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Association between cartilage biomarker level and functional outcome in knee osteoarthritis patients receiving dextrose prolotherapy: a cross-sectional study

Yose Waluyo[1*], Agussalim Bukhari[2], Endy Adnan[3], Sari Rajwani Artika[1], Ahmad Yasin[4], Insani Nanda Wahyuni[1], Budu[5]

[1]Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia;
[2]Department of Clinical Nutrition, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia;
[3]Rheumatology Division, Department of Internal Medicine, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia;
[4]Cerebellum clinic, Makassar, Indonesia;
[5]Department of Ophthalmology, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia;

*Corresponding author:
Yose Waluyo;
Department of Physical Medicine and Rehabilitation, Faculty of Medicine, Universitas Hasanuddin, Makassar, Indonesia;
yose.waluyo@med.unhas.ac.id

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ABSTRACT

Background: Knee osteoarthritis (KOA) is a degenerative joint disease with relatively high prevalence globally and is one of the leading causes of disability in the elderly population. Dextrose prolotherapy (DPT) has been proven effective in improving functional outcomes in knee osteoarthritis. The effect of hypertonic dextrose on cartilage biomarkers has not been evaluated.
Purpose: To evaluate the association between a cartilage biomarker and changes in clinical outcomes among patients with KOA who received dextrose prolotherapy (DPT).
Patients and methods: This study was conducted with a cross-sectional design. Twenty-six participants received DPT at weeks 1, 5, and 9. Our primary measures were urinary c-terminal telopeptides of type II collagen (uCTX-II), measured by an enzyme-linked immunosorbent assay (ELISA), and the WOMAC score, measured at baseline and week 12.
Results: There were significant improvements in all WOMAC subscales and uCTX-II levels after DPT. There is no significant correlation between biomarker levels with the WOMAC score as a functional outcome indicator in KOA after DPT ($p > 0.05$), but there are positive correlations between pain, functional, total WOMAC score, and uCTX-II.
Conclusion: DPT may reduce cartilage degradation and improve functional outcomes in osteoarthritic knees. Significant drops in uCTX-II levels can affect functional outcomes, especially pain, functional and total WOMAC scores.

Keywords: *DPT, functional outcome, knee osteoarthritis, uCTX-II.*
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INTRODUCTION

Knee osteoarthritis (KOA) is a degenerative joint disease with relatively high prevalence globally and has become one of the leading causes of disability in America's elderly population. Based on a study in the United States in 2005, it was found that there were twenty-seven million adults over 18 years old suffering from symptomatic KOA.[1] The World Health Organization (WHO) reported that 40% of 70-year-old adults had KOA, 80% had limited motion, and 25% could not independently perform their daily activities.[2]

Because of its high prevalence and morbidity, many therapies are currently being developed to treat KOA. Based on the Indonesian Rheumatology Association (IRA) recommendations and other international rheumatology guidelines, there are several pharmacological therapies, including injections of corticosteroids and hyaluronan. The use of corticosteroids is still a matter of debate because of the many side effects that can occur, such as suppressing cartilage proteoglycan synthesis, worsening cartilage lesions, and even causing degenerative lesions in normal cartilage.[3,4] Meanwhile, a network meta-analysis with more valid reference observations shows that hyaluronan injection is not significantly different from intra-articular placebo for knee OA therapy and has a relatively higher cost than other commonly used non-operative modalities.[5]

Therefore, several other intraarticular injection therapies are being developed for the treatment of musculoskeletal diseases. Such therapies include platelet-rich plasm injection (PRP) and prolotherapy. Both are considered effective in reducing OA symptoms, but PRP requires a lengthy and costly process to manufacture the substance. Thus, prolotherapy is considered to be more efficient in time and cost.[6]

Prolotherapy is an injection technique that uses specific substances in the articular space, ligament, and tendons. Substances commonly used in this method are dextrose hyperosmolar, morrhuate sodium, and phenol-glycerine glucose.[7] Dextrose prolotherapy (DPT) has been used to effectively treat musculoskeletal disorders such as rotator cuff lesions, plantar fasciitis, low back pain, Achilles tendonitis, and knee osteoarthritis.[8,9]

DPT has been shown to improve functional outcomes in the first and second months after therapy in patients with

KOA.[6] Another study reported similar results that assessed OA's improvement from pain, swelling, knee stiffness, range of motion (ROM), and radiography. Pain at rest, walking or using stairs decreased significantly after the intervention by 44%, swelling decreased by 63%, and knee stiffness decreased by 85%, ROM increased by 14 degrees. Radiographic results also showed improvements in lateral patellofemoral cartilage thickness and reduced osteophyte thickness in the distal femur.[10] Other studies have demonstrated the effects of DPT on cartilage repair through arthroscopic examination.[11]

As we stated, some indicators have been used in evaluating DPT effectiveness in treating KOA, such as functional outcomes, radiological findings (plain x-ray and MRI), and arthroscopy.[6,10,11] There are very few studies that focus on the impact on molecular levels, especially cartilage biomarkers.

Several biomarkers in serum and urine have been investigated for their potential role in the diagnosis, assessment of disease burden, prognosis, and to a lesser extent, responsiveness to treatment in OA.[12] In general, such biomarkers are related to the cartilage turnover processes, or synovial inflammation, associated with OA.[13]

C-telopeptide fragments of type II collagen (CTX-II) are created during articular cartilage breakdown and excreted in urine (uCTX-II).[14] Studies have shown a significant correlation between joint disease duration and increased uCTX-II levels and WOMAC scores. uCTX-II can be found in the initial phase of cartilage degradation before KOA radiological abnormalities can be observed.[15] uCTX-II has the potential as an indicator of therapeutic response. uCTX-II levels decreased significantly in KOA patients treated with glucosamine after one year of follow-up.[16]

Several studies have evaluated the relationship between uCTX-II and functional outcomes in KOA patients, but none has evaluated KOA patients after receiving DPT treatment.[17]

Therefore, this study aimed to investigate the association between uCTX-II levels and functional outcomes (WOMAC score) in individuals with KOA receiving DPT treatment.

METHODS

Study design

A cross-sectional study design was carried out in a clinical outpatient setting. A primary data collection was conducted from November 2019 to February 2020 in Cerebellum private clinic.

Participants

Consecutive participant recruitment was conducted in this study. The inclusion criteria are: (1) adults aged >40 years; (2) diagnosed with KOA based on the ACR 2012 criteria. The exclusion criteria are: (1) receiving any previous intraarticular injection; (2) having used NSAIDs 1 week before intervention; (3) having contraindications of DPT such as abscess, cellulitis, and septic arthritis.

Sample size

Sample size was calculated with $\alpha = 0.05$, $\beta = 0.02$, $r = 0.20$. The total sample size needed was 232 participants, with the dropout rate predicted to be 20.0%. In this study, we only analyzed 26 participants.

Initial assessment

Information about the patients, including demographic data, current disease (symptoms and duration), previous medical history, and medication history, was obtained by a standardized interview, and a general practitioner performed a physical examination before the intervention. Body weight and height were used to calculate the body mass index (BMI).

X-ray images of the affected knee were performed by using AP and lateral aspects. An expert radiologist read x-ray images for the Kellgren-Lawrance (KL) grade to determine the severity of KOA. The KL grading consists of 5 levels from 0 to 4. Grade 0, no radiological findings of osteoarthritis; grade 1, no doubtful narrowing of joint space and possible osteophytic lipping; grade 2, definite osteophytes and possible narrowing of joint space; grade 3, moderate multiple osteophytes, definite narrowing of joint space, small pseudocyst areas with sclerotic walls and possible deformity of bone contour; and grade 4, large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone contour.

Evaluation of functional outcomes

Functional outcomes were evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). The WOMAC questionnaire evaluates five items for pain (range score 0-20), two items for stiffness (range score 0-8), and 17 items for physical function (range score 0-68), with the minimum score being 0 and the maximum 96. The research assistant evaluated WOMAC scores before the intervention and three weeks after the last injection.

uCTX-II evaluation

Random, midstream urine samples were collected. Samples were assayed with an enzyme-linked immunosorbent assay (ELISA) (Human Cross-Linked C-Terminal Telopeptides of Type II Collagen ELISA Kit Cat. No. E3701Hu, Bioassay Technology Laboratory (BT Lab), Shanghai Korain Biotech Co. Ltd, Shanghai, China). uCTX-II was measured before the intervention and three weeks after the last injection.

Dextrose Prolotherapy (DPT) Intervention

Subjects were given 5 mL of 25% dextrose (5 mL 40% dextrose, 2 mL lignocaine/lidocaine, and 1 mL aquadest) for intra-articular injection by using a superolateral approach and 30-40 mL of 15% dextrose (4 mL 40% dextrose, 2 mL lignocaine/lidocaine, and 4 mL aquadest) for periarticular injection in several sites such as the medial collateral ligament, pes anserine, tibial tubercle, coronary ligament, patellar edge, lateral collateral ligament, and tibiofibular ligament. The injection was administered in weeks 1, 5, and 9.

Statistical analysis

All statistical analyzes were performed with SPSS software (version 22, SPSS Inc., Chicago, IL, USA). The normality of the distribution of all variables was analyzed using the Shapiro-Wilk test. The difference between baseline and week 12 was analyzed using the paired t test or the Wilcoxon test if the data are not normally distributed. Pearson or Spearman correlation was

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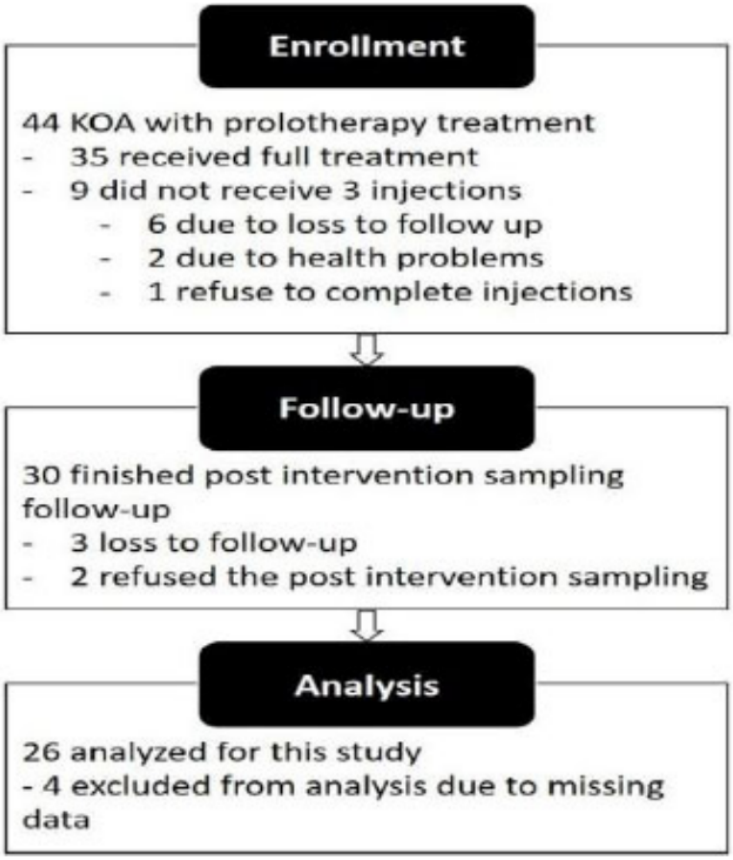

Figure 1. Flow Diagram.

used to examine the association between uCTX-II changes and WOMAC score changes. Correlations with α = .05 were considered statistically significant. A p-value <0.05 was considered significant.

RESULTS

A total of 44 potential participants with KOA who received DPT treatment were evaluated. Eighteen were excluded: nine were lost to follow-up, two had other health problems, one refused to complete the treatment, two refused to participate in post-intervention sampling, and four were excluded from analysis due to missing data (Figure 1).

Group characteristics and descriptive values are presented in Table 1. The mean ± SD age of the 26 subjects (76.9% women) included was 62.69 ± 6.9 years. Most of the participants were overweight – obese (73.1%) and of the moderate-severe grade of KOA (76.9%). The mean ± SD total WOMAC score and uCTX-II level were 36.08 ± 10.07 and 1.19 ± 0.41. This study found significant improvements in all the WOMAC subscale and uCTX-II levels after the DPT intervention (Table 1).

The correlation analysis between the uCTX-II score and the WOMAC score at baseline, follow-up, and change from baseline to follow-up did not reveal significant correlations (Table 2).

DISCUSSION

DPT has been shown to effectively reduce pain and improve functional status in patients with KOA patients and even has better results than HA injections.[18–21] Compared to local anesthesia, DPT showed better results in minimizing pain and improving functional status and was as effective as HA, ozone therapy, or even radiofrequency in the short, medium, and long term.[22,23] However, there is still limited study that evaluates DPT effects in KOA patients on the molecular aspects. Therefore, in this study, we evaluated the effects of DPT at the uCTX-II level in KOA patients.

Immunochemistry studies of CTX-II in animals and humans indicate that the epitope is related to molecules at the cartilage surface and bone-to-cartilage interface at the calcified region.[24,25] As such, uCTX-II excretion may be more significant among those with more severe KOA that includes cartilage defects with full penetration into the bone.[26] Ishijima et al. reported a higher uCTX-II concentration in people with early KOA who had knee pain. They speculated that the mechanism of production might be (1) synovitis resulting from joint debris as articular cartilage degrades or (2) pain in periarticular tissue resulting from altered joint mechanics as joint structure changes.[27]

Other studies have evaluated DPT's effects in improving cartilage damage by using other markers in addition to cartilage biomarkers. Histological evaluation of rabbits with articular defects showed an enhancement of chondrocytes in dextrose and serum autologous groups compared to normal saline injections.[28] Furthermore, the improvement in cartilage defect in patients with KOA with dextrose treatment has been clearly shown in arthroscopy evaluation.[11] In this study, we found there is a significant improvement in uCTX-II level after DPT treatment.

To date, the mechanism of DPT in treating KOA remains unclear. However, the most popular theory is that dextrose with a concentration of more than 10% may stimulate low-grade inflammatory processes by inducing growth factors, such as platelet-derived growth factor, beta transforming growth factor, epidermal growth factor, basic fibroblast growth factor, and insulin-like growth factor.[7,29] These growth factors then stimulate fibroblast activity and improve the healing

Table 1. Subject baseline characteristics and score changes after DPT.

	Baseline	Week 12	Score changes	p-value
Female (n, %)	20 (76.9)			
Age, mean (SD)	62.69 (±6.90)			
Body mass index, No (%)				
< 25	7 (26.9)			
≥ 25	19 (73.1)			
KL grading, No (%)				
1 – 2	6 (23.1)			
3 – 4	20 (76.9)			
WOMAC score, mean (SD)				
Pain (0-20)	7.24 ± 3.16	3.00 ± 2.81	4.24 ± 3.08	≤0.001
Stiffness (0-8)	3.04 ± 2.28	1.40 ± 1.50	1.64 ± 2.27	0.003[a]
Physical Function (0-68)	26.08 ± 8.51	14.44 ± 8.93	11. 64 ± 11.44	≤0.001[a]
Total (0-96)	36.36 ± 10.63	18.84 ± 11.45	17.52 ± 14.18	≤0.001
uCTX-II (ng/ mmol)	1.21 ± 0.39	0.94 ± 0.29	0.27 ±	0.007

**Abbreviations: KL, Kellgren-Lawrance; WOMAC, Western Ontario & McMaster Universities Osteoarthritis Index; uCTX-II, urinary C-Telopeptide fragments of type II collagen; [a]Wilcoxon test*

Table 2. Correlations between uCTX-II and WOMAC score at baseline, follow-up, and change from baseline to follow-up.

	Baseline uCTX-II vs. baseline WOMAC		Follow-up uCTX-II vs. Follow-up WOMAC		Δ uCTX-II vs. Δ WOMAC	
	r	p	r	p	r	p
WOMAC Pain	-0.134	0.523[a]	-0.037	0.859[a]	0.216	0.299[a]
WOMAC Stiffness	-0.275	0.183[b]	0.041	0.845[b]	-0.139	0.509[b]
WOMAC Function	-0.013	0.952[a]	0.135	0.521[a]	0.088	0.677[a]
WOMAC Total	-0.032	0.879[b]	0.104	0.622[a]	0.091	0.665[a]

**Abbreviations: uCTX-II, urinary C-Telopeptide fragments of type II collagen; WOMAC, Western Ontario & McMaster Universities Osteoarthritis Index; Δ, change from baseline to follow-up; r, correlation coefficient; p, level of significance; [a]Pearson correlation test; [b]Spearmann correlation test*

process of ligaments, tendons, and even cartilage, leading to pain and cartilage damage reduction.[30,31]

Although DPT has a positive effect both on functional outcomes and on the uCTX-II level, we did not find a significant correlation between the two of them. In contrast, we found positive correlations between pain, functional, total WOMAC and uCTX-II levels. There are several contradictive studies that evaluate the uCTX-II level and functional outcomes, especially pain score. Klocke et al. reported no correlations between uCTX-II levels and pain scores after corticosteroid injection.[31] Garnero et al. also found no correlation between uCTX-II levels with the WOMAC score in patients with KOA.[32] On the contrary, a previous study by Selistre et al. found that the WOMAC score, mainly pain and physical function, was associated with uCTX-II levels.[17] Based on the Garnero study, uCTX-II was the most predictive biomarker of JSA and minimal JSW, along with S-PIIINP and U-Glc-Gal-PYD. At the same time, the predictor of pain and physical function assessed by the WOMAC index was U-Glc-Gal-PYD, a specific index of synovial tissue activity.[32] Bihlet et al. also reported that uCTX-II was associated with weight-bearing pain, while non-weight bearing was not.[33]

uCTX-II may reflect osteoclastic resorption of calcified cartilage, which is more abundant closer to the bone tidemark, and another report has located the concentration of uCTX-II neoepitope to be highest at the cartilage bone interface.[25,34] As cartilage is aneural, it is not a tissue that can directly generate pain.[35] But changes in articulation caused by structural and associated changes in extracellular matrix turnover in articular cartilages, reflected by biomarkers, can result in the manifestation of pain in other joint tissues.[36–38] This may be a consequence of alterations in joint mechanics that result in structural changes elsewhere and/or the generation of joint debris that cause synovitis. Furthermore, subchondral bone, periosteum, synovium, ligaments, and joint capsule are all richly innervated and contain nerve ending that may be the source of pain in OA patients.[2,39,40] These theories explained the indirect association between uCTX-II and pain in knee OA.

Although this study is the first to report the correlations between uCTX-II levels and functional outcomes in osteoarthritic knees receiving prolotherapy, some limitations should be noted. This study was underpowered because of the lack of samples. We also have a huge dropout rate which is 40%. This study also did not evaluate the previous disease or comorbidities of participants that may have confounded the biomarker levels. The small sample size and homogenous ethnicity of the participants also restrict the generalizability of this study; hence, future studies should examine a larger, more comprehensible, and more representative subject population.

CONCLUSION

Prolotherapy may reduce cartilage degradation and improve functional

outcomes in osteoarthritic knees. The significant decreases in uCTX-II levels can affect functional outcomes, especially pain, functional, and the total WOMAC score. Further research with a larger sample size is needed to evaluate long-term prolotherapy outcomes in osteoarthritic knees based on functional outcomes and restoration of cartilage damage.

ETHICAL CONSIDERATIONS

The study was approved by the Ethics Committee of the Faculty of Medicine, Universitas Hasanuddin, with protocol number UH19100814. We received written consent from each of the patients enrolled in this study.

CONFLICT OF INTEREST

The author reports no conflicts of interest in this work.

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AUTHOR CONTRIBUTION

YW, AB, EA, and B designed the study. AY, SRA, and INW performed the measurements, YW, AB, EA, and B were involved in planning and supervised the work, AY, SRA, and INW processed the experimental data, performed the analysis, and drafted the manuscript. YW aided in interpreting the results and worked on the manuscript. All authors discussed the results and commented on the manuscript.

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