ARAŞTIRMA MAKALESİ/ORIGINAL RESEARCH

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Cartilage Degradation Biomarkers are Elevated in Younger Adults with Patellofemoral Pain Syndrome

Patellofemoral Ağrı Sendromu olan Genç Erişkinlerde Kartilaj Yıkım Biyobelirteçleri Yükselmektedir

Elif Aydın[1], Çiğdem Yenisey[2], Serkan Sabancı[3], İmran Kurt Ömürlü[4], Gülcan Gürer[1]

[1] Aydın Adnan Menderes University, Department of Physical Medicine And Rehabilitation, Aydın, Turkey.
[2] Aydın Adnan Menderes University, Department of Biochemistry, Aydın, Turkey.
[3] Turhal State Hospital, Clinic of Phisical Medicine and Rehabilitation, Tokat, Turkey.
[4] Aydın Adnan Menderes University, Department of Biostatistics, Aydın, Turkey.

ABSTRACT

Objective: Little is known regarding the altered cartilage composition in patients with patellofemoral pain syndrome. Biomarkers can identify early stages of cartilage damage before the overt morphological changes develop. We investigated cartilage degradation biomarkers in order to reveal cartilage damage in patellofemoral pain syndrome.

Method: Serum samples of twenty patients with patellofemoral pain syndrome and twenty healthy control subjects obtained and four different assays were used: Serum levels of C-terminal cross-linked telopetides of type-II collagen (sCTX-II), cartilage oligomeric matrix protein (sCOMP), Collagen Type II- specific neopeptide (sC2M) and Chondroitin sulfate epitope 846 (sCS846). Pain status and functional status were assessed with VAS, The Western Ontario and McMaster Universities Arthritis Index (WOMAC), Kujala patellofemoral scoring system (PFSS) and timed up and go test (TUG).

Results: Significant increases in serum cartilage degradation biomarkers except sCTX-II were observed in patellofemoral pain syndrome. In correlation analysis, there were not any significant association between pain scores, functional status and biomarker levels except, a reverse relationship between sC2M levels and the TUG scores.

Conclusion: Higher levels of cartilage degradation markers revealed ongoing cartilage destruction in patients who suffer patellofemoral pain syndrome and reflect altered cartilage composition in these patients.

Keywords: anterior knee pain, biochemical markers, cartilage, knee, patellofemoral pain syndrome

ÖZ

Giriş: Patellofemoral ağrı sendromu olan hastalarda değişen kıkırdak yapısı ile ilgili çok az şey bilinmektedir. Biyobelirteçler, açık morfolojik değişiklikler gelişmeden önce kıkırdak hasarının erken aşamalarını belirleyebilir. Bu çalışma ile patellofemoral ağrı sendromunda kıkırdak hasarını ortaya çıkarmak için kıkırdak yıkım biyobelirteçlerini araştırdık. **Yöntem:** Bu çalışmada COVID-19 pnömonisi olan 179 hastanın eşlik eden nörolojik bulgu, muayene özellikleri ve laboratuar parametreleri retrospektif olarak değerlendirildi.

Bulgular: Patellofemoral ağrı sendromu olan yirmi hasta ve yirmi sağlıklı kontrol deneğinin serum örnekleri alındı ve dört farklı test kullanıldı: Serum seviyeleri C-terminali çapraz bağlı telopetid tip II kollajen (sCTX-II), kıkırdak oligomerik matriks proteini (sCOMP), Kollajen Tip II'ye özgü neopeptit (sC2M) ve Kondroitin sülfat epitopu 846 (sCS846). Ağrı durumu ve fonksiyonel durum VAS, The Western Ontario ve McMaster Universities Artritis Index (WOMAC), Kujala patellofemoral skorlama sistemi (PFSS) ve time up and go testi (TUG) ile değerlendirildi.

Sonuç: Patellofemoral ağrı sendromunda sCTX-II dışında serum kıkırdak degradasyon biyobelirteçlerinde önemli artışlar gözlendi. Korelasyon analizinde, ağrı skorları, fonksiyonel durum ve biyobelirteç seviyeleri arasında anlamlı bir ilişki yoktu.

Anahtar Kelimeler: ön diz ağrısı, biyokimyasal belirteçler, kıkırdak, diz, patellofemoral ağrı sendromu

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Correspondence: Elif Aydın, Aydın Adnan Menderes University, Department Of Physical Medicine And Rehabilitation, Aydın, Turkey.
E-mail: drebulak@yahoo.com

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INTRODUCTION

Patellofemoral pain syndrome (PFP) is an increasing musculoskeletal problem among young and physically active population. This condition is defined as retro-or peripatellar diffuse pain aggravated by activities that require excessive knee flexion, such as kneeling, squatting, prolonged sitting and stair climbing. The incidence is reported as 4-7 % in highly physically active population that demands an explanation with regards to a possible etiology (1).

Patellofemoral pain syndrome is an umbrella term that can be subdivided into (i) those patients with definite articular surfacedamage(i.e. chondromalacia patella) (ii) those with variable articular surface damage (i.e. lateral facet syndrome) and, (iii) those with rarely articular surface damage (i.e. retinacular pathology, minor tracking variants) (2). Increased biomechanical loads on patellofemoral joint have long been suggested as the possible cause (3). However to date arthroscopy and MRI techniques have been identified cartilage degeneration in only a portion of patients with PFP (4-6).

There are similar cartilage changes in PFP and early-stage osteoarthritis (OA) which suggest excessive cartilage stress in both situations (7). Some authors have been suggested PFP as a preliminary form of patellofemoral OA (8, 9). In early phases of OA an increase in the water content and a disruption at the surface layer of the cartilage is observed. At this very early stage, plain radiograph and standard MRI techniques do not detect early cartilage changes and joint damage. This may explain why former studies could not detect morphological changes in some of the PFP patients. From this point of view biomarkers have drawn great interest in recent years, because such molecular markers can detect early cartilage changes (10-12).

A biomarker refers to a characteristic that objectively measured in biological fluids. They can reflect cartilage, bone and synovial degradation or synthesis. To date, biomarkers that are found to be promising in the identification of early cartilage changes in OA. In a meta-analysis of 7 studies, serum oligomeric matrix protein (sCOMP) a non-collagen biomarker for cartilage degradation was found elevated in those with radiologic stage of Kellgren Lawrence (K/L) grade 1 (12). In a different study, serum cartilage type II procollagen carboxy propeptide (sCPII) was found decreased in those with K/L grade 2 compared to K/L grade 1. In the same study serum hyaluronic acid (sHA) was found increased in K/L grade 2 compared to K/L grade 1 (10). Likewise biomarkers could be helpful in demonstrating cartilage changes in PFP but as far as we know there is limited data in this field. The only study we found has identified increased levels of sCOMP in chondromalacia patella (13).

Considering the high prevalence of PFP among the young population, there is limited evidence addressing the structural cartilage changes associated with this condition. The exact pathogenesis of PFP should be enlightened in order to develop better treatment options. Because of the young age of these patients morphological changes are not prominent on patellar cartilage in PFP (14, 15). It could be hypothesized that cartilage degradation markers may be more useful in identifying early cartilage changes and can help us understand the pathogenesis of PFP.

In this present study, we aimed to establish alteration of cartilage composition in patients with PFP. For this purpose we have used an approach to detect cartilage degradation biomarkers in volunteers with PFP and compared with healthy control subjects.

METHODS

Participants

A total of twenty individuals (13 women, 7 men) with anterior knee pain lasting more than 6 months were included in the study. All participants were aged between 21 and 45 years. Patients were diagnosed as PFP if they have anterior knee pain during activities that require knee flexion such as, squatting, stair climbing, running, cycling or prolonged sitting with flexed knees. Age and sex matched healthy volunteers were recruited as a control group. Those with recent knee surgery, patellar dislocation history, suspicion of the meniscus or ligament lesion, patellar tendon pathology, osteoarthritis and spinal radicular pain

were excluded. Individuals who were older than 45 years old were also excluded in an attempt to avoid increased levels of cartilage biomarkers due to degenerative changes.

Clinical Outcomes

Knee pain was assessed by using visual analogue scale (VAS, 0 to 100) at rest, after prolonged sitting and during stair climbing. The clinical assessment of PFP was also done with The Western Ontario and McMaster Universities Arthritis Index (WOMAC). It is a self-administered questionnaire consisting of 24 items for pain, stiffness and physical function. Higher scores represent worse clinical status.(16) The functional status of the subjects was determined by Kujala patellofemoral scoring system (PFSS) and timed up and go test (TUG). The Kujala PFSS is a 13-item screening instrument designed to assess patellofemoral pain in adolescents and young adults. Total scores range from 0 to 100. Higher scores indicate better functional status (17, 18). The TUG is commonly used to assess an individual's mobility. It measures the time (in seconds) taken by a subject to rise from an armchair, walk at a comfortable and safe pace with his/her regular footwear to a line on the floor three meters away, turn and walk back to the chair and sit down again. The TUG was repeated two times and the average score was taken as the final score. A faster time indicates a better functional performance (19).

Assay of Biomarkers

Four different assays were used in order to reveal cartilage degradation. Serum levels of C-terminal cross-linked telopetides of type-II collagen (sCTX-II) (Elabscience, USA), cartilage oligomeric matrix protein (sCOMP)(Elabscience, USA), Collagen Type II- specific neopeptide (sC2M) (Mybiosource, USA) and Chondroitin sulfate epitope 846 (sCS846) (Mybiosource, USA) levels were measured using an enzyme linked immunosorbent assay (ELISA). Venous blood was withdrawn from both groups and centrifuged at 1000 g for 15 minutes. Serum samples were placed in separate tubes immediately and stored at -80C° until measurement. The ELISA process was performed according to the manufacturer's instructions. Absorbance was evaluated at 450 nm via the ELISA reader.

Statistical Analysis

The suitability of the quantitative data for normal distribution was examined by Kolmogorov-Smirnov test. Intergroup comparisons of normally distributed variables were performed by independent samples t test and descriptive statistics were shown as mean ± standard deviation. The Mann Whitney U test was used for the comparison of non-normally distributed variables between groups and descriptive statistics were given in median (25-75 percentiles). The chi - square test was used to compare the gender variable according to the groups and the results were presented in frequency (%) format. The relationship between the variables was analyzed by Spearman correlation analysis. The results were considered statistically significant when $p < 0.05$.

RESULTS

Demographic variables of the participants are shown in Table 1. The median pain duration of patients with PFP was 2 (0.5-4) years. Visual analogue scores of the patients were; 4 (1.5-5.25) at rest, 6 (3.0-8.0) at prolonged sitting, 8 (6.0-9.25) at climbing stairs. Patients with PFP describe the most severe pain at climbing the stairs. Regarding the functional status of the patients; TUG time was 10 (8.0-11.25) sec, WOMAC score was 45.5 (36.75), and Kujala score was 55 (49.25-61.75).

Table 1 : Demographic Characteristics of the Participants

	PFP group (n= 20)	Control group (n= 20)	P
Age (years)	33.11 (7.76)	32.55 (7.01)	.672
BMI (kg/m^2)	23.82 (4.57)	22.12 (4.47)	.607

Data expressed in mean (SD), PFP : Patellofemoral pain, BMI : body mass index

Further analysis of biomarkers showed that; levels of COMP (Fig 1), C2M (Fig 2) and CS846 (Fig 3) in patients with PFP were significantly different from healthy adults of the same age and sex (Table 2). However, no significant difference was found between the two groups in terms of CTX-II levels (Table 3).

Table 2: Comparison of Cartilage Biomarkers in Serum Blood Samples of Study and Control Groups

	PFP (N:20)	Control (N:20)	P
CTXII	4.62 (1.68)	3.82 (1.97)	.172
COMP	11.01 (7.77-22.24)	2.54 (1.62-4.54)	<0.001
C2M	199.98 (98.34-346.17)	54.7 (43.00-57.25)	<0.001
CS846	15.78 (11.79-20.61)	6.26 (5.74-9.14)	<0.001

Data are expressed in mean ± standard deviation or median (25th-75th percentiles), PFP : Patellofemoral pain, CTX-II : C-terminal cross-linked telopetides of type-II collagen, COMP : cartilage oligomeric matrix protein, C2M : Collagen Type II- specific neopeptide, CS846 : Chondroitin sulfate epitope 846

Table 3: Correlation Coefficients of Serum Cartilage Biomarker Levels and Clinical Parameters

	BMI	Duration	VASr	VASs	VASc	TUG	WOM-AC	Kujala
CTXII	266	046	087	257	246	077	304	-454
COMP	-156	115	392	213	080	-222	050	133
C2M	129	090	177	410	-063	-521*	015	-327
CS846	339	297	046	261	250	236	-057	-051

BMI : body mass index, VASr : visual analogue scale at rest, VASs : visual analogue scale after prolonged sitting, VASc : visual analogue scale during climbing the stairs, TUG : timed up and go test, WOMAC : The Western Ontario and McMaster Universities Arthritis Index, CTX-II : C-terminal cross-linked telopetides of type-II collagen, COMP : cartilage oligomeric matrix protein, C2M : Collagen Type II- specific neopeptide, CS846 : Chondroitin sulfate epitope 846, * P<0.05

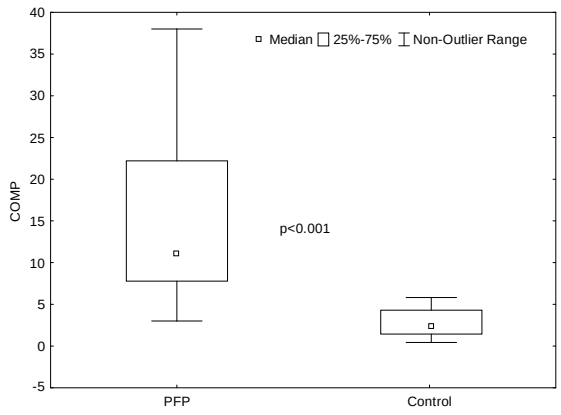

Figure 1. Comparison Serum COMP Levels in PFPand Control Groups

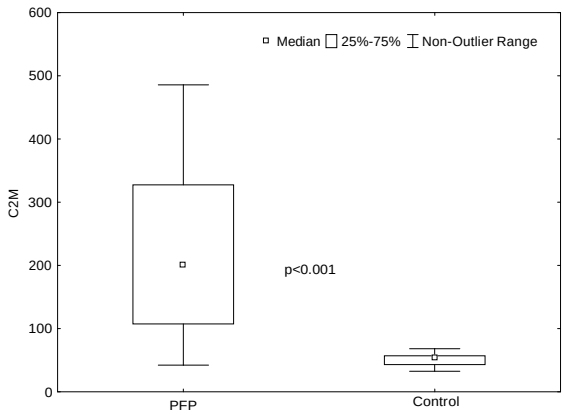

Figure 2. Comparison Serum C2M Levels in PFPand Control Groups

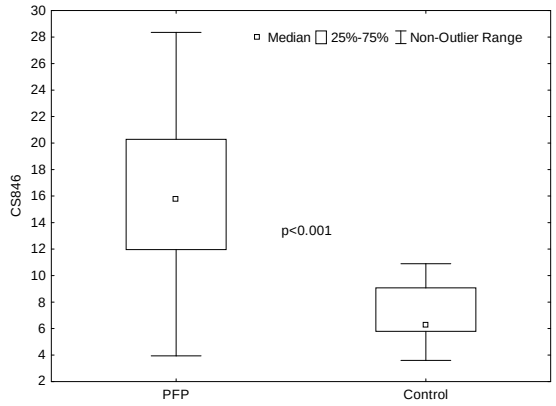

Figure 3. Comparison Serum CS846 Levels in PFPand Control Groups.

In correlation tests, it was found that with increased TUG scores,serum C2M values were decreased.

DISCUSSION

The purpose of the present study was to determine the level of cartilage degradation biomarkers in patients with PFP and compared with healthy individuals. The most prominent result of this study was markedly higher levels of cartilage degradation markers in PFP group. Elevated levels of serum sCOMP, sC2M, and sCS846 revealed ongoing cartilage destruction in patients who suffer PFP. The elevated serum cartilage degradation biomarkers that we found in the PFP group reflect altered cartilage composition in these patients.

Long-term follow-up studies have been revealed lack of morphological cartilage damage in PFP (20, 21). It has been suggested that because of the young age of the patients with PFP, changes in cartilage composition might be more prominent than morphological cartilage defects. Based on this hypothesis, a quantitative magnetic resonance study has been performed to investigate the cartilage composition in patients with PFP. Patellar and femoral cartilage relaxation times in T1ρ and T2 mapping have been compared in patients with PFP and healthy control subjects. Unfortunately, no significant difference was observed in this patient group compared to the control group (22). In addition, a biomarker study has been revealed elevated sCOMP levels, which indicate articular cartilage degradation in 18 patients with chondromalacia patella (13).

There are plenty of data associating early stages of cartilage damage with higher sCOMP levels in different joints. Femoroacetabular impingement is suggested as a preliminary form of hip OA and a recent meta-analysis revealed that, COMP was positively associated with femoroacetabular impingement even after adjusting for concurrent knee and hip OA. Serum COMP levels have also been found in association with pre-radiographic hip OA (23, 24). The relationship between cartilage damage and five different cartilage destruction markers was investigated in patients who underwent knee arthroscopy or total knee arthroplasty. The authors concluded that among these biomarkers sCOMP and sHA levels are most successful predicting early cartilage damage (25). Based on these previous data, the elevated sCOMP levels that we found in patients with PFP reveal significant cartilage damage which could be a possible early predictor of OA at this site.

CTX-II is predominantly known as a cartilage degradation marker. However, in this study, we observe a significant increase in serum cartilage destruction biomarkers of patients with PFP except CTX-II levels. In a 5-year longitudinal study, OA patients were divided into two groups as progressors and non-progressors, and serum tip II A prokollajen N-terminal propeptid (PIIANP), and CTX-II levels were measured at baseline, 2nd, 3rd, and 5th years in both groups. Increased serum PIIANP and urinary CTX-II levels were found to be consistent with progressive OA over 5 years. In our study, we could not find a significant relationship between sCTX-II levels and PFP. This may be because we look at serum CTX-II levels, not urinary CTX-II. A study by Luo et al shows that serum CTX-II levels and urinary CTX-II levels may differ from each other and serum CTX-II has a limited value (26).

Another important point about CTX-II is that the unique release pattern and its relationship with metabolic bone biomarkers which are different

from other cartilage degradation markers (27, 28). There is a strong correlation between CTX-II levels and bone degradation markers, and therefore it has been suggested that CTX-II levels do not only reflect cartilage destruction but are primarily released from calcified cartilage by osteoclastic resorption (10, 27). This may be another reason why CTX-II levels in our study did not have any relationship with PFP as seen with other cartilage destruction biomarkers.

Ideally, biomarkers should be able to detect disease severity. In our study, cartilage destruction markers were found to be higher in patients with anterior knee pain compared to those without pain. However, we did not find any significant correlation between cartilage destruction biomarkers and pain duration, pain severity and functional status. Similarly, in a former study that investigates early knee osteoarthritis; serum cartilage type II collagen cleavage by collagenase (sC2C), urinary CTX-II, serum cartilage type IIprocollagen carboxy propeptide (sCPII) and sHA were found to be higher in patients with pain than in patients without pain. However, the researchers did not perform a correlation analysis between cartilage biomarkers and severity of pain (10).

As in every study, the current study has some strong and weak points. The strengths of our study are that we recruit individuals less than 45 years of age to eliminate the contribution of cartilage destruction of other degenerative joints. As, after advanced ages the cartilage destruction biomarker heights may arise from other degenerative joint problems. Furthermore, it is an objective way to investigate cartilage destruction with serum levels of cartilage specific biomarkers. On the other hand, the small sample size is the most important limitation of this study. However, the results revealed a convincing statistical significance. Second limitation, serum samples were collected at any time of the day. Diurnal fluctuation of some biomarkers has been previously reported (29).

Conclusion

Increased serum levels of cartilage degradation biomarkers were found in patients with patellofemoral pain syndrome, suggesting a process leading to cartilage destruction in this young active population. Considering that with increasing loss of cartilage, people with PFP might be more prone to degenerative knee problems in the future. This information highlights the importance of early detection and immediate treatment of PFP.

Acknowledgements

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Conflict of Interest

The authors declare that they have no conclift of interest regarding content of this article.

Ethics Committee Approval

The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines. All patients provided written informed consent. Approval was obtained from the local ethics committee (no: 2015/727) and voluntary consent was obtained from all subjects at the beginning of the study.

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Consent to participate

Informed consent was obtained from all individual participants included in the study.

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