Serum COLL2-1 In Rheumatoid Arthritis: Its Relation to Disease Activity and Severity

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Abstract:

Background: Rheumatoid arthritis is a chronic inflammatory disease characterized by proliferation of immunocompetent cells within synovial membranes. Type II collagen is the main protein component and specific for hyaline cartilage. **Aim:** This work aimed to measure serum level of Coll2-1, in RA patients, study its association with disease activity and/or severity, and to determine its ability as a biomarker of the disease status. **Patients and methods:** This study was conducted on: Forty rheumatoid arthritis patients together with twenty primary knee OA patients and twenty volunteers as control groups. For RA patients; full history was obtained then clinical examination was performed. Disease activity was assessed by DAS-28 and disease severity by Rheumatoid Arthritis Severity Scale (RASS). X- rays of both hands and feet graded by the Larsen score. Routine laboratory tests and serum Coll2-1 level was measured by ELISA. **Results:** Statistically significant increase in the mean serum Coll2-1 levels among RA and OA patients compared to the healthy controls (p= 0.001 each). No difference was found between RA and OA (p=0.14). Significant positive correlations ($p<0.05$) between serum level of Coll2-1 in RA patients with patients' ages**,** morning stiffness duration**,** tender and swollen joints number , ESR, CRP, DAS-28, radiological grading and RASS. **Conclusion:** This study highlighted the importance of Coll 2-1 biomarker reflecting disease activity and the destructive processes emerging in the joints of RA patients. It could be a promising tool in the pathogenesis of significant joint activity signaling cartilage and joint destruction.

Key words: Coll2-1, Rheumatoid arthritis, Biomarkers.

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease of unknown etiology characterized by swelling, tenderness, and destruction of the affected synovial joints, leading to severe disability and premature mortality **(1).** It is the most common autoimmune inflammatory arthritis in adults **(2).**

In most patients, RA has an insidious onset. The pathogenesis of RA is not completely understood. An external trigger (e.g., cigarette smoking, infection, or trauma) that triggers an autoimmune reaction, leading to synovial hypertrophy, chronic joint inflammation along with the potential for extra-articular manifestations, is theorized to occur in genetically susceptible individuals. Synovial cell hyperplasia and endothelial cell activation are early events in the pathologic process that progresses to uncontrolled inflammation with subsequent cartilage and bone destruction **(3).**

The evaluation of activity in a rheumatic disease has fundamental importance for therapeutic decisions and for the establishment of prognosis in such patients. Although traditionally, this evaluation has been performed in a purely orientation form from the physicians and the patients' impressions. Among different methods; the Health Assessment Questionnaire-Disability Index (HAQ-DI) of Stanford, the ACR20-50-70 scores and the combined disease activity score-28 are commonly used (DAS-28 **(4).**

Articular cartilage is mainly composed of water, collagen (most abundantly type II), proteoglycans (aggrecan), glycoproteins and chondrocytes. A balance between catabolic and anabolic processes normally maintains integrity of tissue; such balance allows keeping the mechanical and physiological properties of cartilage **(5)**.

Extensive work over the past decade has identified a significant number of cartilage degradation related biomarkers, including urinary C terminal telopeptides of type II collagen (uCTX-II); serum cartilage oligomeric matrix protein (COMP); serum and urine Coll2–1 and Coll2–1NO2 **(6).**

Coll 2–1 is a peptide of 9 amino acids that found to be released in serum as a result of collagen type II degradation not only in osteoarthritis patients but also in rheumatoid arthritis patients **(5)**.

Aim of the Work

This study aimed to measure serum level of **Coll2-1,** in RA patients and to study its association with disease activity and/or severity, also to determine its ability as a biomarker of the disease status.

Subjects and Methods

This case control study was conducted on 40 patients with rheumatoid arthritis (group I) and 2 control groups (group II and group III) as follow:

Group (1): Forty rheumatoid arthritis (RA) patients diagnosed according to the American College of Rheumatology/ European League against Rheumatism **(ACR/EULAR)** 2010 criteria **(1).**

Patients were recruited from the attendants of the inpatients' and the outpatient's clinic of Rheumatology, Rehabilitation and Physical Medicine department, Benha University Hospitals between 2016 and 2020.

The control groups were selected as follow:

Group (II): Twenty primary knee OA patients, who fulfilled the criteria of the American College of Rheumatology **(ACR) (7).**

Group (III): Twenty apparently healthy subjects.

The control groups were age and sex matched to RA patients.

Exclusion criteria included: Age < 16 years, Systemic disorders, such as diabetes, hematological diseases (coagulopathies), severe cardiovascular diseases, chronic liver and kidney disease or malignancy. Infectious disorders e.g., septic arthritis, viral arthritis, fungal arthritis and patients suffered from other rheumatic diseases such as spondyloarthropathies, systemic lupus erythematosus or dermatomyositis and others.

Study approval: The study was approved by Research Ethics Committee, Faculty of Medicine, Benha University, Egypt. The aim and methods of the study was explained to all participants, and an informed written consent was obtained from all participants**.**

All RA patients were subjected to complete history taking, thorough clinical examination with special attention to the musculoskeletal system. Pain was measured by the visual analog scale (VAS) **(8)**, Clinical assessment of disease activity, using the modified disease activity score of joint count (DAS-28) **(9)**, assessment of disease severity was done using the

Rheumatoid Arthritis Severity Scale (RASS) **(10)**. Radiological evaluation included X- ray both hands and feet, postero-anterior views for RA patients graded by Larsen score **(11)**. The following laboratory investigations were ordered; Complete blood count (CBC) by Sysmex 5000 counter, Erythrocyte sedimentation rate (ESR) by the Westergren method, C-Reactive protein (CRP) by quantitative Nephelometry, Liver function tests [Serum Glutamic Pyruvic Transaminase (SGPT), serum glutamic-oxaloacetic transaminase (SGOT)], serum creatinine, Rheumatoid factor (RF) by Latex agglutination test, Anti-cyclic citrullinated peptide anti-bodies (Anti-CCP) by ELISA. Serum Coll2-1 concentration was measured by enzyme linked immunosorbent assay (ELISA) according to manufacture instructions (Artialis SA Liège – Belgium and purchased from Sigma for chemicals, Cairo, Egypt).

Statistical Analysis:

The collected data were computerized and statistically analyzed using SPSS program (Statistical Package for Social Science) version **25**.**0**. Data were summarized as mean ± SD. The mildest observation, after arranging data into ascending or descending manner for calculating the median. Chi square test was used to calculate difference between qualitative variables. Unpaired t-test was used for comparison of the mean differences of two groups. One-way analysis of variance (ANOVA) was used for comparison of more than two groups. Pearson's correlation coefficient and linear regression analysis were used. $P < 0.05$ was considered significant.

Results

This study included 40 RA patients, 33 females (82.5%) and 7 males (17.5%), whose ages ranged between 30 and 50 years (mean ± SD 41.69 ± 6.29 years). The control group of primary knee OA patients included 14 females (70%) and 6 males (30%) whose ages ranged between 31 and 49 years (mean ± SD 43.24 ± 6.54 years). The second control group of apparently healthy volunteers included 13 females (65%) and 7 males (35%) whose ages ranged between 35 and 47 years (mean ± SD 39.91 ± 4.29 years). No statistical significance differences ($p<0.05$) were observed between the studied groups regarding age and sex distribution.

Clinical data, disease markers and laboratory parameters among RA patients are expressed in table **(1).**

Comparisons among the studied groups regarding mean serum Coll 2-1 level are shown in (**Table 2). —Table (3):** Non-significant ($p>0.05$) differences of mean serum COLL2-1

levels were reported among RA patients regarding the presence or absence of some clinical manifestations. Correlations of serum Coll 2-1 level with RA patients' demographic data, clinical features, and Larsen score **(table 4).** Among the studied RA patients; there were 2 RA patients (5%) in remission, 3 patients (7.5%) in a low active disease state, 20 (50%) patients with moderate activity and 15 patients (37%) with a highly active disease.

- There was a statistically significant increase in the mean serum Coll 2-1 **level** with increased disease activity (p=0.02) among group I cases being higher in patients with a highly active disease (**Table 5)**.
- Comparison of mean serum COLL2-1 as regard grading of Larsen score are expressed in **table (6).**

Table (1): Clinical data, disease markers and laboratory parameters among RA patients

Variable	**Group I (RA)** Mean ± SD
Disease duration (years)	6.51 ± 5.70
Articular manifestations	
Morning stiffness duration (minutes)	120 ± 65.53
Tender joints number	4.9 ± 3.18
Swollen joints number	2.53 ± 1.72
Extra articular manifestations n=40 (%)	
-Rheumatoid nodule	16 (40%)
-Neurological features:	
(Carpal tunnel syndrome)	10 (25%)
-Pulmonary features:	
Pleurisy	10 (25%)
Interstitial lung disease	2 (5%)
-Sicca symptoms	8 (32%)
-Gastrointestinal manifestations:	
Gastritis	35 (87.5%)
-Raynaud's phenomenon	1 (2.5%)
-Cutaneous vasculitis	5 (12.5%)
Disease parameters (Mean ± SD)	
Visual analogue scale (VAS)	43.5 ± 20.32
Disease activity score (DAS)28 ESR	4.63 ± 1.16
Functional impairment	36.63 ± 19.91
Physical damage	27.5 ±18.71
Rheumatoid Arthritis Severity Scale	22.92 ± 16.48

Laboratory parameters:	
RBCs (106/cmm)	4.42 ± 0.54
Hb (g/dl)	10.2 ± 1.3
WBCs (103/cmm)	6.5± 1.6
Platelets (103/cmm)	262.7 ± 83.14
ESR (mm/hr)	38.95 ± 17.5
CRP (mg/L)	30.38 ± 21.57
ALT(U/L)	32.25 ±3.35
AST (U/L)	31.35 ± 4.26
Creatinine (mg/dl)	0.95 ± 0.17
RF titer (U/ml)	25.38 ± 11.71
Anti-CCP Abs titer (U/ml)	34 ± 30.72

SD: Standard deviation**.**

Table (2): Comparison among the studied groups regarding mean serum Coll 2-1 level

Variable	**Group I (RA) (n=40)**	**Group II (OA) (n=20)**	**Group III (Controls) (n=20)**	**F**	**P**	**LSD**
Coll 2-1 (nM)						0.14 NS 1
Mean± SD	186.39±24.2	195.56±28.4	116.57±8.0	**78.8**	**<0.001****	**<0.001** 2**
Range	122 - 227	144.6 – 271.1	99.3–127.5			**<0.001** 3**

F: ANOVA test, LSD: Least significance difference, **: Highly significant (p<0.001).

P1: Group I versus Group II, **P2:** Group I versus Group III, **P3**: Group II versus Group III.

Table (3): Comparisons of mean serum COLL2-1 as regard to disease manifestations

Clinical manifestations	**n(%)**	**Serum Coll2-1(nM)** ***Mean ± SD***	**P-value**
Rheumatoid nodule	Yes 16 (40%)	190.1 ± 13.23	0.06
	No 24 (60%)	177.64 ±26.11	
Neurological features: Carpal tunnel syndrome	Yes 10 (25%)	172.8 ± 23.45	0.07
	No 30 (75%)	186.9 ±23.11	
Pulmonary features:	Yes 10 (25%)	193.22 ±18.14	1.34
	No 30 (75%)	183.2 ±25.9	
Sicca symptoms	Yes *8 (32%)*	191.6 ± 16.28	1.29
	No 32 (68%)	185.28 ±25.66	
Cutaneous vasculitis	Yes 5 (12.5%)	187.34 ± 16.73	0.92
	No 35 (87.5%)	180.25 ± 25.3	

SD: Standard deviation, n: Number, nM: Nanomolar

Table (4): Correlations of serum Coll 2-1 level with RA patients' demographic data, clinical features, laboratory parameters and Larsen score

Variable	Group I (RA) (n=40)	
	R	**P**
Age	0.64	<0.001**
Disease Duration	0.36	0.02*
Morning stiffness duration	0.26	0.01*
Tender joints number:	0.33	0.04*
Swelling joints number:	0.40	0.01*
VAS	0.39	0.01*
DAS 28 ESR	0.43	0.006*
Functional impairment	0.61	0.001**
Physical damage:	0.46	0.003**
RASS	0.23	0.01*
Hb	0.16	0.33 NS
ESR	0.43	0.006*
CRP	0.42	0.007*
RF titer	0.08	0.61 NS
Anti CPP titer	0.23	0.16 NS
Larsen score	0.45	0.01*

r: Pearson's & spearman's correlation coefficient

NS: Non-significant (p>0.05) * Significant (p<0.05) ** highly significant (p<0.001)

Table (5): Comparisons of Coll 2-1 level regarding disease activity in group I

Disease activity grading		N	Coll2-1 nM Mean±SD	F	P
RA activity:	Remission (< 2.6)	2	172.1±19.66		
(DAS 28)	Low Disease Activity (2.6 - 3.2)	3	174.73±34.96		
	Moderate Disease Activity (>3.2-5.1)			3.73	0.02*
	High Disease Activity (>5.1)	20	178.76±24.02		
		15	**201.21±16.23**		

SD: Standard deviation F: ANOVA test NS: Non significant (P>0.05) *Significant (p<0.05)

Table (6): Comparison of Larsen score grading among RA patients regarding mean serum COLL2-1

Variable	Grade 0-2 (*n*=23)	Grade 3-5 (*n*=17)	F- ratio	P- value
Coll 2-1 nM				
Mean ± SD	174.98 ± 24.53	203 ± 10.40	**19.38**	**0.0009***
Range	122- 217	193- 227		

Discussion

RA is characterized by synovitis and joint tissue destruction**.** Because cartilage loss is the hallmark of RA, thus the destruction and remodeling of articular cartilage in arthritis involves increased cartilage matrix lysis and synthesis. This can be monitored by measurement of cartilage-derived synthesis and degradation products of matrix molecules released into synovial fluid (SF) and serum **(12)**.

In this work, there were highly statistically significant increase in the mean serum Coll2-1 levels among RA and OA patients compared to the healthy controls (p= 0.001 each). No difference was found between the mean serum Coll 2-1 level between RA and OA (p=0.14).

In agreement with this outcome a previous study **(13)** reported that in OA and RA, the serum Coll2-1 levels were found to be significantly increased compared to the controls of the same range of age indicating that the rate of type II collagen degradation is increased in both diseases. They also observed the diagnostic value of Coll2-1 whose concentration increases in OA population by comparison to age-matched healthy subjects. In addition, the authors notified that neither the age and nor the gender modified the Coll2-1 serum level in healthy subjects aged from 20 to 65 years.

Concerning disease manifestations of our RA patients. non- significant differences of mean serum COLL2-1 levels were reported among RA patients regarding the presence or absence of some clinical manifestations [rheumatoid nodules (p=0.06), neurological features (p=0.07), pulmonary features (p=1.34), sicca symptoms (p=1.29) and cutaneous vasculitis (p=0.92)].

In this study, we found a statistically significant positive correlation between serum level of Coll2-1 in RA patients with patients' ages (***r*=0.64, p=<0.001).** This

finding corroborated previous studies demonstrating an increase of type II collagen breakdown products in the urine **(14),** synovial fluid **(15)** and cartilage explants **(16)** of OA patients.

In the same way, assessing the relationship between serum Coll2-1 level with disease activity and severity of RA patients can be a start to understand and describe the significance of collagen type II degradation markers in predicting future progression and complications and thus taking early treatment measures to reduce those complications.

A potential role of Coll2-1 in RA has been determined as its levels significantly correlated with DAS28 (***r***= 0.43, p= 0.006). Moreover, the higher level of the disease activity of RA patients, the higher levels of Coll2-1 indicating the possible benefit of using serum Coll2-1 levels in monitoring RA disease activity.

In 2003 **(17),** some authors reported that levels of cartilage degradation products in early RA were not elevated above levels in OA. They also stated that there is evidence of extensive changes in extracellular matrix turnover involving both proteoglycan and Type II collagen. Levels of the C2C collagen II cleavage neoepitope correlate with measures of local and systemic inflammation and with synovial fluid MMP-1 and TNF levels, directly implicating these molecules in Type II collagen cleavage in vivo in inflammatory arthritis.

In this study, we found statistically significant positive correlations of serum level of Coll2-1 among RA patients with duration of morning stiffness (***r***=**0.26, p= 0.01*),** tender joints number (***r***= **0.33, p= 0.04)** swollen joints number **(*r*=0.40, p=0.01)** and acute phase reactants ESR and CRP (***r***= **0.43, p= 0.006 and *r*= 0.42, p=0.007** respectively).

This may coincide with our finding of a significant positive correlation between Coll2-1 and disease duration (***r***= **0.36**, p=**0.02)** in our RA patients.

However, others reported that **serum Coll2**-1 did not significantly correlate with CRP levels (13).

In our study there were positive correlations of the mean Coll 2-1 serum level with Larsen radiological grading (***r***=0.45, p= 0.01*****), RA severity assessed by RASS (***r***=0.23, p=0.01), functional impairment (***r*=0.61, p=0.001**)** and physical damage (***r***=0.46, p=0.003) in RA patients being associated with most severe changes.

In the current study; significant differences were reported between RA patients with different Larsen score grading as regard mean serum COLL2-1 (P=0.0009).

A subgroup of patients with RA (3%–27%) have elevated levels of antibodies against fibrillar collagen type II (CII) (anti-CII), especially around the time of RA diagnosis, whereafter levels decline (**18)**.

In (2016), some investigators reported that anti-CII was associated with higher CRP values at baseline and the first follow-up visits; and the same was evident for ESR, DAS28 and DAS28CRP among RA patients. Anti-CCP on the other hand was associated with higher disease activity later during the 5-year follow-up and with CRP and ESR during the full period. Thus, they concluded that the association of anti-CII with a distinct RA phenotype characterized by acute but transient inflammation around the time of diagnosis (19).

Although anti-CII were not investigated in our study, among our RA patients, we also observed insignificant correlations of serum level of Coll2-1 with RF factor titer (***r***= 0.08, p=0.61) and anti-CCP titer (***r***=0.23, p=0.16).

In 2002, collages observed through their study that Type II collagen (CII) is excessively degraded in RA and OA, an effect believed to result from its cleavage by collagenases which is up-regulated in experimental models of RA (**20)**.

Some investigators found increased levels of C-terminal crosslinking telopeptide of type II collagen (CTX-II) in in urine of active RA patients, and these levels correlated with the extent of joint destruction **(21)**.

Moreover; collages in 2015 **(22)** described that anti-CII bound to CII in surface bound immune complexes (IC) can induce pro-inflammatory cytokines and chemokines from mononuclear cells (MNC) and polymorphonuclear granulocytes (PMN) thus, Anti-CII are functionally active.

In fact, some few studies measured levels of collagen degradation products before and after applying different therapeutic methods to assess the effect of these therapeutic methods in slowing down the process of collagen degradation and its reflection on levels of collagen degradation products in serum, thus they further prove that Coll2-1 resulting from cartilage degradation may be used in monitoring the response to specific treatment. Serum Coll2-1 was measured before and after PRP injection in patients suffering from knee OA and the authors concluded that the reduction in the serum

Coll2-1 following intra-articular PRP injection was significant **(23)**.

Conclusion:

This study highlighted the importance of Coll 2-1 biomarker in reflecting disease activity and the destructive processes emerging in the joints of RA patients. It could be a promising tool in the pathogenesis of significant joint activity signaling cartilage and joint destruction.

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