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Assessment of synovial repair in primary knee osteoarthritis after platelet rich plasma (PRP) intra-articular injection

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Abstract

Primary knee osteoarthritis (KOA) is a persistent condition marked by the gradual deterioration of the joint and cartilage loss on its surfaces. Recently, platelet-rich plasma (PRP) was considered a biological intervention that alleviates symptoms and restricts the advancement of primary KOA in patients. This study aimed to evaluate the effect of intra-articular PRP injections on synovial repair through cytokine assays in 20 patients with primary KOA. Patients received two intra-articular PRP injections, spaced one month apart. The role of PRP was assessed by measuring Transforming growth factor beta (TGF-β) and interleukin-17 (IL-17) levels in synovial fluid before and after the injections. Both visual analogue scale and Western Ontario and McMaster Universities Osteoarthritis index were assessed before and after intervention. IL-17 and TGF-β levels were measured in the synovial fluid using sandwich ELISA technique before the first PRP intra-articular injection and one month after the second injection to assess the synovial repair after PRP injection. Our results showed that the synovial IL-17 levels significantly decreased by 75.21% (p<0.0001) after intra-articular knee injection, dropping from a range of 102.3–293 (median 173.5: 139.7– 224.5) to 17.86–106 (median 36.38: 23.57– 50.32). In contrast, synovial TGF-β levels significantly increased by 80.3% (p<0.0001) after intra-articular knee injection, rising from 124–545.5 (mean ± SD: 256.22 ± 123.56) to 693.3–3226 (mean ± SD: 1521.6 ± 765.46). In conclusion, intra-articular PRP administration in primary KOA patients is associated with increased levels of TGF-β and decreased levels of IL-17 in the synovial fluid of the joint. These changes in cytokine levels suggest that PRP treatment effectively reduces inflammation and may contribute to pain relief in primary KOA.

Keywords: Primary Knee osteoarthritis, Interleukin-17, TGF-β, platelet rich plasma (PRP).

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Introduction

Primary knee osteoarthritis (KOA) is a persistent condition characterized by the gradual breakdown of joints and the erosion of cartilage on their surfaces. This degenerative process within the joint alters both the catabolic and anabolic functions of chondrocytes. Consequently, when the joint is affected, it can adversely impact other components, potentially resulting in meniscus degeneration, bone irregularities, sclerosis, subchondral tissue

swelling, and occasional inflammation of the synovial membrane. This condition diminishes patients' functional abilities and lowers their quality of life due to the emergence of pain, stiffness, and restricted joint mobility.[1]

Before resorting to surgical measures, traditional interventions such as non-steroidal and steroidal anti-inflammatory treatments, pain relievers, corticosteroid administrations, and hyaluronic acid (HA) injections are commonly used to address joint pain.[2]

Platelet-rich plasma (PRP) has become a viable biological intervention for individuals with primary KOA, aiming to alleviate symptoms and halt disease progression.[3] PRP is a blood derivative rich in growth factors, including platelet-derived growth factor, transforming growth factor beta (TGF-β), and insulin-like growth factor 1. Additionally, growth factors like basic fibroblast growth factor and vascular endothelial growth factor found in PRP play roles in promoting cartilage formation. Together, these components within PRP can stimulate a natural recovery and healing process, aiding in the regeneration of cartilage tissue.[4]

Biomarkers provide insights into alterations in chondrocyte metabolism and the extent of joint damage in primary KOA. The burden of disease, investigative, prognostic, efficacy of intervention, and diagnostic classification system has recently become a standard method for categorizing these markers.[5]

Interleukin 17 (IL-17) serves as a cytokine that triggers multiple catabolic pathways, leading to damage in cartilage and tissues. Its characteristics make it a particularly compelling biological indicator, notably in conditions like rheumatoid arthritis (RA) and primary KOA. On the other hand, TGF-β is believed to promote the activity of mesenchymal stem cells and chondrocyte growth while inhibiting catabolic processes.[6].

This study sought to assess the effectiveness of intra-articular PRP injections on synovial tissue repair by analyzing cytokine levels in 20 participants diagnosed with primary KOA. The research focused on measuring specific cytokines to determine how PRP influences the biological environment within the joint, aiming to provide insights into the potential therapeutic benefits of PRP in promoting synovial healing and reducing inflammation in patients suffering from primary KOA.

Subjects and Methods

This study recruited 20 participants diagnosed with primary KOA, with a gender-balanced distribution, aged between 29 and 58 years. These participants were recruited from the outpatient clinic of the Department of Physical Medicine, Rheumatology and Rehabilitation, Ain Shams University Hospitals.

Assessment of disease activity was done according to clinical picture, laboratory and radiological findings, obtained from hospital records. Their body mass index (BMI) ranged from 21 – 33.2 with mean ±SD of 28.53 ± 3.42. The Erythrocyte sedimentation rate (ESR) ranged from (5-35) with median (interquartile range, IQR) 14 (10–20), while C reactive protein (CRP) ranged from 0.1 – 10.9 with median (IQR) 2.4 (1.25–2.85). Both visual analogue scale (VAS) and Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) were assessed for all participants before (baseline assessment), one month after the first intra-articular knee injection with PRP (2nd visit) and one month after the 2nd injection (3rd visit).

Laboratory analysis was conducted at the Department of Clinical Pathology, Ain Shams University Hospital from September 2022 to September 2023.

Blood sample collection and PRP preparation

Blood samples from the patients were obtained using sterile techniques. A blood sample (10-15 ml) was drawn via vein puncture and placed in citrate in Falcon tubes. These samples were then subjected to a two-step centrifugation process through a platelet concentration system (Centerion 2006, England). All patients received PRP injection twice, within a 4-week interval.

Knee Synovial fluid level of both IL-17 and TGF-B were measured before and one month after intra-articular knee injection using the sandwich ELISA technique.

Synovial fluid analysis

IL-17 and TGF-β levels were measured in synovial fluid, which was aspirated and collected in vacutainer tubes. The samples were left at room temperature for two hours and then centrifuged for 15 minutes at 1000g. The resulting supernatant was extracted and kept at -80◦C for subsequent analysis. Level of IL-17 and TGF-β in the synovial fluid was measured using Sandwich ELISA technique with commercially available kits. The IL-17 levels were measured using the Human IL-17 ELISA Kit (Catalog Number: ab100556, Abcam, Cambridge, UK), which has a sensitivity of <10 pg/ml and a detection range of 15.63-1000 pg/ml. For TGF-β, the Human TGF-β1 ELISA Kit (Catalog Number: ab100647, Abcam, Cambridge, UK) was used, with a sensitivity of 18 pg/ml and a detection range of 18–4000 pg/ml.

The assays were conducted according to the manufacturers' protocols, involving the binding of the target cytokines to a solid-phase antibody, followed by detection with a biotinylated secondary antibody and a substrate reaction. The optical density (OD) was measured using a Multiskan FC Microplate Photometer (Thermo Fisher Scientific, Waltham, MA, USA) at 450 nm, with a correction at 540 nm. Cytokine concentrations were determined by comparing the OD values to a standard curve generated with the kit's standards. Data for this study were obtained from Ain Shams University Hospitals records, including clinical, laboratory, and radiological findings.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (IBM SPSS) version 23. Quantitative variables are described using measures such as mean, standard deviation (SD), range, median, and interquartile range (IQR), while qualitative parameters are represented as counts and percentages. When comparing groups based on qualitative data, the Chi-square test was employed. When comparing two independent groups with quantitative data that followed a parametric distribution, the independent t-test was utilized. For comparisons involving more than two groups under the same conditions, the One-Way ANOVA test was applied. Conversely, when dealing with data that did not follow a parametric distribution, the Mann-Whitney test was used. For comparing two paired groups with quantitative data that did not follow a parametric distribution, the Paired t-test was employed. When evaluating more than two paired groups under similar conditions, the Repeated Measures ANOVA was utilized. For data sets that did not adhere to a parametric distribution, the Wilcoxon Rank test was used for paired comparisons, and the Friedman test was applied for more than two paired groups. To determine the relationship between two quantitative variables within the same group, the Spearman correlation coefficient test was conducted. A 95% confidence interval was established with a permissible margin of error of 5%. Based on this criterion, a *p*-value below 0.05 was categorized as significant.

Results

Descriptive characteristics of the study participants

The study included 20 patients with primary KOA. Clinical and demographic characteristics are depicted in Table 1.

Table 1. Characteristics and demographic information of the 20 study participants.

Studied parameters		Obtained data
Age	Mean ± SD	39.4 ± 10.41
	Range	29 – 58
Gender	Females	10 (50.0%)
	Males	10 (50.0%)
BMI kg/m^2	Mean ± SD	28.53 ± 3.42
	Range	21 – 33.2

BMI: Body Mass Index.

The patient's hemoglobin (HB) ranged from 10-16 mg/dl with mean ±SD of 12.41 ± 1.49, WBCs count ranged from 4.3 -10 with mean ±SD of 7.26 ± 1.95, and PLT count ranged from 4.3 – 10 with mean ±SD of 281.15 ± 94.53. Their ESR ranged from 5-35 with median (IQR) of 14 (10–20), CRP ranged from 0.1 -10.9 with median (IQR) of 2.4 (1.25–2.85), Table 2.

Table 2. Laboratory and radiographic data of the 20 study participants.

Studied parameters		Obtained data
HB	Mean ± SD	12.41 ± 1.49
	Range	10 – 16
WBC	Mean ± SD	7.26 ± 1.95
	Range	4.3 – 10
PLT	Mean ± SD	281.15 ± 94.53
	Range	136 – 498
ESR	Median (IQR)	14 (10–20)
	Range	5 – 35
CRP	Median (IQR)	2.4 (1.25–2.85)
	Range	0.1 – 10.9

HB: hemoglobin; WBC: white blood cells; PLT: platelets; ESR: erythrocyte sedimentation rate; CRP: c-reactive protein.

Data in Table 3 indicates a statistically significant reduction in both VAS and WOMAC scores during the initial and subsequent visits compared to their levels before the intra-articular knee injection, (p <0.0001 and p<0.001, respectively).

Table 3. Visual analogue scale (VAS) score and Western Ontario and McMaster Universities Osteoarthritis index (WOMAC) during the patients' three visits.

Studied parameter		Before	1st visit	2nd visit	t p-value
VAS	Median (IQR)	7 (6-8)	6 (5-6)	4 (3.5-4)	<0.0001
	Range	5-9	3-7	2-5	
WOMAC	Mean ± SD	64.90 ± 10.92	54.80 ± 10.54	38.45 ± 11.23	<0.001
	Range	50-84	38-76	24-61	

VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis index. t: t-test
$p \leq 0.05$ is significant.

Table 4 depicts a statistically significant decline in the level of IL-17 after the intra-articular knee injection [36.38 (23.57 – 50.32)] than before the intra-articular knee injection [173.5 (139.7 – 224.5)] (p<0.001) and with a percentage reduction of 75.21±14.92.

Table 4. Comparison between interleukin **(**IL)-17 level before and after intra-articular knee injection among the 20 studied patients.

IL-17	Intra-articular knee injection		% of reduction	‡ p-value
	Before	After	Mean ± SD	
Median (IQR)	173.5 (139.7 – 224.5)	36.38 (23.57 – 50.32)	75.21 ± 14.92	< 0.001
Range	102.3 – 293.9	17.86 – 106.2		

IL-17: interleukin 17; IQR: inter quartile range. $p \leq 0.05$ is significant. ‡: Wilcoxon Ranks Signed test

Table 5 shows that there was a statistically significant increase in the level of TGFβ after the intra-articular knee injection [1521.6 ± 765.46] than before the intra-articular knee injection [256.22 ± 123.56] (p<0.001) and with a percentage increase of 80.3±12.31.

Table 5. Comparison between transforming growth factor beta (TGF-β) level before and after the intra-articular knee injection among the 20 studied patients.

TGFβ	Intra-articular knee injection		TGF % of increase	•p-value
	Before	After	Mean ± SD	
Mean±SD	256.22 ± 123.56	1521.6 ± 765.46	80.3 ± 12.31	<0.001
Range	124 – 545.5	693.3 – 3226		

TGF-β: transforming growth factor beta. $p \leq 0.05$ is significant. •: Paired t-test.

Discussion

Primary KOA stands as the predominant inflammatory joint condition in orthopedics. Its primary characteristic involves the gradual deterioration and depletion of articular cartilage, coupled with alterations in joint structure and functionality. Additional pathological indications include changes in the meniscus, periarticular ligaments, subchondral bone, and synovium.[7]

Various approaches exist for treating primary KOA, encompassing pharmacological, non-pharmacological, and surgical interventions.[8] Lately, healthcare professionals have utilized intra-articular injections such as hyaluronic acid (HA), PRP, and bone marrow concentrate for managing primary KOA.[9]

Research on PRP injections for primary KOA has produced controversial findings. While some studies highlighted its advantages, others failed to show its superiority over alternative treatments.[10] A significant number of these studies indicating positive outcomes for PRP injections in primary KOA exhibited notable biases and quality concerns. These issues encompassed inadequate statistical analyses, selective reporting, questionable blinding methods, and inconsistencies in the systematic reviews. Furthermore, the lack of standardization in PRP and the grouping of various related products under a single term have contributed to additional confusion in field.[11]

Most of the studies assessed effects of PRP using subjective clinical scores such as WOMAC and VAS scores. These measures center on patients' subjective perceptions concerning symptoms, functional performance, and overall quality of life.[12,13] Only a few studies incorporated objective measures to assess PRP effects, such as changes in the biomarkers of synovial fluid.[14]

The objective of this study was to assess the impact of intra-articular PRP injections on the knee joint's functional status. This evaluation was based on measurements of WOMAC and VAS scores, as well as levels of IL-17 and TGF β in the knee synovial fluid, both before and after the intra-articular injection.

Upon comparing the VAS scale and WOMAC score before and after the intra-articular knee injection, a statistically significant improvement was observed post injection (p<0.001). These findings align with outcomes of a previous study involving 90 primary KOA patients, where PRP and HA intra-articular injections were evaluated as monotherapies. Both groups exhibited enhanced clinical outcomes in International Knee Documentation Committee (IKDC) and VAS scores six months post-injection, with the PRP group demonstrating superior results over the HA injected group.[12] Similarly, Jevsevar et al., 2013 reported improved function and pain relief one-year post-PRP injection.[15]

Consistent outcomes were reported by Spaková et al., 2012,[13] who analyzed 120 KOA patients after PRP and HA injections, respectively. After 3- and 6-month follow-ups, the PRP group displayed significantly improved WOMAC Index and Numeric Rating Scale scores

compared to the HA group. In 2016, Meheux and colleagues conducted a meta-analysis of six studies involving 739 patients, revealing notable improvements in pain and physical function with PRP injections up to 12 months post-treatment. Notably, PRP outperformed HA in terms of clinical outcomes and WOMAC scores from 3 to 12 months post-injection.[10]

Furthermore, a study by Raeissadat et al., 2020, involved 23 bilateral KOA patients. These participants were divided into control and treatment groups, with the latter receiving PRP injections in two sessions spaced a month apart. Eight months post-treatment, significant enhancements in pain reduction and quality of life were observed in the treated group.[16]

Also, McLarnon and Heron, 2021,[17] published a systematic review and meta-analysis study, which included eight studies and 648 patients that compared the effect of intra-articular steroids versus PRP injections in KOA patients. The study concluded that PRP notably outperformed in alleviating osteoarthritis symptoms such as functionality, pain, and stiffness at 3, 6, and 9 months following the intervention ($p < 0.01$).

On the other hand, other studies documented that intra-articular PRP injection has no beneficial effect rather than different treatment modalities like intra-articular HA and steroids injection. For instance, Cole et al., 2017[18], performed a randomized controlled trial to assess both the clinical and biological impacts of intra-articular PRP injections compared to intra-articular HA injections in patients diagnosed with mild to moderate KOA. They published that both groups showed clinical improvement after injection, however, there was no discernible difference between both groups at any designated time point for the primary outcome measure. Also, Joshi et al., 2017[19] carried out another randomized controlled trial, comparing the clinical outcomes of PRP and steroid injections separately in patients with late-stage KOA and reported that a single injection from PRP and steroids has the same effect.

Additionally, Huang et al., 2019, conducted a randomized controlled trial,[20] examining the effects of intra-articular PRP, HA, and steroids on 120 KOA patients, categorizing them into three distinct groups. While they found no notable improvements in WOMAC scores among the groups three months post-treatment ($p>0.05$), intra-articular PRP demonstrated markedly superior WOMAC scores at 6, 9, and 12 months following the intervention.

Most previous studies depended mainly on subjective measures in assessment of response to PRP injections, but few studies used objective tools to avoid bias like analysis of synovial fluid cytokines levels measurement.

In the present study, by comparing pre and post injection IL17 as well as TGF-β synovial fluid levels in all patients, we found that there was a highly statistically significant decline in IL-17 levels and increase in TGF-β levels (p-value<0.001) post intra-articular knee injection.

In 2023, Li T. et al.,[21] conducted a study involving 70 patients who were randomly assigned to receive intra-articular injections of either PRP or HA in a blinded manner. Before and after the intervention, they assessed the concentrations of inflammatory cytokines present in the synovial fluid. They reported significant reductions in the inflammatory cytokines including IL-6, IL-1β, tumor necrosis factor (TNF)-α, IL-17A, and IL-10 levels in the synovial fluid compared to before injection levels ($p<0.05$). Moreover, the patients who received intra-articular knee injections with HA or PRP exhibited notably improved WOMAC and VAS scores versus controls ($p<0.05$).

Furthermore, our findings align with those of Lisi et al., 2018.[22] In their study, which involved 30 KOA patients treated with PRP injections, they observed a statistically significant improvement in symptoms and enhanced functional scales compared to the control group that received HA. Such objective metrics fortify the evidence base and offer a more comprehensive understanding of PRP's therapeutic efficacy.

In conclusion, intra-articular PRP injection in primary KOA may help in decreasing joint inflammation in the form of decreasing synovial IL-17 and improving the regenerative power of the synovium by increasing the level of TGF-β as well as improving patients' symptoms and alleviates pain.

Author Contributions

MGZ; designed and approved the whole research protocol. NB; contributed to the protocol design, revised laboratory work, and approved the final paper version to be published. NHE; supervised sample collection according to inclusion criteria, revised clinical data, diagnosis, and patient classification. FA; monitored the laboratory work and interpreted the data. EMB; collected the samples and patient's clinical data, carried out the laboratory work and analyzed it, carried out statistical analysis and drafted the paper.

Declaration of Conflicting Interests

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Ethical approval

the study protocol was reviewed and approved by the Ethical Committee of the Faculty of Medicine, Ain Shams University (FMASU MD 253/2022).

Informed consent

Prior to being included in the study, each participant provided a written informed consent.

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