RESEARCH ARTICLE

Histopathological and immunohistochemical study in the anterior and posterior cruciate ligament of the knee with rheumatoid arthritis in Iraqi patients

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Background: Rheumatoid arthritis (RA) causes structural changes and inflammatory responses which damage the knee tissues that include the cruciate ligaments. Scientists will gain knowledge about ligament involvement in chronic joint diseases through their research to detect these changes.

Objective: The research aims to evaluate histopathological changes together with CD16 and CD68 protein expression and ecto-5'-nucleotidase (NTD/CD73) enzyme function in ACL and PCL tissues from RA patients who receive total knee arthroplasty.

Methods: Fifty ACL and fifty PCL samples were obtained from RA patients classified according to the 2010 ACR/EULAR criteria. The researchers conducted histopathology tests along with immunohistochemistry analysis of CD16 and CD68 markers and NTD enzyme histochemistry tests.

Results: Both ligaments exhibited fibrocyte proliferation, inflammatory infiltration, fibrin deposition, and vascular changes, with more pronounced alterations in the ACL. CD16 positivity reached 92% in the ACL and 96% in the PCL, whereas CD68 was positive in 98% of ACL samples and 94% of PCL samples. NTD activity ranged from weak to strong in both ligaments but showed higher scores in the ACL. Statistical analysis confirmed significant immunohistochemical and enzymatic differences between ACL and PCL.

Conclusion: The ACL and PCL tissues from RA patients show major inflammatory and degenerative damage which affects the ACL more than the PCL. The research results demonstrate how RA affects different ligaments but they do not provide any evidence to support removing cruciate ligaments as a treatment option. The research requires non-RA controls to establish the relationship between enzyme activity and staining intensity.

Keywords: rheumatoid arthritis, anterior cruciate ligament, posterior cruciate ligament, histopathology, CD16, CD68, ecto-5'-nucleotidase

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Introduction

The human knee is a complex structure comprising multiple bones and soft tissue structures [1]. It includes bones, cartilage, ligaments, tendons, and muscles [2]. It has four primary ligaments: anterior cruciate ligament (ACL), posterior cruciate ligament (PCL), lateral collateral ligament (LCL), and medial collateral ligament (MCL). The function of ligaments is to stabilize the knee by resisting forces and moments [3]. ACL bonds the anterior proximal termination of the tibia to the posterior distal feature of the femur. Another ligament is the PCL, which links the posterior proximal exterior of the tibia to the anterior distal external of the femur bone medial. Also, MCL stabilises the distal femur's interior faces to the proximal tibia [4].

Rheumatoid arthritis (RA) is a chronic inflammatory disorder that affects the joints and is associated with swelling, stiffness, and pain. Advanced disease stages can lead to substantial loss of functioning and mobility. RA is an autoimmune disease whereby the body's immune system attacks its tissues [5,6]. The development of RA is driven by changes in the synovium, and aggregation of T lymphocytes and B lymphocytes are also found at a lower percentage [7]. Lymphocyte aggregates are observed in 50-60% of RA patients, and these groups can be surrounded by plasma cells [8]. In contrast, macrophages can infiltrate them, also causing joint erosion, secreting principally proinflammatory cytokines such as TNF-α and IL-1 [9]. 5'-Nucleotidase (NTD) (EC3.1.3.5), also referred to as 5'-ribonucleoside phosphohydrolase, is the enzyme that catalyzes the extracellular conversion of 5'-AMP to adenosine (AD) and is in charge of dephosphorylating extracellular mononucleotides in a wide range of biological systems [10]. In addition to reflecting cell-mediated immunity, AD has a role in the development of lymphocytes and their function, as well as the conversion of monocytes into macrophages [11]. This study aimed to research the histological changes in ACL and PCL and the immunohistochemistry (CD16, CD68) of knee RA patients. In addition, our studies focus on NTD changes in ACL and PCL of patients with RA.

Methods

Ethical consideration

The College of Science, Mustansiriyah University's ethics committee approved this work (Ref. BCSMU/0824/0005), according to the Declaration of Helsinki.

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Patients consent statement
Informed consent was obtained from all participants.

Study design and participants
The study included 50 randomly selected patients: 31 males with an age range of 59-79 years and 19 females with an age range of 53-80 years with RA from Ghazy Al-Hariri Hospital for Surgical Specialties/Medical City.

The 2010 ACR/EULAR Classification Criteria served as the basis for rheumatoid arthritis diagnosis through their evaluation of joint symptoms and serological markers and acute-phase reactant levels and symptom duration. The research team obtained clinical information from each patient through three categories of data which consisted of disease duration and morning stiffness status and their current medication list including corticosteroids and csDMARDs and biologic agents when needed. The laboratory tests consisted of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibodies (anti-CCP) and C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). These parameters were obtained from the patients' medical records to ensure accurate classification and homogeneity of the cohort.

Type of sampling and reasons for selection
ACL and PCL knee tissue samples were obtained from all RA patients for histopathological and Immunohistochemical studies during knee replacement.

Inclusion criteria
Patients were diagnosed by a professional doctor (Figure 1).

Exclusion criteria
Patients with malignancy, liver, kidney, or cardiac issues, as well as those with any other autoimmune inflammatory illness, were excluded from this study.

Data collection and clinical assessment
Tissue samples were obtained from formalin-fixed 10% paraffin-embedded tissue blocks, which were then cut into sections five μm thick. These sections are routinely stained with Haematoxylin and Eosin, as outlined in [12], for histopathological study and Immunohistochemical staining was deparaffinized in xylene, then decreasing grades of ethanol and incubated with phosphate-buffered saline. Antigen retrieval as required by the primary antibody. for histopathological study and immunohistochemical staining were deparaffinized in xylene, followed by treatment with decreasing grades of ethanol, and then incubated with phosphate-buffered saline. Antigen retrieval as required by the primary antibody.

Immunohistochemistry Protocol
The laboratory team executed immunohistochemical staining through established methods which they used to achieve consistent results. Sections were deparaffinized, rehydrated, and subjected to heat-induced antigen retrieval using citrate buffer (pH 6.0) for 20 minutes at 95°C. The primary antibodies included anti-CD16 (clone EPR21884, Abcam, catalog no. ab218108; dilution 1:200) and anti-CD68 (clone KP1, Abcam, catalog no. ab955; dilution 1:300). The sections underwent 60 minutes of primary antibody incubation at room temperature before they underwent Abcam HRP/DAB kit polymer-based detection with DAB chromogen system. The study used human colon adenocarcinoma tissue as a positive control for CD16 staining and tonsillar tissue as a positive control for CD68 staining. The researchers omitted the primary antibody from their samples to serve as their negative control samples. Two independent histopathologists evaluated all slides without knowing the results to determine their reliability through Cohen's kappa coefficient for interobserver agreement assessment.

The staining protocol utilised monoclonal antibodies for CD16 and CD68, sourced from a commercially available kit (Abcam, Pathn Situ). Tissues from the anterior cruciate ligament (ACL) and posterior cruciate ligament (PCL) were fixed and dehydrated using a mixture of absolute alcohol and cold acetone for varying durations before being embedded in paraffin wax.

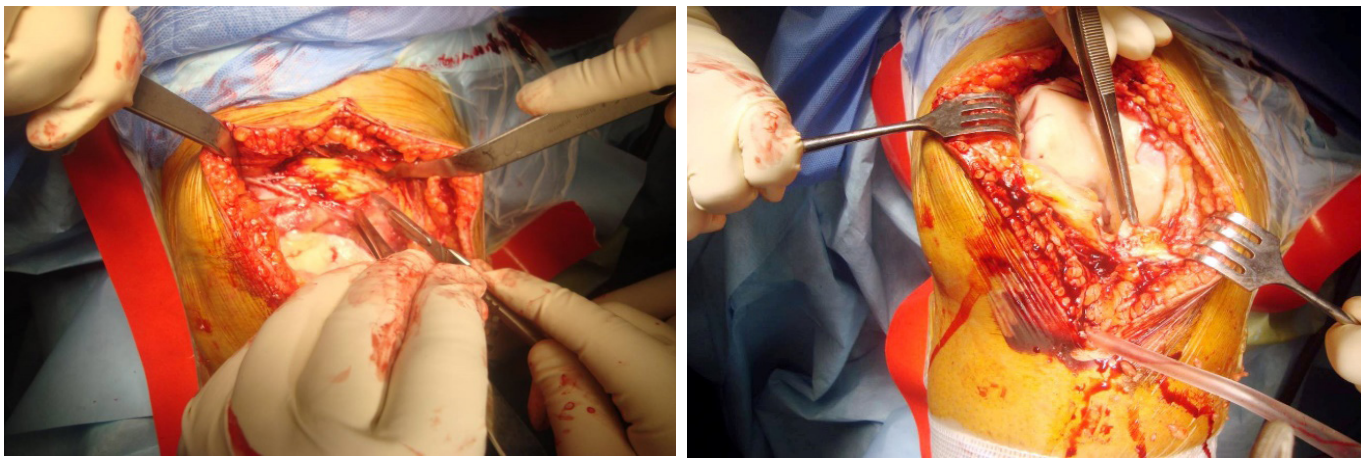

Fig. 1. Knee tissues of RA patient during operation of total knee replacement

NTD Enzyme Histochemistry Protocol

The research focused on ecto-5'-nucleotidase (CD73/NT5E) which functions as an extracellular membrane-bound nucleotidase that transforms AMP into adenosine. The paraffin sections required 5 µm thickness for deparaffinization and rehydration before they received the reaction mixture which contained 5'-AMP as the substrate and lead nitrate as the capture reagent according to the Wachstein–Meisel method. The reaction took place at 37°C for 45 minutes which produced a black granular precipitate that showed the enzyme was active. Slides were rinsed in Tris buffer, counterstained with hematoxylin, and mounted. The researchers evaluated enzyme activity through a three-point scoring system which operated at a semi-quantitative level.

0 = no activity, 1 = weak activity,2 = strong activity. Two researchers who did not know the results evaluated the staining intensity of the samples and they used Cohen's kappa statistic to measure their agreement [13].

Statistical Analysis

Data were analyzed using SPSS version 26 (IBM Corp., Armonk, NY, USA). The chi-square test analyzed CD16 and CD68 expression scores between ACL and PCL groups by examining categorical variables. Effect sizes together with 95% confidence intervals used to determine the size and exactness of ligament type differences. Cohen's kappa coefficient assessed the interobserver reliability between IHC and enzyme histochemistry scoring results. The value 0.05 established as the significant p-value threshold which they used for all their statistical evaluations.

Results

Histopathological study of ACL and PCL

Histological examination for ACL biopsy of knee RA patient shows congestion of blood vessels and disordered location of collagen fibers. On the other hand, all sections illustrate the degeneration and proliferation of fibrocytes. In addition, inflammatory cell infiltration with degeneration changes. Also, fibrin deposition and neo-formation of blood vessels can be found in Figure 2.

Our results in Figure 3 for PCL samples of knee RA patients revealed the proliferation of fibrocytes and deposition of fibrin in many areas, with aggregation of inflammatory cells. All study samples also show edema, inflammatory cell infiltration, and increased blood vessels.

Immunohistochemical study of CD16 and CD68

The results of the current study showed that the highest rate of positive expression for CD16 was in the ACL and PCL of knee RA patients in Table 1, as the number of positive samples of ACL reached 46 cases with a rate of 92%, [14] (32%) cases within Score +1, and 30 (60%) within score +2 versus 4 (8%) case with a loss of expression], compared

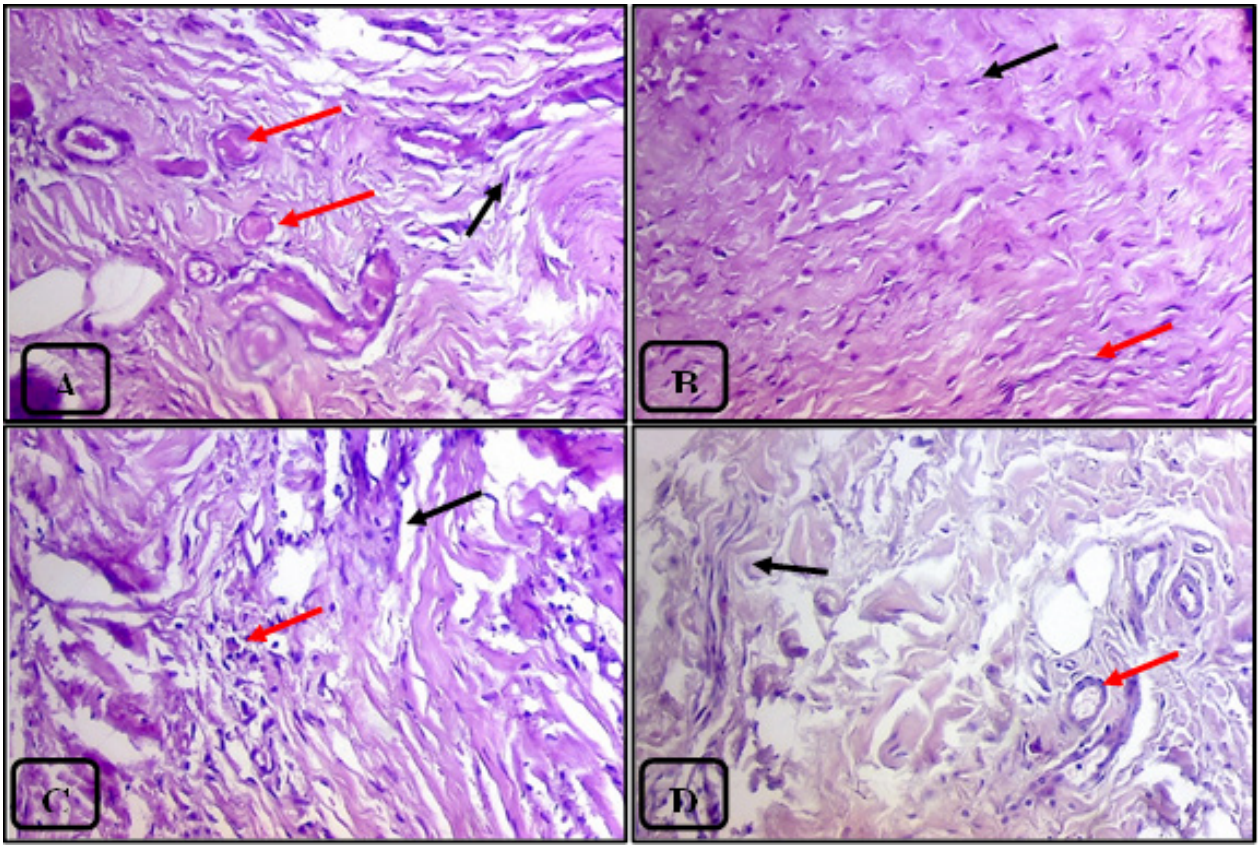

Fig. 2. Section in the ACL of knee RA patient demonstrates: (A) congestion of blood vessels (red arrows) with disordered locating collagen fibers (black arrow), (B): degeneration (red arrow) and proliferation of fibrocytes (black arrow), (C): inflammatory cells infiltration (red arrow) with degeneration changes (black arrow), (D): deposition of fibrin (black arrow) and neo-formation of blood vessels (red arrow) (Haematoxylin and Eosin staining, X10).

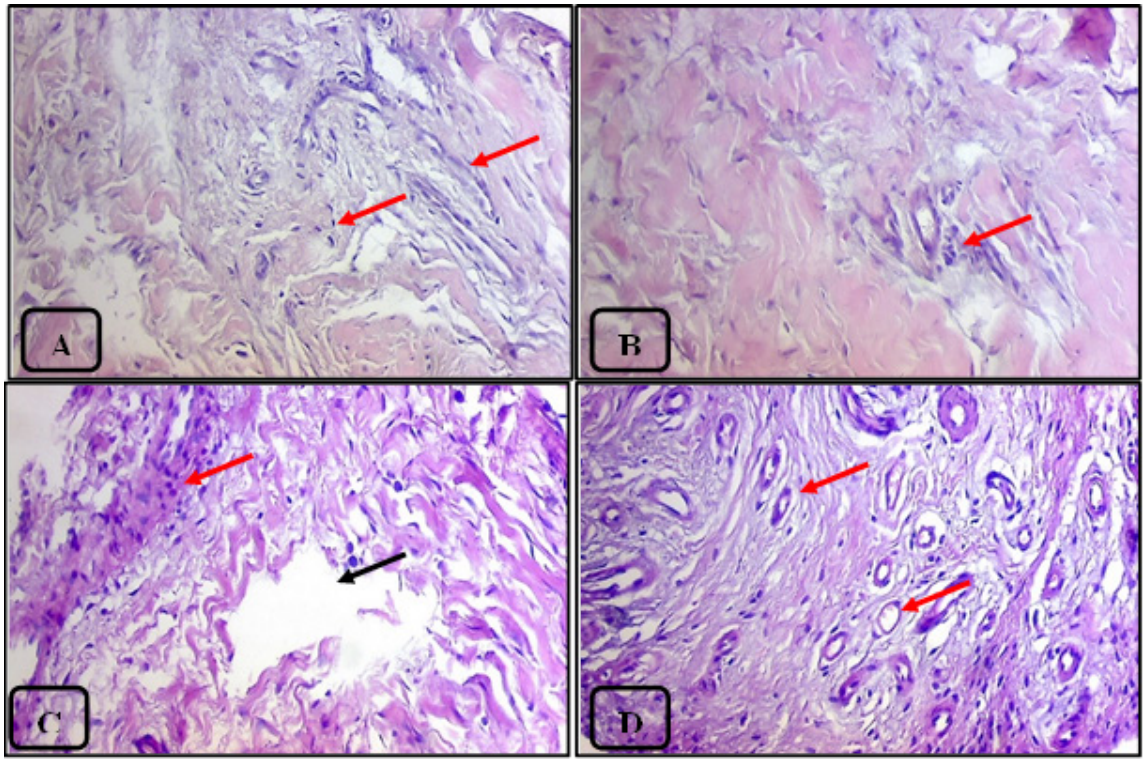

Fig. 3. Section in the PCL of knee RA patient demonstrates: (A): proliferation of fibrocytes, (B): deposition of fibrin in many areas with aggregation of inflammatory cells (red arrow), (C): edema (black arrow) with inflammatory cells infiltration (red arrow), (D): increased formation of blood vessels (red arrow) (Haematoxylin and Eosin staining, X10).

Table 1. Intensity of CD16 Expression in ACL and PCL Tissues of RA Patients

CD16 Score	ACL (n=50)	PCL (n=50)	ACL (%)	PCL (%)
0 (Negative)	4	2	8%	4%
+1 (Weak)	16	26	32%	52%
+2 (Strong)	30	22	60%	44%
Total	50	50	100%	100%

Scores were defined as: 0 = no staining, +1 = ≤10 positive cells per field, +2 = >10 positive cells per field. Percentages recalculated for consistency with sample numbers. Chi-square: χ^2= 4.28, p 0.117.

to the PCL of knee RA group that showed positive expression in 48 (96%) cases 26 (52%) within Score+1 weak and 22 (44%) subjects within the score + 2 versus 2 (4%) case showed loss of expression within a score0] (Figure 4). There was no significant link between CD16 expression score (negative, weak, strong) and ligament type (ACL vs PCL), according to a Chi-square test (χ^2 = 4.28, p 0.117).

For the expression of CD68 macrophage, immunohistochemical staining was performed in ACL and PCL tissue sections of RA patients. Table 2 shows the intensity of CD68 expression of positive samples of ACL reached 49 cases with a rate of 98%, [13] (30%) cases within Score +1, and 34 (68%) within a score +2 versus 1 (2%) case with a loss of expression], compared to the PCL of knee RA group that showed positive expression in 47 (94%) cases 21 (42%) within Score+1 weak and 26 (52%) subjects within the score + 2 versus 3 (6%) case showed loss of expression within a score0] (Figure-5). Chi-square analysis revealed no statistically significant correlation between ligament type (ACL versus PCL) and CD68 expression intensity (χ^2 = 3.06, p 0.21), although a higher prevalence of strong CD68 expression was observed in ACL samples.

Enzyme histochemical study

NTD in knee ligaments of RA patients showed severe activity of an enzyme in ACL (Figure 6D), while the PCL demonstrated moderate activity of the NTD enzyme (Figure 6C).

NTD has been recognised as the enzyme responsible for the dephosphorylation of extracellular mononucleotides across various cellular systems. It also catalyzes the extracellular conversion of 5'-AMP to AD.

Discussion

The research shows that RA patients experience severe inflammatory and degenerative changes in their ACL and PCL because their disease condition causes their synovial tissue to stay active while their body produces increasing amounts of cytokines in their microenvironment. The histopathological results which included fibrocyte proliferation and inflammatory cells and fibrin accumulation and new blood vessel formation matched previous studies about RA-related tissue remodeling which shows synovial inflammation spreading past joint capsule boundaries to impact surrounding connective tissue areas [5,7,8,9]. The

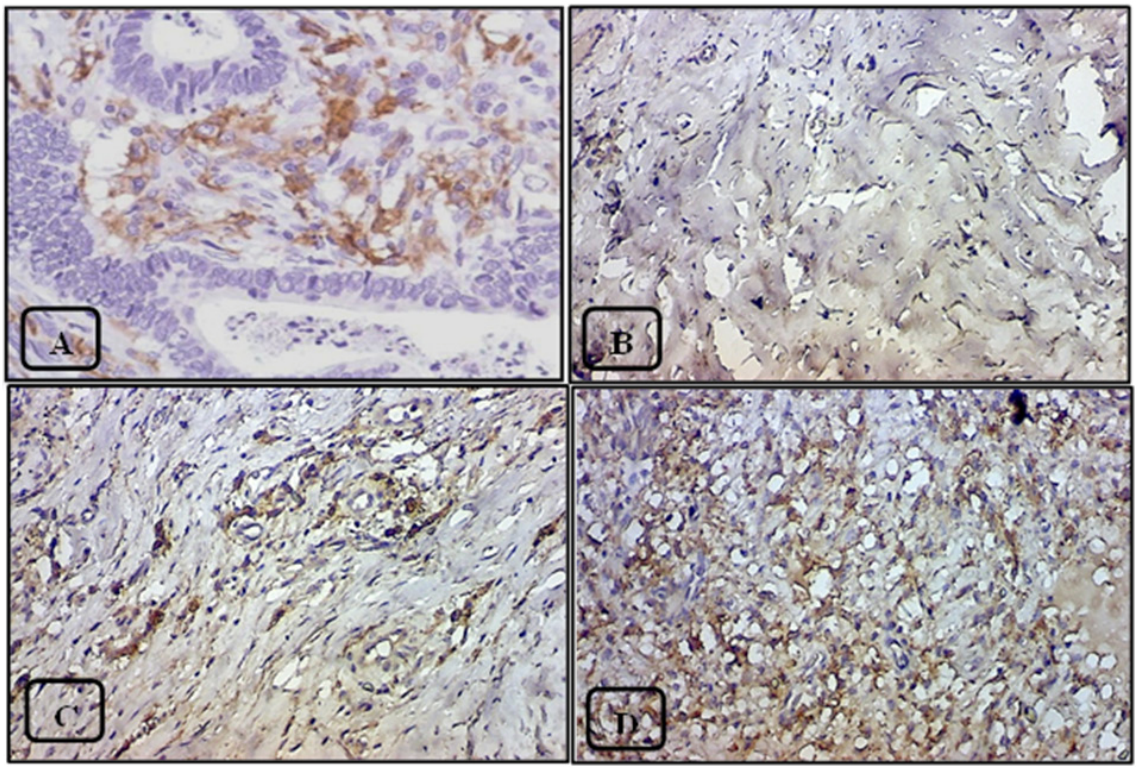

Fig. 4. Immunohistochemical staining method detection of CD16, A: positive control in human colon adenocarcinoma tissue, B: Negative (0), C: Weak (+1) positive expression, D: Strong (+2) positive expression in knee ligaments tissue of RA patients (X10).

Table 2. Intensity of CD68 Expression in ACL and PCL Tissues of RA Patients

CD68 Score	ACL (n=50)	PCL (n=50)	ACL (%)	PCL (%)
0 (Negative)	1	3	2%	6%
+1 (Weak)	15	21	30%	42%
+2 (Strong)	34	26	68%	52%
Total	50	50	100%	100%

Chi-square: $\chi^2 = 3.06$, df = 2, p = 0.21.

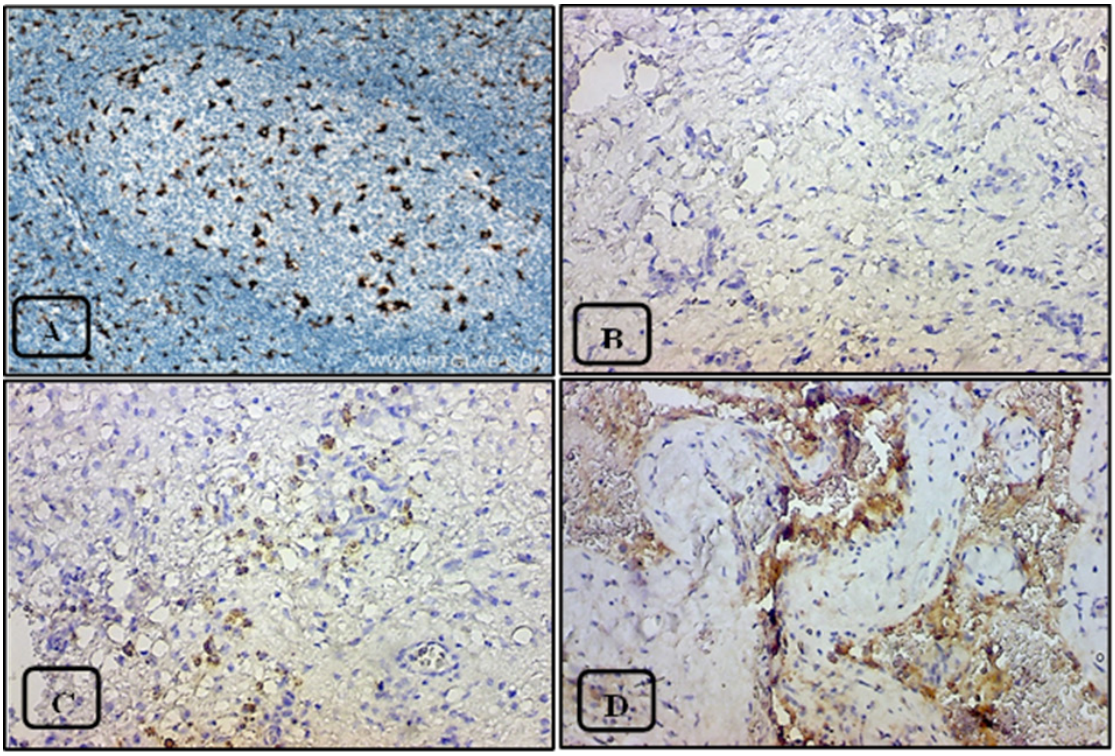

Fig. 5. Immunohistochemical staining method detection of CD68, A: positive control in human tonsillitis tissue, B: Negative (0), C: Weak (+1) positive expression, D: Strong (+2) positive expression in knee ligaments tissue of RA patients (X10).

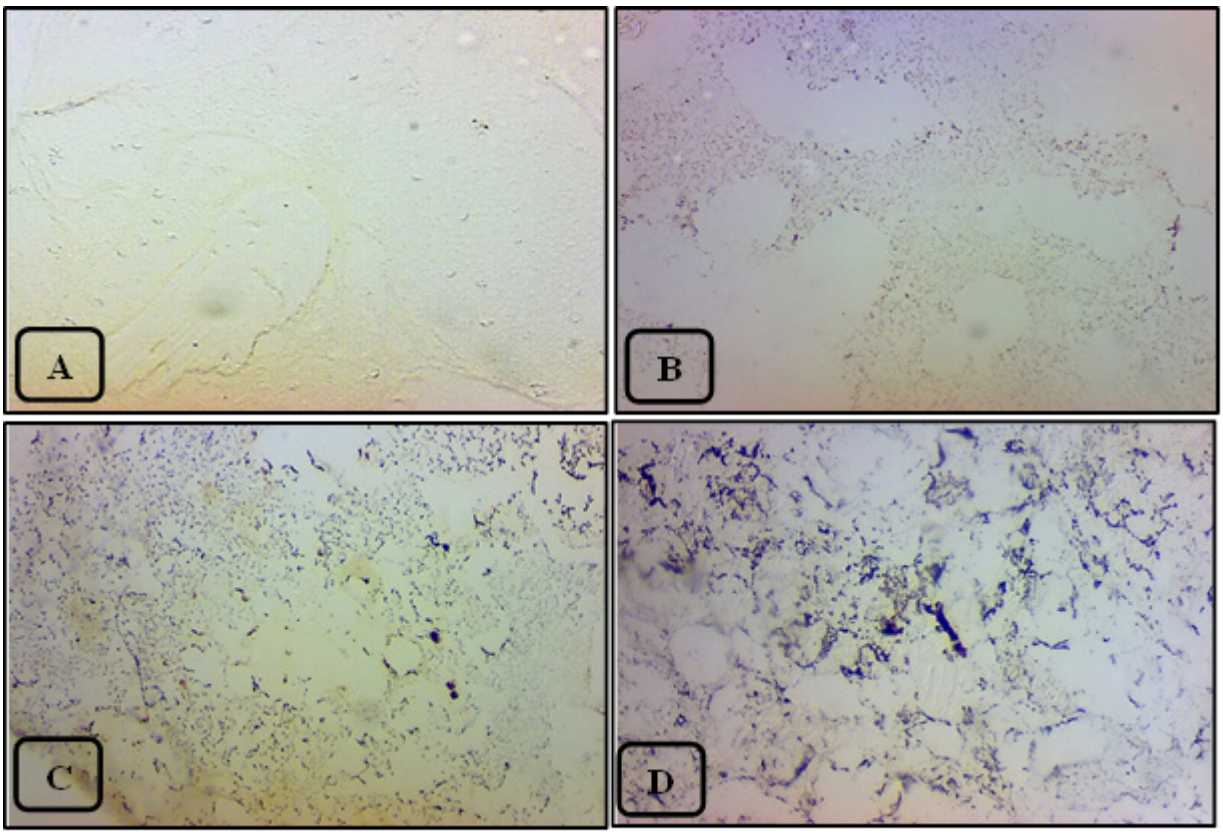

Fig. 6. Cross-section in the ligament of knee RA patient demonstrate, A: nagetive, B: weak, C: modarte in PCL, D: sever in ACL activity of NTD enzyme in fibrocytes (black color) (X10).

observed changes indicate that cruciate ligaments function as active components which participate in the inflammatory process which develops because of ongoing immune system activation in RA [14,51].

The cruciate ligaments show inflammatory and structural changes which include vascular proliferation and fibrin accumulation that matches RA disease mechanisms which allow leukocytes to stay in periarticular tissues through neo-angiogenesis [9,16,17]. The histological results showed that blood vessels became more dense which allowed monocytes and macrophages to penetrate the tissue and our tissue samples showed higher levels of CD16 and CD68 proteins. Research studies demonstrate that macrophages serve as the main effector cells in RA because they regulate cytokine production which results in matrix destruction and prolonged tissue damage [23,26,27]. Rather than reflecting mechanical injury, the pattern of involvement observed in this study supports the concept that cruciate ligaments undergo inflammatory transformation as part of the systemic RA process [18,15].

The marked presence of inflammatory infiltrates and the disorganization of collagen bundles observed in both ligaments further support the notion that RA induces a localized destructive process within connective tissues, mediated by sustained cytokine exposure and matrix-degrading enzymes. The breakdown of extracellular matrix and arthritic joint ligament remodeling occurs through the combined action of metalloproteinases and catabolic substances which activated synoviocytes and macrophages produce [7,9,16]. The study results show elevated CD16 and CD68 expression which matches the inflammatory pattern because monocyte-derived macrophages tend to accumulate in RA-affected tissues to promote angiogenesis and fibroblast activation and matrix degradation [19,20]. The research indicates that RA-related ligament changes result from an immune system attack on deep stromal tissues rather than being a result of joint degeneration [18,21].

The ACL shows greater changes than the PCL because its structural makeup together with the surrounding tissue environment controls how many inflammatory cells can enter the joint space in RA. Research shows that RA tissue becomes susceptible because of three elements which affect blood vessel patterns and synovial tissue placement and the first structure of extracellular matrix [18,21]. The ACL shows increased exposure to synovial fluid and joint cavity inflammatory mediators which makes it more likely to develop inflammatory remodeling at an earlier stage. The study supports this interpretation because we detected elevated NTD activity in the ACL which matches the pattern of adenosine metabolism and the involvement of macrophages and lymphocytes in long-term tissue inflammation [22,23]. The various factors show that RA leads to different degrees of cruciate ligament damage because these structures link to rheumatoid synovial tissue through their immune system and body structure characteristics.

The two ligaments showed intense CD16 and CD68 immune cell staining which confirms that monocyte–macrophage lineage cells function as the main cause of tissue destruction in RA patients. The CD16+ monocyte population which grows in number during RA develops into cells that become more mobile while producing elevated levels of inflammatory mediators when they migrate to periarticular regions to generate inflammation which leads to tissue damage [23,24]. The CD68+ macrophage population serves as a disease activity indicator which causes joint damage through their TNF-α and IL-1β and matrix metalloproteinases secretion [25,26,27]. The ACL and PCL samples contained elevated marker levels which scientists previously discovered during studies about RA disease severity and local inflammation that occurs when macrophages accumulate. The ACL shows increased expression because it faces higher levels of synovial inflammatory mediators which supports the theory that cruciate ligaments face direct immune system attacks instead of developing through mechanical wear [18,21].

The ACL demonstrates elevated NTD (ecto-5′-nucleotidase/CD73) activity which reveals that this ligament has an increased local inflammatory response. The enzyme CD73 functions to transform AMP molecules found outside cells into adenosine which controls immune cell activation and macrophage development and maintains long-term inflammatory responses [28,29]. Research has shown that RA patients produce elevated levels of adenosine which exists in their blood serum and synovial fluid to control T-cell function and macrophage direction and cytokine production [30-34]. The ACL demonstrates improved enzymatic performance because its adenosine production system boosts its activity to fight against the rising number of inflammatory cells which display CD16 and CD68 markers. The adenosine pathways which control macrophage remodeling activities and tissue destruction make it possible for NTD activity in the ACL to explain the severe histopathological changes found in this structure [27,31]. The results show that adenosine metabolism plays a role in how different ligaments become involved in RA while supporting the idea that cruciate ligaments actively participate in RA immunopathology instead of simply being affected by the disease process.

The result shows RA inflammation damages both cruciate ligaments through histopathological and immunohistochemical and enzymatic tests which reveal the ACL contains more immune cells and shows elevated NTD activity than the PCL. The observed patterns stem from structural and environmental factors which affect the degree of inflammatory tissue transformation instead of showing any need for surgical intervention. The findings help scientists understand how RA affects different ligaments but readers need to understand these results through the study's restricted methodology. The study lacks a non-RA control group and quantitative molecular assays which prevent scientists from applying the observed staining intensities to other situations. The research needs to include control tissues together with longitudinal sampling and advanced molecular quantification methods to determine the exact mechanisms which make RA patients more prone to specific ligament injuries [18,21,31,34].

Limitations

The research contains multiple restrictions which affect how readers should understand the study results. The study lacks a non-RA control group which prevents scientists from establishing clear reference values for cruciate ligament immunohistochemical and enzymatic activities. The semi-quantitative scoring system used for CD16, CD68 and NTD evaluation delivers useful comparative data although it fails to substitute for quantitative molecular tests which would offer exact expression level measurements. The research used two observers who evaluated the results without knowing the outcomes through a larger review panel with digital image-analysis tools would have produced more accurate scoring results. The research findings from this study remain specific to histopathological research because the sample size works for this type of study yet it restricts the ability to apply these results to RA patients in general. The study design prevents researchers from determining how RA affects ligaments throughout time. Research needs to study control tissues through quantitative molecular tests and prolonged clinical observations to identify the specific mechanisms which lead to cruciate ligament changes in RA patients.

Conclusions

The research shows that rheumatoid arthritis patients have both their anterior and posterior cruciate ligaments which show major inflammatory and degenerative changes. The ACL displayed higher immune cell presence together with elevated CD16 and CD68 markers and elevated NTD (CD73) enzyme activity than the PCL which indicates RA chronic inflammation affects these ligamentous structures at different levels. The research shows that cruciate ligaments actively take part in RA-related tissue transformation instead of experiencing damage only through mechanical stress or subsequent degenerative changes. The study results do not validate any particular surgical method including ligament extraction because such recommendations need to be proven through clinical results and studies that compare different treatment approaches. The research requires additional studies which should include non-RA control groups and quantitative molecular testing and extended clinical observations to identify the exact mechanisms which cause RA to affect ligaments.

Authors' contributions

AKC and SAHAS: conceptualisation, methodology, investigation, results, writing—original draft, writing—review and editing, project administration, supervision.

Conflict of interest

None to declare.

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