has the potential to be a prognostic marker of disease progression. *Sharif et al.,* [20] found serum COMP concentration at baseline was significantly higher in the OA progressors compared with the non-progressors and the AUC was significantly higher in the progressors compared with the non-progressors and also that serum COMP concentrations were higher during periods of radiographic progression and identified periods of progression. *Fernandes et al.,* [21] reported that patients with symptomatic knee OA presented significantly higher serum COMP levels compared to healthy controls and to those with non-symptomatic narrowing of the articular space. Patients with clinical evidence of knee OA and without radiological abnormalities (K/L grade 0 or 1) had intermediate serum COMP levels, significantly higher than those observed in healthy controls.

Recently, *Kraus et al.,* [22] reported that serum COMP correlated negatively with total joint space narrowing burden. *Berry et al.,* [23] found COMP was significantly associated with a reduced rate of medial cartilage volume loss.

Regression analysis for estimated serum COMP levels versus clinical and demographic data for differentiation between cases with and without radiological findings defined estimation of serum COMP as significant predictor in two models and BMI in one model and test validity character determination for assigned cutoff points defined serum COMP at 1097.5 ng/ml as the best cutoff point with high sensitivity (87.7%), positive predictive value (92.6%) and accuracy (84.3%) for differentiation between patient with and without radiological manifestations of OA and serum COMP at 1290 ng/ml showed 100% specificity and positive predictive value and accuracy rate of 65.7% for diagnosis of the presence of radiological findings of OA. These finding go in hand with *Hunter et al.,* [24] who performed a logistic regression to examine the relation of levels of cartilage biomarker to the risk of cartilage loss in any knee and reported that with the exception of COMP, none of the other biomarkers was a statistically significant predictor of cartilage loss. *Kraus et al.,* [22] reported that biomarkers and demographics predicted 35-38% of variance in total burden of OA (total joint space narrowing or osteophyte).

The reported association between knee clinical and radiological features of OS, serum COMP and BMI spot line on a possible role for weight burden on the initiation and/or progression of OA and indicated the necessity for weight reduction as a prophylactic and/or therapeutic line for OA patients. Such assumption was supported by the findings of *Richette et al.,* [25] who investigated the effect of massive weight loss on knee pain and disability, low-grade inflammation and metabolic status and joint biomarkers in obese patients with knee OA and found massive weight loss improves pain and function and decreases low-grade

inflammation and concluded that change in levels of joint biomarkers with weight loss suggests a structural effect on cartilage.

In conclusion, estimation of serum COMP level could be considered as screening modality for patients with knee pain and using cutoff point of 1097.5 ng/ml helps to define patients free of OA and cutoff of 1290 ng/ml could define patients with OA. However, wider scale studies are recommended for establishment of cutoff points and defining the benefit of weight reduction as prophylactic and/or therapeutic modality.

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