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The Relationship Between The Clinical and The Radiological Findings of Gonarthrosis with Adamts5 Protease Enzyme in Synovial Liquid

Gonartrozun Klinik ve Radyolojik Bulgularinin Sinovyal Sividaki Adamts5 Proteaz Enzimi ile İlişkisi

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ABSTRACT

AIM: This study aimed to investigate the relationship between ADAMTS5 levels in synovial fluid and the clinical, radiological, and functional status in patients diagnosed with knee osteoarthritis (OA).
MATERIAL AND METHOD: A total of 240 patients aged 18–75 years who presented with knee pain and were diagnosed with primary knee OA based on the American College of Rheumatology (ACR) criteria between January 2016 and December 2022 were retrospectively evaluated. Patients with previous intra-articular injections, knee surgeries, inflammatory rheumatic diseases, neurological disorders, or malignancies were excluded. A control group was formed from patients with meniscal tears who underwent arthroscopy and were classified as Kellgren-Lawrence grade 0. Synovial fluid samples were obtained from all participants, and ADAMTS5 levels were measured using the ELISA method. The primary outcome measures included radiological OA severity (Kellgren-Lawrence grading), functional status (WOMAC score), and synovial ADAMTS5 levels. The relationships among these parameters were statistically analyzed using non-parametric tests, with p-values <0.05 considered significant.

RESULTS: Synovial ADAMTS5 levels showed a statistically significant correlation with OA stage, patient age, and WOMAC scores ($p<0.05$). However, no significant association was found with sex or affected side. Lower ADAMTS5 levels were observed in more advanced stages of OA and were inversely correlated with functional impairment, suggesting a potential biomarker role for ADAMTS5 in disease progression.

CONCLUSION: Decreasing synovial ADAMTS5 levels with aging may contribute to the pathogenesis of knee OA. These findings support the potential use of ADAMTS5 as a biomarker for evaluating OA progression. Further research involving larger patient populations may facilitate the development of novel therapeutic strategies targeting ADAMTS enzymes in degenerative joint diseases.

Keywords: Osteoarthritis, WOMAC score, ADAMTS5, aggrecanase

ÖZET

AMAÇ: Bu çalışmanın amacı, diz osteoartriti (OA) tanısı alan hastalarda sinovyal sıvıdaki ADAMTS5 düzeyleri ile klinik, radyolojik ve fonksiyonel bulgular arasındaki ilişkiyi değerlendirmektir.

GEREÇ VE YÖNTEM: Ocak 2016 - Aralık 2022 tarihleri arasında, diz ağrısı nedeniyle başvuran ve Amerikan Romatoloji Koleji (ACR) kriterlerine göre primer diz OA tanısı konan 18–75 yaş arası 240 hasta retrospektif olarak değerlendirildi. Eklem içi enjeksiyon öyküsü, geçirilmiş diz cerrahisi, inflamatuvar romatizmal hastalıklar, nörolojik hastalıklar ve malignite varlığı dışlama kriterleri arasında yer aldı. Menisküs yırtığı nedeniyle artroskopi yapılan ve radyolojik olarak OA saptanmayan hastalar (Kellgren-Lawrence evre 0) kontrol grubu olarak alındı. Tüm hastalardan sinovyal sıvı örnekleri alındı ve ADAMTS5 düzeyleri ELISA yöntemiyle ölçüldü. Birincil sonuç ölçütleri arasında radyolojik OA şiddeti (Kellgren-Lawrence derecelendirmesi), fonksiyonel durum (WOMAC skoru) ve sinovyal ADAMTS5 düzeyleri yer almaktadır. Bu parametreler arasındaki ilişkiler, non-parametrik testler kullanılarak istatistiksel olarak analiz edilmiş olup, p-değerleri <0.05 anlamlı olarak kabul edilmiştir.

BULGULAR: Sinovyal sıvılardaki ADAMTS5 seviyeleri ile hastalığın evresi, hastaların yaşı ve WOMAC puanları arasında istatistiksel olarak anlamlı bir ilişki tespit edildi ($p<0.05$). Ancak, sinovyal sıvılardaki ADAMTS5 seviyeleri ile hastaların cinsiyeti ve hastalıklı tarafları arasında istatistiksel olarak anlamlı bir korelasyon bulunmamıştır. Daha düşük ADAMTS5 seviyeleri, osteoartritin ileri evrelerinde tespit edilmiş olup, fonksiyonel yetersizlikle ters korelasyon göstermiştir. Bu bulgu, ADAMTS5'in hastalık progresyonunda potansiyel bir biyobelirteç olarak rol oynayabileceğine işaret etmektedir.

SONUÇ: Sinovyal ADAMTS5 düzeylerinin yaşlanma ile azalması, diz osteoartritinin patogenezine katkıda bulunabilir. Bu bulgular, ADAMTS5'in OA ilerlemesini değerlendirmede potansiyel bir biyobelirteç olarak kullanımını desteklemektedir. Daha geniş hasta popülasyonlarını içeren ileri araştırmalar, dejeneratif eklem hastalıklarında ADAMTS enzimlerini hedefleyen yeni terapötik stratejilerin geliştirilmesini kolaylaştırabilir.

Anahtar Kelimeler: Osteoartrit, WOMAC skoru, ADAMTS5, agrekanaz

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INTRODUCTION

Osteoarthritis (OA) is a chronic degenerative disease characterized by subchondral sclerosis, osteophyte development, and progressive cartilage deterioration, particularly in weight-bearing joints (1). This disorder, alternatively referred to as degenerative arthritis, osteoarthrosis, or hypertrophic arthritis, is characterized by the progressive degeneration of joint cartilage. The condition has the potential to manifest in several synovial joints, with a higher prevalence reported in the knees, hips, foot, spine, and hands. Approximately 40% of persons aged 65 and above experience symptoms of both gonarthrosis and coxarthrosis, with gonarthrosis being more prevalent than coxarthrosis (2).

Unfortunately, our understanding of the pathophysiology and etiology of OA is still inadequate. The initiation of cartilage degradation is believed to be influenced by a combination of metabolic, genetic, biochemical, and biomechanical variables (3). Osteoarthritis (OA) not only induces pain in the joints but also leads to diverse levels of functional impairment and a decline in overall quality of life. The risk of disability linked to osteoarthritis (OA) in older individuals is similar to that of cardiovascular disease. According to recent studies conducted by the World Health Organization (WHO), gonartrhrosis ranks as the eighth most prevalent cause of disability in men and the fourth most common cause of impairment in women (2). Osteoarthritis is a prominent contributor to physical disability, resulting in escalated healthcare costs and a deterioration in overall quality of life.

One often employed approach for assessing the extent of osteoarthritis (OA) involves the examination of joint space using direct X-ray imaging. Nevertheless, given that the results obtained from direct X-rays may not become apparent during the initial phases of the illness, it becomes imperative to employ more precise techniques for timely detection. Currently, magnetic resonance imaging (MRI) is used for this purpose, and specific biochemical markers are also deemed valuable in diagnosing osteoarthritis (OA). Furthermore, the identification of genetic markers that contribute to an individual's susceptibility to the disease can facilitate the utilization of genetic tests for the purpose of early detection. Examining the causes and development of this disease, finding hereditary elements, and determining additional factors that increase the risk have become more and more important for early detection and treatment, therefore preventing substantial socioeconomic damages.

The proteinases belonging to the ADAMTS enzyme family play a crucial role in various physiological and pathological processes within the human body. Its involvement in the degradation of cartilage matrix in conditions like rheumatoid arthritis and osteoarthritis is widely recognized (4). The increasing popularity of A Disintegrin-like and Metalloproteinase with Thrombospondin type-1 motif (ADAMTS) proteinases can be attributed to their significant role in disease pathophysiology (5). The heightened attention towards ADAMTS proteinases can be attributed to their potential as candidate genes in drug development investigations for conditions such as osteoarthritis, as well as their capacity to impede tumor formation in malignancy.

This study focused on ADAMTS5, a member of the ADAMTS proteinase family that has been the subject of investigation in the field of arthritis genesis in recent times. This study aimed to assess the correlation between the functional status, clinical and radiological observations of individuals diagnosed with knee osteoarthritis (OA) who were receiving care at the Orthopedics and Traumatology clinic, and the concentrations of the ADAMTS5 enzyme in the synovial fluid of the knee joint.

MATERIAL AND METHOD

Local Ethics Committee has granted approval for this study (Date and number: 13.04.2016&2016/4). The participants who were part of the study were provided with comprehensive information regarding the research. The study has not received any financial support from any institution or organization, and the scientists have personally funded the expenses associated with the research.

The sample for our study consisted of 240 participants who reported experiencing knee pain from January 2016 to December 2022. The study included individuals within the age range of 18 to 75 who had been diagnosed with primary knee osteoarthritis (OA) based on the criteria established by the American College of Rheumatology (ACR). Additionally, participants who were planned to undergo intra-articular injections or surgery for the knee joint were also included in the study. Patients who did not receive a diagnosis of osteoarthritis (OA) but were undergoing knee arthroscopy for meniscus issues (referred to as Stage 0 patients) were also included in the study.

The study excluded patients who met the following criteria:

1. Individuals that are afflicted with inflammatory rheumatic illnesses
2. Individuals who have undergone intra-articular glucocorticoid injections within the previous year
3. Individuals who have undergone intra-articular hyaluronic acid injections during the previous year
4. Individuals who had already undergone knee joint surgery
5. Individuals afflicted with neurological and neuromuscular disorders
6. Individuals diagnosed with cancers
7. Individuals with primary etiologies of gonarthrosis

The demographic information of the participants involved in the study was documented. Patients were subjected to comparative knee radiographs while bearing weight on their feet in both anterior-posterior and lateral positions, with flexion at 30 degrees. The patients' radiographs were assessed using the Kellgren-Lawrence (K-L) scale, which involved categorizing them into five distinct groups based on their stage, ranging from stage 0 to 4. The Western Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaire was utilized to evaluate the pain, stiffness, and physical functioning of the patients' knee joints.

Synovial fluid samples from study participants' knee joints were stored at -80°C for later analysis. ADAMTS5 levels were measured using a Human ADAMTS5 ELISA Kit, employing micro-wells coated with specific antibodies. The process involved binding the antigen to specific antibodies, adding a biotinylated secondary antibody linked to Streptavidin-HRP, and introducing tetramethylbenzidine (TMB) to produce a color change proportional to the antigen quantity. The reaction was stopped, and absorbance was measured at 450 nm using an ELISA reader to determine ADAMTS5 concentrations based on standard curves. The ELISA procedure involved preparing reagents, standard solutions, and serum samples, then adding serum, ADAMTS5 antibody, and Streptavidin-HRP to designated wells. After incubation and washing, Chromogen solutions A and B were added, followed by a stop solution, and absorbance was measured to quantify serum ADAMTS5 using GEN 5 software.

The data analysis was conducted using IBM SPSS Statistics 17.0. The normality of the distribution of continuous and discrete numerical variables was assessed using the Kolmogorov-Smirnov test, while the homogeneity of variance was examined using the Levene test. The descriptive statistics for continuous and discrete numerical variables were presented using the median (minimum-maximum), whereas for categorical variables, the number (%) was provided. The Mann-Whitney U test was employed to evaluate the disparities among groups in non-normally distributed discrete or continuous numerical variables in cases where there were two independent groups. If there were more than two groups, the Kruskal-Wallis test was utilized to ascertain the significance of the disparity. After obtaining significant results using the Kruskal-Wallis test statistic, Conover's multiple comparison test was utilized to identify the factors responsible for the observed difference. The Spearman's correlation coefficient was employed to examine the presence of statistically significant associations between continuous and discrete numerical variables. The statistical significance of the results was determined to be $p < 0.05$.

RESULTS

Our study involved the evaluation of data from a sample of 240 individuals, with ages ranging from 20 to 85. The patients had an average age of 60.7±17.1 years. Of the total cases, 81 (33.8%) were identified as male, while 159 (66.2%) were identified as female. In 123 (51.3%) cases, the injured side was on the right, in 75 (31.2%) cases it was on the left, and in 42 (17.5%) cases it was bilateral. The data presented in

Table 1: Demographic and Clinical Characteristics of Cases

Variables	n=240
Age (years)	60.7±17.1
Age Range (years)	20-85
Gender	
Male	81 (33.8%)
Female	159 (66.2%)
Side	
Right	123 (51.3%)
Left	75 (31.2%)
Bilateral	42 (17.5%)
Stage	
0	27 (11.3%)
1	54 (22.5%)
2	51 (21.2%)
3	54 (22.5%)
4	54 (22.5%)

indicates that out of the total instances, 27 (11.3%) were classified as Stage 0, 54 (22.5%) as Stage 1, 51 (21.2%) as Stage 2, 54 (22.5%) as Stage 3, and 54 (22.5%) as Stage 4.
A statistically significant disparity in median ADAMTS5 levels was seen across the various stages in our investigation (p<0.001). The median ADAMTS levels of Stage 1, 2, 3, and 4 exhibited a substantial decrease in comparison to Stage 0 (p<0.001). Nevertheless, the distribution of median ADAMTS levels between Stage 1, 2, 3, and 4 did not exhibit any statistically significant disparity (p>0.05).

Table 2: WOMAC Subscale and Total Scores and ADAMTS Levels According to Stages in Cases

Variables	Stage 0	Stage 1	Stage 2	Stage 3	Stage 4	p-value†
WOMAC A	0 (0-1)a,b,c	5 (3-6)d,e,f	10 (7-13)a,d,g,h	15 (11-17)b,e,g,i	18.5 (16-20)c,f,h,i	<0.001
WOMAC B	0 (0-1)a,b,c	2 (1-2)d,e,f	3 (2-4)a,d,g,h	5 (3-6)b,e,g,i	7 (6-8)c,f,h,i	<0.001
WOMAC C	0 (0-4)a,b,c	17 (14-19)d,e,f	33 (29-38)a,d,g,h	50 (45-56)b,e,g,i	66 (62-68)c,f,h,i	<0.001
WOMAC Total	0 (0-6)a,b,c	24 (18-27)d,e,f	46 (39-54)a,d,g,h	70.5 (61-77)b,e,g,i	92 (84-96)c,f,h,i	<0.001
ADAMTS	941.6 (719.5-992.6)a,b,c,j	162.2 (92.1-984.1)j	137.1 (60.3-815.7)a	135.3 (61.4-214.6)b	149.4 (91.3-983.6)c	<0.001

† Kruskal-Wallis test; a: Statistically significant difference between Stage 0 and Stage 2 (p<0.001), b: Statistically significant difference between Stage 0 and Stage 3 (p<0.001), c: Statistically significant difference between Stage 0 and Stage 4 (p<0.001), d: Statistically significant difference between Stage 1 and Stage 2 (p<0.05), e: Statistically significant difference between Stage 1 and Stage 3 (p<0.001), f: Statistically significant difference between Stage 1 and Stage 4 (p<0.001), g: Statistically significant difference between Stage 2 and Stage 3 (p<0.05), h: Statistically significant difference between Stage 2 and Stage 4 (p<0.001), i: Statistically significant difference between Stage 3 and Stage 4 (p<0.05), j: Statistically significant difference between Stage 0 and Stage 1 (p<0.001).

demonstrate a statistically significant and inverse association between Stage and ADAMTS5 (r=-0.315, p=0.004)

Figure 1: ADAMTS Levels According to the Stages of Cases

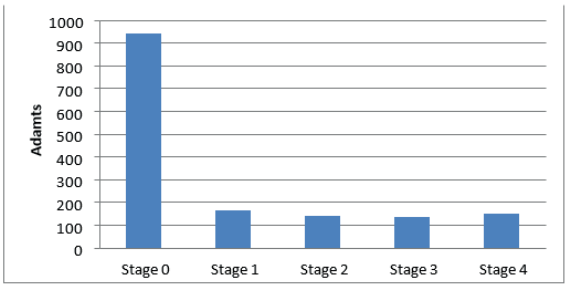


Table 3: WOMAC Subscale and Total Scores and ADAMTS Levels According to Gender in Cases

Variables	Male	Female	p-value†
WOMAC A	12 (0-19)	11 (0-20)	0.710
WOMAC B	3 (0-7)	4 (0-8)	0.458
WOMAC C	36 (0-66)	35 (0-68)	0.741
WOMAC Total	52 (0-92)	52 (0-96)	0.699
ADAMTS	137.1 (73.1-983.6)	155.8 (60.3-992.6)	0.270

† Mann-Whitney U test.

demonstrates that there were no statistically significant disparities between males and females in relation to the median values of WOMAC A, WOMAC B, WOMAC C, WOMAC total, and ADAMTS (p>0.05).

A substantial and negative connection was seen between age and ADAMTS (r=-0.329, p=0.003), as well as between stage and ADAMTS (r=-0.315, p=0.004) (Table 4).

Significant and negative correlations were observed between WOMAC A and ADAMTS (r=-0.305, p=0.006), WOMAC B and ADAMTS (r=-0.278, p=0.013), WOMAC C and ADAMTS (r=-0.322, p=0.004), and WOMAC total and ADAMTS (r=-0.308, p=0.005)

Table 4: Correlation Coefficients and Significance Levels between Age, Stage, WOMAC Subscale and Total Scores, and ADAMTS Levels in Cases

	Correlation Coefficient	p-value†
Age	-0.329	0.003
Stage	-0.315	0.004
WOMAC A	-0.305	0.006
WOMAC B	-0.278	0.013
WOMAC C	-0.322	0.004
WOMAC Total	-0.308	0.005

† Spearman's correlation test.

A substantial and positive correlation was observed between age and stage (r=0.696, p<0.001)

The results indicate that age exhibited statistically significant and favorable associations with WOMAC A (r=0.694, p<0.001), WOMAC B (r=0.706, p<0.001), WOMAC C (r=0.693, p<0.001), and WOMAC total (r=0.700, p<0.001)

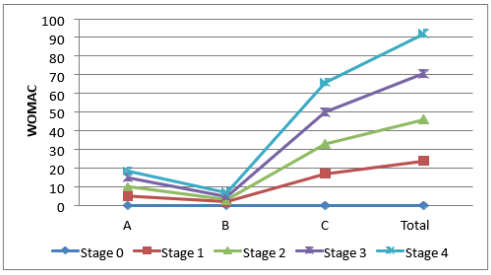
Table 5: Correlation Coefficients and Significance Levels between Age, Stages, and WOMAC Subscale and Total Scores in Cases

	Age	Stage
Correlation Coefficient	p-value†	Correlation Coefficient
Age	-	-
Stage	0.696	<0.001
WOMAC A	0.694	<0.001
WOMAC B	0.706	<0.001
WOMAC C	0.693	<0.001
WOMAC Total	0.700	<0.001

† Spearman's correlation test.

The study found a strong and statistically significant correlation between stage and WOMAC A (r=0.972, p<0.001), WOMAC B (r=0.950, p<0.001), WOMAC C (r=0.978, p<0.001), and WOMAC total (r=0.978, p<0.001)

Figure 2: WOMAC Subscale and Total Scores According to the Stages of Cases



The median ADAMTS levels did not show any statistically significant difference based on the affected side (p=0.074)

Table 6: WOMAC Subscale and Total Scores and ADAMTS Levels According to Sides in Cases

Variables	Right	Left	Bilateral	p-value†
WOMAC A	10 (0-20)a	9 (0-19)b	17.5 (14-20)a,b	<0.001
WOMAC B	4 (0-8)a	2 (0-8)b	7 (4-8)a,b	<0.001
WOMAC C	34 (0-68)a	29 (0-68)b	65 (47-68)a,b	<0.001
WOMAC Total	48 (0-96)a	42 (0-95)b	91 (66-96)a,b	<0.001
ADAMTS	155.8 (60.3-984.1)	157.5 (73.1-992.6)	134.5 (84.9-326.7)	0.074

† Kruskal-Wallis test; a: Statistically significant difference between Right and Bilateral (p<0.001), b: Statistically significant difference between Left and Bilateral (p<0.001).

There was a statistically significant similarity in median ages between female and male patients (p=0.090). Nevertheless, there was a notable disparity in median ages based on the affected side, with the bilateral group exhibiting a higher median age in comparison to the right and left sides (p<0.001). The median ages varied significantly throughout stages (p<0.001), with Stage 0 having a significantly lower median age compared to Stages 1, 2, 3, and 4 (p<0.01). Furthermore, the median age of Stage 1 exhibited a statistically significant decrease compared to Stage 3 and 4 (p<0.01), whereas Stage 2 shown a statistically significant decrease compared to Stage 4 (p<0.001)

Table 7: Ages of Cases According to Gender, Side, and Stages

Variables	Age	p-value
Gender		0.090†
Male	60 (22-84)	
Female	69 (20-85)	
Side		<0.001‡
Right	60 (20-80)a	
Left	60 (21-84)b	
Bilateral	74.5 (67-85)a,b	
Stage		<0.001‡
0	23 (20-28)c,d,e,f	
1	56 (40-74)c,g,h	
2	62 (50-83)d,i	
3	69.5 (47-80)e,g	
4	73 (66-85)f,h,i	

† Mann-Whitney U test; ‡ Kruskal-Wallis test; a: Statistically significant difference between Right and Bilateral (p<0.001), b: Statistically significant difference between Left and Bilateral (p<0.001), c: Statistically significant difference between Stage 0 and Stage 1 (p=0.006), d: Statistically significant difference between Stage 0 and Stage 2 (p<0.001), e: Statistically significant difference between Stage 0 and Stage 3 (p<0.001), f: Statistically significant difference between Stage 0 and Stage 4 (p<0.001), g: Statistically significant difference between Stage 1 and Stage 3 (p=0.005), h: Statistically significant difference between Stage 1 and Stage 4 (p<0.001), i: Statistically significant difference between Stage 2 and Stage 4 (p<0.001).

The median phases between males and females did not show any statistically significant difference (median stage 2) (p=0.731). Nevertheless, a notable disparity in median stages was observed based on the affected side, whereas the bilateral group (median stage 4) exhibited a greater median stage in comparison to both the right (median stage 2) and left sides (median stage 2) (p<0.001).

DISCUSSION

Osteoarthritis is characterized by the progressive disintegration of cartilage, the development of osteophytes, and the sclerosis of the subchondral region, particularly in joints that bear weight (7). Multiple studies have indicated that advanced age is a notable risk factor for osteoarthritis (8-11). Although osteoarthritis affects a little 0.1% of individuals between the ages of 25 and 34, it surpasses 80% in those aged 65 and beyond.

Matrix metalloproteinases (MMPs), especially those abundant in tissue, have a vital function in the deterioration of cartilage in osteoarthritis (OA). Three enzymes, namely Collagenases, Stromelysins, and Gelatinases, are observed to be increased in individuals with osteoarthritis within this family. Collagenases are accountable for the inherent degradation of collagen, stromelysins for the degradation of proteoglycan, and gelatinases, particularly MMP-2 and MMP-9, are primarily responsible for the degradation of denatured collagen (gelatin), but they also contribute to the breakdown of native collagens such as type IV, as well as other extracellular matrix components including elastin, laminin, and fibronectin (12-14).
The proteases ADAM, ADAMTS, and MMP exhibit a close relationship with one another. The ADAMALYSIN group encompasses thrombospondin motif-containing disintegrin and metalloproteinases (ADAMTS) as well as disintegrin motif-containing metalloproteinases (ADAM). The functions of these proteases in the mechanisms of extracellular matrix injury and repair have been widely recognized (15). The actions of ADAMTS enzymes are manifested by the degradation of the extracellular matrix's structural proteins, including collagen, versican, and aggrecan.

Currently, research has shown a strong correlation between ADAMTS and osteoarthritis. Nevertheless, further investigation is required to reveal novel approaches for the diagnosis and treatment of the disease. Hence, our research examined the correlation between osteoarthritis (OA) and ADAMTS5, a constituent of the ADAMTS protease family, which has recently been researched for its influence on the development of arthritis.
In contrast to previous studies involving ADAMTS4 knockout mice, Glasson et al (16). provided evidence indicating that ADAMTS5 knockout mice exhibited resilience to osteoarthritis. The researchers proposed that ADAMTS5, also known as aggrecanase-2, serves as the predominant aggrecanase in mice.
Echtermeyer et al. observed that syndecan-4 stimulates the activation of ADAMTS5 and inhibits cartilage deterioration in mice treated with a syndecan-4-specific antibody. This suggests that inhibiting syndecan-4 could be effective in treating cartilage damage in osteoarthritis (17).
Bau et al. observed a modest elevation in the expression levels of ADAMTS4 and ADAMTS5 in the cartilage of persons diagnosed with advanced knee osteoarthritis, in comparison to the cartilage tissue of healthy individuals (18).
The study conducted by Kevorkian et al. revealed an upregulation of ADAMTS2, ADAMTS12, ADAMTS14, and ADAMTS16 genes in human osteoarthritic cartilage, while a downregulation of ADAMTS1, ADAMTS5, ADAMTS9, and ADAMTS15 genes was seen (19).

The study conducted by Zhang et al. (year) examined the presence of ADAMTS4, ADAMTS5, and their proteolytic product ARGxx in the synovial fluids of 144 patients, which bears resemblance to our own research. The participants were classified into three distinct cohorts according to the extent of cartilage impairment: early, moderate, and advanced phases. The expression levels of ADAMTS4, ADAMTS5, and ARGxx in synovial fluids of patients were assessed through the utilization of ELISA and Western blot techniques. The early-stage OA patient group had notably elevated levels of ADAMTS4 and ARGxx expression. In addition, the levels of ADAMTS4, ADAMTS5, and ARGxx were considerably elevated in the advanced-stage OA patient group compared to the moderate-stage OA patient group. A link was observed between the expression of ARGxx and both ADAMTS4 and ADAMTS5 (20).

The study conducted revealed a statistically significant disparity in the median levels of ADAMTS5 among different phases (p<0.001). The median ADAMTS levels of Stage 1, 2, 3, and 4 exhibited a substantial decrease in comparison to Stage 0 (p<0.001). Nevertheless, there was no significant difference observed in the median ADAMTS levels throughout Stages 1, 2, 3, and 4 (p>0.05). There was a statistically significant negative correlation (r=-0.315, p=0.004) observed between stage and ADAMTS5. The findings of this study indicate a possible association between the lowering of

aggrecan and the development and advancement of osteoarthritis. Our investigation found a statistically significant and negative connection (r=-0.329, p=0.003) between age and ADAMTS5. The findings of this study suggest that there is a negative correlation between age and the concentration of ADAMTS5 in synovial fluid, which is associated with the onset of osteoarthritis.

In the course of our investigation, we have identified a statistically significant and negative association between WOMAC A and ADAMTS5 (r=-0.305, p=0.006), WOMAC B and ADAMTS5 (r=-0.278, p=0.013), WOMAC C and ADAMTS5 (r=-0.322, p=0.004), as well as WOMAC total and ADAMTS5 (r=-0.308, p=0.00). The rise in WOMAC scores as the illness advances, coupled with the statistically significant and negative association between WOMAC scores and ADAMTS5, suggests that ADAMTS5 may play a role in the decline of joint function in osteoarthritis.

In our investigation, there was no statistically significant disparity observed between males and females with regards to the median levels of WOMAC A, WOMAC B, WOMAC C, WOMAC total, and ADAMTS (p>0.05). The observed phenomenon can be ascribed to the even proportion of male and female patients throughout the various stages.

The study findings indicate that there was no statistically significant variation in median ADAMTS5 levels based on the disease's sides (p=0.074). While it was observed that individuals with bilateral involvement exhibited lower levels of ADAMTS5 in comparison to those with unilateral involvement, it is important to note that a statistically significant difference could not be established. This lack of significance may be attributed to the limited sample size of the study.

The results of this study demonstrate a statistically significant inhibitory relationship between ADAMTS5 levels and the stage of osteoarthritis. Nevertheless, additional investigations involving a larger sample size of patients are necessary in order to validate these results.

Research Strengths and Limitations

The substantial sample size of our study (n=240) is a primary strength, enhancing the statistical power of the results and their applicability to a broader array of contexts. This study examined ADAMTS5, a protease that has received less attention than ADAMTS4 in previous research. ADAMTS5 is recognized for degrading aggrecan, albeit to a lesser extent than ADAMTS4. Our research contributes to the expanding evidence that ADAMTS5 may serve as a valuable biomarker for the severity of knee osteoarthritis and its impact on functionality. Utilizing both clinical (WOMAC) and radiological (Kellgren-Lawrence) metrics enhances the comprehensiveness of evaluating disease development and its correlation with biochemical markers. However, there are several issues with our study. The research indicated that ADAMTS5 exhibited a negative correlation with illness stages and WOMAC scores. However, the cross-sectional nature of the study necessitates cautious interpretation of the findings, as they do not allow for causal inferences. These limitations may complicate direct comparisons with studies examining the synergistic effects of ADAMTS4 and ADAMTS5. The bilateral involvement group had reduced ADAMTS5 levels; however, the absence of statistical significance may be attributed.

CONCLUSION

This study aimed to assess the association between clinical and radiological indicators and the ADAMTS5 protease enzyme in synovial fluid among individuals diagnosed with gonarthrosis. Specifically, we investigated the correlation between disease stage and side, WOMAC score, age, patient gender, and ADAMTS5 concentrations in synovial fluid. The study revealed a statistically significant association between ADAMTS5 and the illness stage, patient age, and WOMAC scores. Nevertheless, neither the gender nor the affected sides of the patients exhibited a statistically significant correlation with ADAMTS5. The findings of this study indicate that there is a correlation between the decline in aggrecan levels in synovial fluid and the development and advancement of osteoarthritis as individuals age. In light of forthcoming investigations encompassing a more extensive cohort of individuals, there exists the potential to devise pharmaceutical interventions targeting enzymes implicated in the degradation of cartilage matrix, specifically ADAMTS enzymes, within the context of pathological conditions such as osteoarthritis and rheumatoid arthritis.

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