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ORIGINAL A R T I C L E

The use of collagen type-II as an indicator for assessment regeneration effect post intra-articular pure-PRP injection in KOA patient

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Abstract

Background: knee osteoarthritis (KOA) is a complex disease that causes metabolic, structural, biochemical, and functional alterations in afflicted tissues. Physical examination and radiological findings are the present methods for the diagnosis of knee osteoarthritis. Traditionally, KOA medication focused on symptom management. Clinical trials focused on delaying or reversing disease development have gained popularity in recent years. PRP is among the medicinal approaches used to manage KOA.Purpose: By assessing the cartilage degradation marker collagen-II, the study's aim was to figure out whether the use of pure-PRP may help KOA patients' damaged cartilage layers regenerate.
Methods: This non-randomized controlled trial study involved 66 patients with knee OA and 28 healthy control subjects from December 2021 to February 2022. There were 2 categories of knee OA patients: 34 with moderate (grade-3) and 32 with mild (grade-2) KOA. So, every group of KOA patients is divided into three subgroups based to the frequency of injections (single, double, or triple) in addition to severity. Based on clinical and radiological data using the Kellgren-Lawence (KL) 0–4 grading system, the patients' diagnoses and classifications are made. This study was designed at AL-Imam Ali hospital, Babylon governorate, Iraq and approved by the medical human research ethics committee at Al-Qadisiyah university/ collage of medicine.
Result: The findings of this investigation show that the serum collagen type-II content was considerably greater in KOA patients were compared to control subjects, and in moderate compared to mild KOA as the severity of the disease progressed. But following pure-PRP injection, the serum level of collagen type-II did not significantly decrease, and increasing the number of injections had no better effect.
Conclusions: PRP therapy was generally acceptable for patients in terms of improving symptoms and there were no complications following injection. However, there is insufficient indication that platelet rich plasma regenerates cartilage damage in knee OA patients, as there was no significant decrease in the amount of collagen type-II.

Keywords: KOA, PRP, Collagen type-II.

1 Introduction

Osteoarthritis (OA) represents the most common type of arthritis, with the knee being the most frequently affected joint [1]. The knee joint is formed by three main tissues: articular cartilage, synovial fluid, and bone; all three are influenced by the KOA. As a result, are identified as potential targets biomarkers for OA [2]. In osteoarthritis, these biochemical markers are molecular molecules that appear during the physiological process of the bone and cartilage matrix, and even pathological processes can be identified in different body fluids such as synovia, serum, and urine [3]. Monitoring tissue components or their remnants that liberated from joint cartilage and bone into different body fluids could be one way to detect tissue matrix changes in KOA. Such biomarkers have the potential to be used to monitor the outcome of medication on tissue [4]. These cartilage breakdown components such as collagen type-II are leaked into the synovial fluid, and their identification have been investigated as a potential diagnostic indicator for the onset and development of OA. The degradation byproducts of cartilage at afflicted region as well as in the bloodstream have been recognized as indicators for KOA [5].

Type II collagen degradation and reduction are common in osteoarthritic cartilage. Chondrocyte hypertrophy is thought to be the cause of the decrease in type II collagen in osteoarthritic cartilage. In addition to the structural function of collagen type II, it is a significant extracellular molecule that can regulate proliferation, differentiation, and metabolism of chondrocytes in a similar mechanism to soluble signals [6]. Along with osteoarthritis progression, the collagen in chondrocytes of cartilage extracellular matrix undergoes irreversible degradation, making the CTX-II suited to use as a biomarker for the destruction of articular cartilage. As the structural biomarker can be detected in different samples such as serum, synovial fluid, and urinary samples, it has the potential to be utilized as an indicator tool. marker or in monitoring osteoarthritis progression [7]. During remodeling of cartilage, the matrix degradation enzymes involve the collagenase and gelatinase that belong to the matrix metalloproteinase (MMP) accountable for the splitting of collagen type II and aggrecan in a consecutive manner [8].

plasma rich-platelets are defined as a volume of autologous liquid portion of blood with platelet concentrations greater than the usual baseline obtained through whole blood centrifugation [9]. Traditionally, treatment of KOA has centered on symptom

improvement. But, in recent years, the importance of developing innovative strategies has increased for treatments that aim to delay or even reverse progression of the disorder [10]. Currently, the management strategy of KOA with pharmacological therapy can temporarily improve pain and functional limitation, but not delay or cessation progression of disease. In addition, many patients have not capable to tolerate the use of these oral pharmacological therapy for long periods due to several side effects. For these reasons, intra- articular injections (IAIs) have been recommended as a suitable alternative treatment option to delay disease progression and surgical intervention treatments [11,12]. PRP, among all the possibilities, is one of the most frequently utilized intra-articular therapeutic options in the management of KOA [13]. The utilization of autologous plasma enrich in platelets injection as a method of treatment for KOA is being supported [14]. There are three major contributing factors to the high trend for autologous blood-derived therapeutic interventions for patients with KOA. First, PRP is regarded as a potentially beneficial therapy by both patients and physicians. Second, it is straightforward to apply because the preparation is technically quick and uncomplicated, and the management principle is non-invasive. Third, PRP is most likely safe when patient-specific bioactive molecules that are adequately concentrated from the person's own plasma can be used, preventing several adverse effects and drug reactions [15]. Although there are several strategies for producing platelet concentrates, they may be complicated in their applications as each approach produces a varied biological product with possible applications. The current study relied on the usage of pure-PRP [16]. However, the presence of high leukocyte concentration means the presence of significant levels of inflammatory mediators in LR-PRP could stimulate catabolic and inflammation modifications in order to cancel out the positive impact of bioactive material on repairing the tissue and adverse the articular damage progression in KOA [17]. Growth factor content and catabolic pro- inflammatory cytokines are regulated by cell-confined PRP, according to Sandman et al. Platelets enhance anabolic signaling molecules while leukocytes increase catabolic signaling molecules, implying that platelet concentrates contain less or no leukocytes [18].

2 Methods and Materials

2.1 Study populations

The study includes patients with mild and moderate KOA and control group as illustrated in Figure-1 bellow:

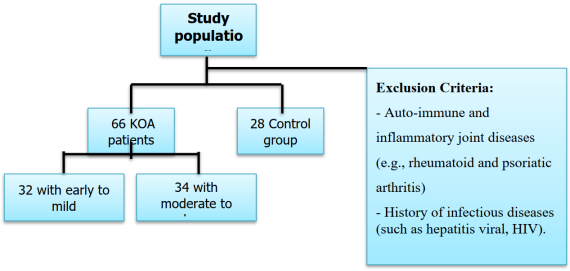

Figure 1: Study population included in this study.

2.2 Sample collection

Under aseptic environment from each patient about 5ml of venous blood was collected in a 6ml gel tube at baseline and three months after injection with PRP. Then after, the blood was allowed to stand at room temp. for 15 min. Then, the sample was centrifuge at 4000 rpm for 5 minutes to obtain serum. The collected serum converted into Eppendorf tube and label, then kept at (-80 degrees Celsius) until usage.

2.3 PRP preparation

Pure-PRP for this study was made by employing the Bussat et al. [19] technique with a two-step separation procedure, as shown in Figure 2. below:

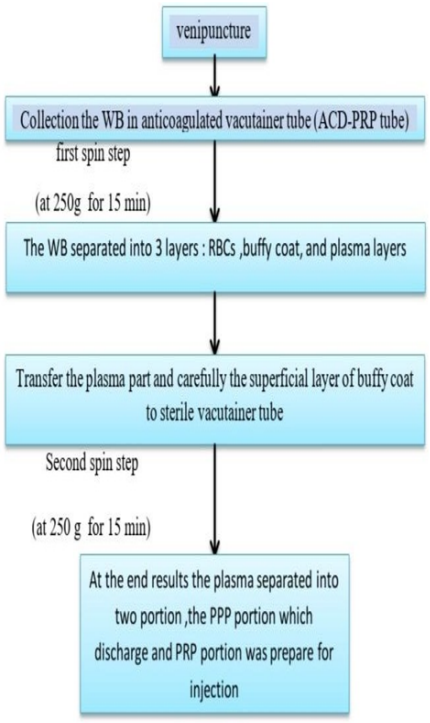

Figure 2: Flowchart of PRP preparation.

2.4 Determination the concentration of biomarker

The serum concentration of collagen type-II, was measure by Eliza system by Eliza sandwich technique using Elabscience kits as illustrated in Figure-3 below:

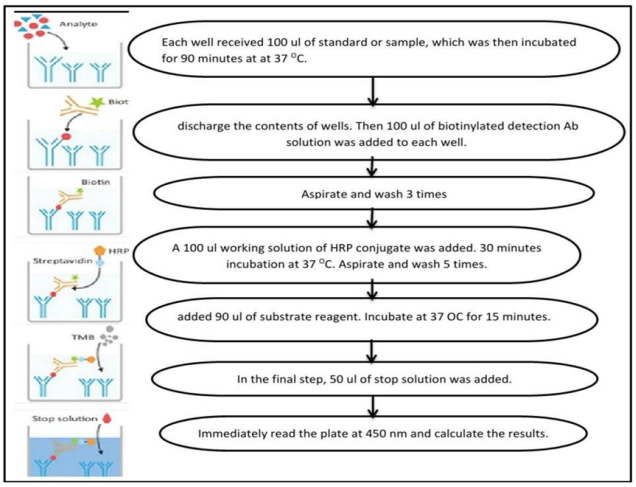

Figure 3: The Eliza assay procedure to estimate the concentration of collagen-II

2.5 Statistical analysis

statistical package for the social sciences (SPSS) version 21 and Microsoft Excel 2019 was used to summarize, analyze, and show data. The numerical data was reported as (Mean ± SD). Categorical data, on the other hand, was described as a number and percentage. independent sample student t-test; Yates correction test; chi-square test and paired sample t-test used to measure the degree of significant. The statistical significance level was set at ($p < 0.05$).

3 Result

Characteristic	KOA group $n = 66$	Control group $n = 28$	p
Age (years)			
Mean ±SD	53.06 ± 9.27	44.36 ± 8.65	0.004 I **
Range	32 -66	32 -58	0.56
Male, n (%)	22 (33.3 %)	8 (28.6 %)	1.000 Y NS
Female, n (%)	44 (66.7%)	20 (71.4%)	
BMI (kg/m2)			
Mean ±SD	27.60 ± 3.94	24.38 ± 1.83	0.006 I ** NS
Range	20.20 - 37.13	21.05 - 26.81	

Table 1: Demographic features of patients with knee osteoarthritis and control group

The demographical features of patients with KOA as compare to control are shown in Table-1. Mean age

of those with knee osteoarthritis (KOA) was significantly higher than control, 53.06 ± 9.27 years versus 44.36 ± 8.65 years, respectively (p =0.004). With respect to gender, the males were 33.3% and that of females was 66.7% and the female to male ratio was 2:1; regarding to the frequency distribution no statistically significant different among the patients and control subjects according to gender (p = 1.000). However; significant difference in the mean of body mass index (BMI) among KOA group and control group, 27.60 ± 3.94 kg/m2 versus 24.38 ±1.83 kg/m2, respectively (p = 0.006).

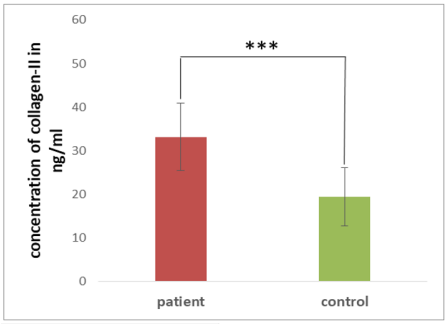

Figure 4: Bar-chart show a comparison of collagen type-II between knee osteoarthritis patients and control group; ***: significant at p ≤ 0.001

A comparison of serum level of collagen type-II between mild and moderate disease before treatment as shown in Figure-5. The mean serum collagen type-II was significantly higher in patients with moderate disease as comparison with mild disease, 27.59 ± 4.77, 38.36 ± 6.20, respectively at statistically significant p.value (p < 0.001).

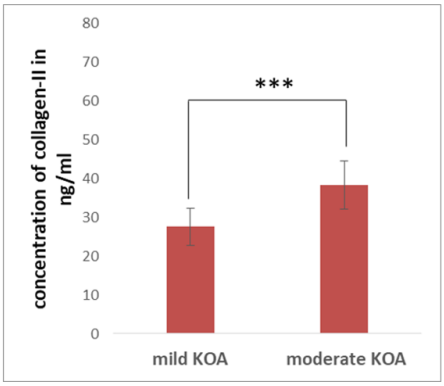

Figure 5: Bar-chart show a comparison of the level of collagen type-II between mild and moderate disease before treatment; ***: significant at p ≤ 0.001

A Comparison of serum level of collagen type-II between mild and moderate disease after treatment as shown in Figure-6. The mean serum collagen type-II was significantly higher in those patients with moderate disease as comparison with mild disease, 25.39 ± 4.18, 36.43 ± 7.02, respectively at statistically significant p.value (p < 0.001).

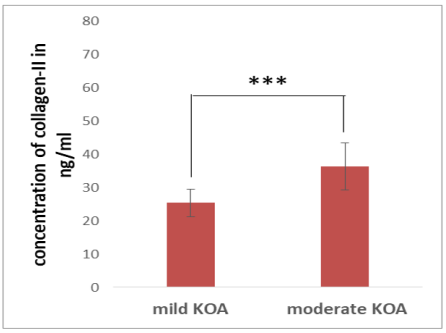

Figure 6: Bar-chart show a comparison of the level of collagen-II between mild and moderate disease after treatment; ***: significant at p ≤ 0.001

A comparison of serum collagen type-II before and after 3 months of treatment in mild disease as shown in Figure-7. This study shown there was no significant improvement in the mean level of serum collagen type-II among those with mild KOA after 3 months as compare to baseline the mean level was, 27.59 ± 4.77, 25.39 ± 4.18, respectively at significant p.value (p =0.163).

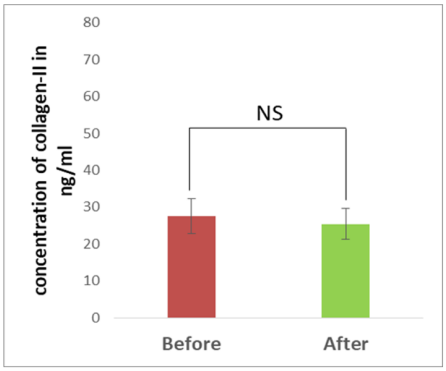

Figure 7: Bar chart show a Comparison of serum collagen type-II before and after treatment in mild disease; NS: no significant at p > 0.05

A comparison of serum collagen type-II before and after treatment in moderate disease as shown in Figure-8. This study shown there was no significant improvement in the mean level of serum collagen type-II among those with mild KOA after 3 months as compare to baseline the mean level was, 38.36 ± 6.20, 36.43 ± 7.02 (p =0.309).

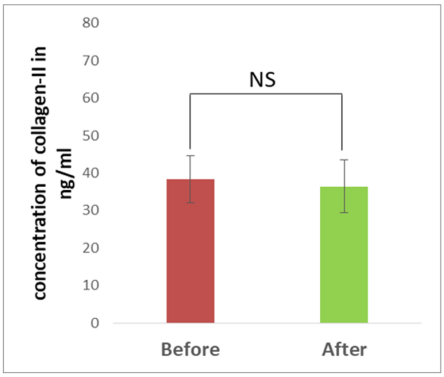

Figure 8: Bar chart show a Comparison of serum collagen type-II before and after treatment in moderate disease NS: no significant at $p > 0.05$.

A comparison of serum collagen type-II before and after treatment in mild disease according to the number of injections as shown in Figure 9. Single

injection, double injections, and triple injections resulted in no significant improvements after 3 months of intervention with pure-PRP as no significant reduction was seen in collagen type-II level at ($p < 0.05$), where the mean values before versus after 27.10 ± 3.25, 27.75 ± 1.22 (P= 0.893); 28.40 ± 5.46, 26.03 ± 5.52 (P= 0.345); 27.09 ± 6.00, 22.27 ± 2.46 (P= 0.080), for single, double, triple injection, respectively.

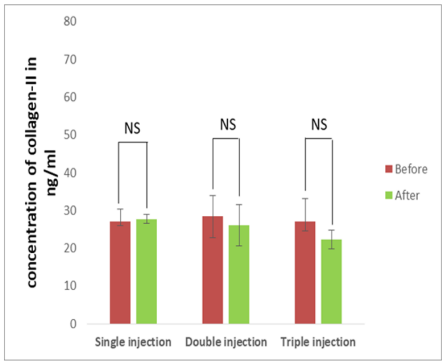

Figure 9: Bar-chart show a Comparison of serum collagen type-II before and after treatment in mild disease according to the number of injections; NS: no significant at $p > 0.05$.

A comparison of serum collagen type-II before and after treatment in moderate disease according to the number of injections as shown in Figure-10. Single injection, double injections, and triple injections resulted in no significant improvements after 3 months of intervention with pure-PRP as no significant reduction was seen in collagen type-II level at ($p < 0.05$), where the mean values before versus after 38.42 ± 8.10, 37.12 ± 6.25 (P= 0.499); 36.76 ± 4.43, 34.99 ± 9.94 (P= 0.686); 39.88 ± 5.44 , 36.92 ± 6.01 (P= 0.345), for single, double, triple injection, respectively.

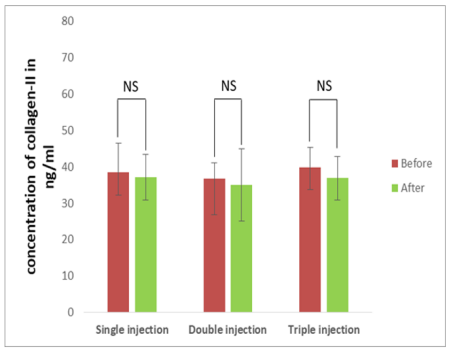

Figure 10: Bar-chart show a comparison of serum collagen type-II before and after treatment in moderate disease according to the number of injections; no significant at $p > 0.05$.

4 Discussion

Estimation of collagen type-II in serum of KOA and healthy control groups as well as in mild and moderate KOA

Type II collagen is an important element of articular cartilage, and KOA is characterized by the degeneration of this collagen. cartilage collagen turnover products can be present and detected in body fluids such as synovia, urine, and serum. A collagen-II biomarker has been developed that can be employed to evaluate collagen formation and breakdown and so provide concept about cartilage metabolism [20]. The current study found significantly elevation of serum collagen-II in patient with KOA and when compare this elevation with healthy population show significantly different between the level patient and control so that these result show agreement with Garnero P. showed that Type II collagen levels are significantly higher in individuals with knee osteoarthritis, and they are among the prospective markers that could be used in diagnostic strategy and monitoring of disease-modifying medications [21]. Sharif M et al., found the Changes in peripheral concentrations of biological indicators of metabolism, such as higher blood and urine levels of collagen type-II, suggest that the progress of KOA [22]. Valdes AM et al., found that collagen type-II is the most useful biochemical marker for diagnosis and predicting progression and incidence KOA [23]. According to the findings by Ali et al., the levels of collagen type II levels were elevated in KOA patients than in normal subjects. Subgroup evaluation showed that the level of collagen type-II increased with the severity of KOA. So, it is believed that collagen type-II could be a promising biomarker for future diagnosis [24]. In terms of KOA severity, there was a high considerable increase in systemic level of collagen type-II in patients with mild-KOA compared to moderate-KOA in the current study, which can be used to reflect disease prognosis and in the evaluation of disease modifying treatment strategy. These results

consistent with Xu Q, and his colleagues, showed that serum collagen type-II were observed to be greater in patients with KOA than in control subjects. Collagen type II concentrations were significantly greater in KOA patients with K-L grade-4 compared to those with K-L grades-2 and -3. Furthermore, those with KOA with K-L grade-3 had considerably higher levels of collagen type II than those with KOA with K-L grade-2. Collagen type II concentrations in KOA patients were shown to be significantly linked with the severity of the disorder as measured by KL grading criteria [25]. In contrast, the study also show inconsistency with Deberg et al. there was no correlation among serum of collagen type-II level and radiographic KOA severity [26].

A compared the impact of pure-PRP intra-articular injections on collagen type-II before and after intervention to examine their ability to regenerate the articular damaged collagen in KOA patients.

The American Academy of Orthopedic Surgeons (AAOS) study group concluded that there is insufficient data to make a recommendation for or against the use of IA PRP injection in their guidelines for patients with symptomatic knee OA [27]. Furthermore, the heterogeneity of individuals and the absence of radiological and biochemical indicators in most prior trials to increase the specificity of diagnosis of KOA mean that the application of PRP requires sufficient confirmation from well- designed clinical studies to justify PRP intervention for KOA [28]. Because type II collagen represents the most prevalent component in hyaline cartilage, serum levels of this protein could be used to predict response to therapy in KOA [29]. The current results show there are no statistically differences in the mean score of level of collagen type-II pre-intervention and post- intervention with pure-PRP and also show there is no difference in the number of injections where the results show no significant difference in either single or triple injection. The finding of the current consistent with Kuculmez Oet al. [30], shows there was no discernable improvement in the degradation of cartilage biomarkers of Type II collagen after PRP intervention. So, there is no significant evidence to indicate there is actual regeneration of the damaged articular cartilage despite there being little decrease in the mean value, especially in multiple injections. This result disagreement with the current study. Fawzy RM et al., Three months following PRP injection treatment, there was a dramatic decline in serum collagen-II concentration in KOA patients. [31].

5 Conclusions

PRP therapy was generally acceptable for patients in terms of improving symptoms and there were no complications following injection. However, there is insufficient indication that platelet rich plasma regenerates cartilage damage in knee OA patients, as no significant decrease in the amount of collagen type-II.

Conflict of Interest: None

Ethical consideration: from ethical committee in the Conflict of Interest: None

Ethical consideration: from ethical committee in the University of Al-Qadisiyah, Al-Diwanya , Iraq.

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