Effectiveness of the use of non-hydrolysed type II collagen in the treatment of osteoarthritis: a systematic review and meta-analysis

Eficácia do uso de colágeno não hidrolisado tipo II no tratamento da osteoartrite: uma revisão sistemática e uma meta-análise

DOI:10.34119/bjhrv6n1-131

Recebimento dos originais: 23/12/2022
Aceitação para publicação: 24/01/2023

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ABSTRACT

Objective: To evaluate the effectiveness of treating osteoarthritis with the use of type II non-denatured collagen (UCII). Methods: This is a study of systematic review and meta-analysis based on searches for randomized controlled clinical trials carried out in the PUBMED, SciELO, ScienceDirect and Google Scholar databases. 2009 and 2020 studies that analyzed the effectiveness of UCII in the treatment of patients with osteoarthritis using clinical and / or radiographic criteria and based on WOMAC and VAS scores were included. Results: A total of 4.850 references were found in the literature. When applying the inclusion criteria, there were only 4 studies suitable for selection, and 3 of them were possible to be included in the

meta-analysis. All studies were carried out in patients with knee osteoarthritis and the total sample was 202 patients. Meta-analysis of WOMAC and VAS scores was performed in the three independent studies according to the intervention adopted, and heterogeneity was not significant in both ($\tau^2 = 0.0$; $I^2 = 0\%$). In the WOMAC and VAS scores, the point estimate for the difference in standardized means was -0.44 (95% CI=-0.72 to -0.16; 0.002) and -0.37 (95% CI = - 0.65 to -0.09; 0.010) respectively, thus, the intervention group had positive effects and favorable results compared to the control group. There was no publication bias for the WOMAC and VAS outcomes; Conclusion: Based on the results of this study, the use of the UCII is effective in the treatment of osteoarthritis to improve parameters of pain and mobility on WOMAC and VAS parameters.

Keywords: osteoarthritis, treatment, UC-II.

RESUMO

Objetivo: Avaliar a eficácia do tratamento da osteoartrite com o uso de colágeno não desnaturado tipo II (UCII). Métodos: Este é um estudo de revisão sistemática e meta-análise baseado em pesquisas de ensaios clínicos controlados aleatórios realizados nas bases de dados PUBMED, SciELO, ScienceDirect e Google Scholar. Foram incluídos estudos de 2009 e 2020 que analisaram a eficácia da UCII no tratamento de pacientes com osteoartrite utilizando critérios clínicos e/ou radiográficos e baseados nos escores WOMAC e VAS. Resultados: Um total de 4.850 referências foram encontradas na literatura. Ao aplicar os critérios de inclusão, houve apenas 4 estudos adequados para seleção e 3 deles foram possíveis de serem incluídos na meta-análise. Todos os estudos foram realizados em pacientes com osteoartrose do joelho e a amostra total foi de 202 pacientes. A meta-análise dos escores WOMAC e VAS foi realizada nos três estudos independentes de acordo com a intervenção adotada, e a heterogeneidade não foi significativa em ambos ($\tau^2 = 0,0$; $I^2 = 0\%$). Nos escores WOMAC e VAS, a estimativa de pontos para a diferença de médias padronizadas foi de -0,44 (95% CI=-0,72 a -0,16; 0,002) e -0,37 (95% CI = - 0,65 a -0,09; 0,010) respectivamente, assim, o grupo intervenção teve efeitos positivos e resultados favoráveis em comparação com o grupo controle. Não houve viés de publicação para os resultados da WOMAC e da VAS; Conclusão: Com base nos resultados deste estudo, o uso do UCII é eficaz no tratamento da osteoartrite para melhorar os parâmetros de dor e mobilidade nos parâmetros WOMAC e VAS.

Palavras-chave: osteoartrose, tratamento, UC-II.

1 INTRODUCTION

Osteoarthritis (OA) is considered the main pathology of joint involvement in the elderly population, being responsible for several symptoms that interfere in the quality of life of these patients, such as: joint stiffness, reduced mobility and musculoskeletal pain. [1] It is estimated that around 15% of the world's population and around 50% of the population over 60 years of age suffer from OA, mainly knee OA. [2,3]

Articular cartilage is an extremely specialized and resistant avascular connective tissue. Collagen is the most abundant family of proteins in its extracellular matrix (ECM), represented mainly by type 2 collagen, which makes up 75% of the entire matrix and acts directly in the

mechanism of protection against traction forces, which is very affected in osteoarthritis. [3,4] Cartilage degeneration is mainly caused by proteolytic enzymes, metalloproteinases (MMP) being the most important of them. It is known that MMPs are normally inactive, like zymogens, but they can be activated by inflammatory cytokines and growth factors, present in the pathogenesis of osteoarthritis. [3]

In recent years, new proposals for therapeutic measures for OA have emerged, consisting of the use of drugs that would possibly modify the progression of the disease, reducing the degeneration of the cartilage tissue and providing its regeneration. Among the therapies there is the use of drugs called SYSADOA (symptomatic slow-acting drugs for OA), a group that have been studying glucosamine, chondroitin, diacerein, viscosupplementation with corticosteroids and hyaluronic acid and, more recently, collagen derivatives. The two main groups of collagen are undenatured collagen (UC) and hydrolyzed collagen (CH). [5]

Undenatured collagen (UC), especially type II UC, appears to be linked to a process called oral tolerance, in which the immune response is suppressed when oral antigens are administered. Furthermore, UC-II seems to be able to inhibit T cells and stimulate the production and recruitment of regulatory T cells (Treg) for the affected joint, producing anti-inflammatory cytokines that stimulate the production of cartilage matrix by chondrocytes. The matrix has amino acids that are also found in UC-II and that are necessary for the synthesis and repair of connective tissue. [5–7]

Therefore, the aim of this study is to evaluate the effectiveness of the treatment of osteoarthritis with the use of type II non-denatured collagen (UCII) and the therapeutic response through functional assessment and joint pain.

2 METHODOLOGY

This systematic review study was carried out in accordance with the PRISMA Statement (2009) protocol. [8] A search was carried out in electronic databases, with language restriction for English, Spanish and Portuguese, for clinical trials that evaluated the efficacy of using type II non-hydrolyzed collagen in the treatment of patients with osteoarthritis. The PUBMED, SciELO, ScienceDirect and Google Scholar databases were consulted. The descriptors used were “osteoarthritis”, “osteoarthrosis”, “UCII”, “native collagen type II” and “undenatured collagen type II”.

The inclusion criteria were organized according to the acronym PICO (Participants, Interventions, Comparator and Outcomes). So, were included randomized controlled clinical trials, carried out between 2009 and 2020, which aimed to study the effectiveness of UCII in

the treatment of patients with osteoarthritis, whose diagnosis had been obtained through clinical criteria and/or radiographic tests, and that evaluated its effectiveness based on the WOMAC and VAS scores.

The WOMAC score is used to assess the progression of osteoarthritis in the knee and hip. This index has the disadvantage of being specific for the knee and hip, however, it is capable of analyzing various aspects of health and well-being of patients. [9] The visual analogue scale (VAS) is used to investigate the patient's joint pain. [10] In some studies analyzed, the VAS scales at rest and in movement were used.

The Jadad scale was used to assess the quality of the articles, with the criterion for inclusion being a score equal to or greater than three. [11] Duplicate articles published in years prior to 2009 and non-randomized clinical trials performed in healthy patients or in situations of joint and/or bone diseases of other etiologies were excluded.

For the qualitative analysis, the sample size, general characteristics of the study population, intervention performed, comparison of the outcome between the intervention and control groups through the assessment of WOMAC and VAS scores and the conclusion of clinical trials were considered.

For the quantitative analysis, the standardized mean difference was used, dimensionless because the articles have different scales with no raw data that allow conversion to the same dimensional scale.

The analyzes were conducted using a random effects model, as there were differences in study designs between the analyzed works. Heterogeneity was evaluated through the parameters τ^2 and I2, in addition to a critical analysis of the designs and methodologies used. Risks for publication bias were examined using a funnel plot. Sensitivity analysis performed after critical review of included and excluded articles, seeking to assess the impact of arbitrary decisions on the review process. All analyzes were conducted using the Review Manager program (version 5.4 The Cochrane Collaboration, 2020).

3 RESULTS

A total of 4.850 references were found in the literature. When applying the inclusion criteria, there were only 4 studies suitable for selection, and 3 studies were considered homogeneous and used in the meta-analysis (Figure 1). [6,7,12] The total sample of the studies was 573 patients, but only 481 reached the end of the research. All records found were written in the English language.

Based on the raw data sent, i the study of Bakilan (2009) et. al., the mean and standard deviation (SD) of the differences between the pre-treatment (Ti) and final (Tf) evaluations were obtained. Based on the study data, the means for the control group were estimated. The SD of the control group was adopted based on the values calculated for the intervention group.

A graphical extraction in the Crowley et.al (2016) study was used (through DigitizeIt software), followed by an estimate of the SD of the differences (Tf - Ti) based on the correlation coefficient extracted from the raw data sent by Bakilan (2009).

The characteristics (author and year of publication, journal of publication, total sample, age and sex of the sample, severity of knee osteoarthritis, follow-up time, and type of study) of the four clinical trials selected for qualitative analysis are shown in Table 1.

All studies were performed in patients with knee osteoarthritis. In evaluating the interventions performed, the action of UCII was compared with that of the association of glucosamine hydrochloride and chondroitin sulfate (G+C) in two studies, and in one of them it was also compared with placebo. [6,7] In another study, UCII was associated with acetaminophen and compared with a placebo containing only acetaminophen. [12] Only in one study was there an intervention only with the UCII. [13] For a better analysis of each intervention and study outcome, Table 2 illustrates the intervention group and the control group, in addition to the doses administered for each group, and the initial and final WOMAC and VAS scores, demonstrating their respective outcomes. Only two studies [7,12] demonstrated results for the subdivisions of the WOMAC classification (pain, stiffness and function) and one of them [12] also demonstrated the subdivision of the VAS scale (rest and movement). The three studies that participated in the meta-analysis are highlighted in bold in Table 2.

Meta-analysis of WOMAC and VAS scores was performed in the three independent studies according to the intervention adopted.

In the WOMAC score, the point estimate for the difference in standardized means was -0.44 (95% CI=-0.72 to -0.16; 0.002) as shown in Figure 2. Given that, there is a significant relevance of the use of UC II in the treatment of pain, stiffness and joint function compared to the control group.

In the VAS score, the point estimate for standardized mean differences was -0.37 (95% CI = -0.65 to -0.09; 0.010) as shown in Figure 2. There was significant relevance with the use of UC II in pain management compared to control groups.

Heterogeneity was not significant ($\tau^2 = 0.0$; $I^2 = 0\%$) in the analysis of both scores.

The meta-analysis of the WOMAC and VAS scores showed significant and positive effects of the treatment of osteoarthritis with type II collagen in relation to the use of other interventions adopted in the control groups.

The funnel plot graph is presented in visual analysis with a symmetrical distribution, which may conclude that there is no publication bias for the WOMAC and VAS outcomes (Figure 3)

4 DISCUSSION

The use of SYSADOA in the treatment of osteoarthritis has been seen promisingly over the years. Thus, a wide variety of studies have been published in order to prove its effectiveness. UC II among the drugs used for the treatment of OA has occupied a position of greater evidence, since its role in the renewal of collagen in the joint has been increasingly observed. [14]

In our study, the meta-analysis showed the efficacy of using UC II in osteoarthritis with significant and positive effects on the WOMAC and VAS scales when compared to other interventions used in the control groups. Aspects such as pain, stiffness and joint function showed significant improvement relevance when compared to the control. It was also evidenced the improvement of the VAS score with relevance in the use of the UC II compared to the control group.

The sample heterogeneity was not significant in both scores, confirming that there was no selection bias in the study population.

Our results were different from the systematic review by Van Vijven (2012) where there was no significant improvement in pain and function in UC II compared to glucosamine, but it was significant in the WOMAC scores. [5] Results also confirmed by the non-systematic review de Prabhoo (2018) where the use of UC II had significance in the improvement of the three WOMAC scores and in the VAS indexes when compared to the control groups, he also used the Lequesne's functional scale, which showed a 20% improvement in use UCII when compared to the control. [3]

Mehra (2019) highlights the good tolerability and safety in the use of UCII, with less than 5% of patients with adverse effects and significant results in the WOMAC and VAS indices in evaluations of 30, 60 and 90 days of use in patients with osteoarthritis of knee. These data were also confirmed by the study by Crowley (2009), demonstrating improvement in the various aspects of pain (VAS) when compared to UCII and glucosmin+chondroitin, also showing an improvement in the Lequesne's functional scale when compared to the control.

These results confirm once again what in vitro studies, such as the one by Bagi (2017) where rats submitted to partial meniscectomy had less joint wear and more function in the operated limb when using UC II compared with not using. The rats in the model showed less loss of cartilage matrix and less cartilage degradation when using the UCII. [15]

In addition to these studies, it was evidenced in the work of Gupta (2009), carried out in horses with moderate to severe osteoarthritis, with symptoms such as difficulty walking, stiffness and swelling of the joint and joint pain, that the effectiveness of using type II collagen is superior in the treatment of OA in relation to the use of glucosamia and chondroitin.[16] Positive results started to be observed from 30 days after the beginning of the administrations and after 5 months of treatment the horses were very active and performing their daily activities normally.

The effectiveness of UCII was also evaluated through a clinical trial described by Bagchi (2002). The study was carried out with five women between 58 and 78 years who suffered from significant joint pain and a daily dose of 10 mg/day of UCII was used for 42 days. This can lead to a significant reduction in pain, morning stiffness, stiffness after rest periods, pain that worsens with the use of the affected joint, and loss of range of motion and joint function. [17]

The safety and toxicity of using undenatured type II collagen was evaluated in the study by Marone (2010). [18] In tests in female rats, the capacity for acute oral toxicity by the administration of oral UCII was studied in relation to mortality, signs of toxicity and changes in the behavior of these animals. After 14 days of observation and administration of 5,000 mg/kg, none of the rats showed changes with the use of the drug at this dosage. Thus, in addition to being an effective therapy, the use of type II collagen seems to be safe in its indicated doses.

Our study presented as a limitation a small number of references found that met the criteria of a randomized controlled clinical trial, as well as access to confidence intervals and requested data.

However, the good results of the application of UC II in OA could be seen through the WOMAC and VAS questionnaires. Furthermore, the studies were carried out in patients with knee osteoarthritis, which limited our perception to the involvement of only one joint, despite this being the most incident of the pathology in the world.

Thus, it is relevant to produce more studies that assess the effectiveness of UCII in the treatment of osteoarthritis in order to constantly seek a better quality of life for the large number of patients who suffer from the disease.

5 CONCLUSION

Based on the results of this study, the use of the UCII is effective in the treatment of osteoarthritis to improve parameters of pain and mobility on WOMAC and VAS parameters.

SUPPORT SOURCES

This study did not receive any financial support from public, commercial or non-profit sources.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest in the preparation and execution of this work.

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ANEXOS

Figure 1: Prism Organization Chart

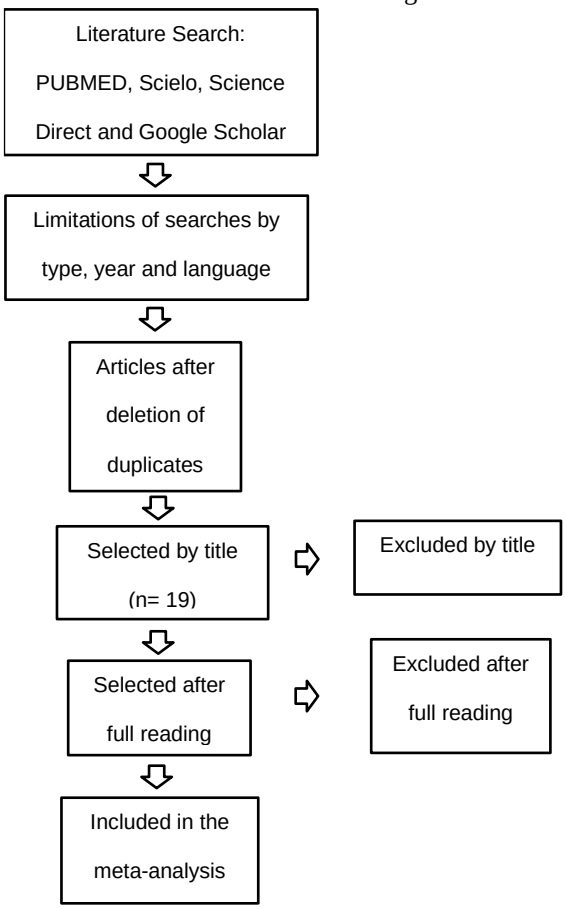

Table 1: Characteristics of the Works.

Author/Year	Journal	Total N	Age/Sex	Gonarthrosis severity	Follow-up time	Type of Study
Crowley et al., 2009	International Journal of Medical Sciences	52	45 - 75 years old F: 22 M: 30	Moderate and longer than 3 months	90 days	Double-Blind Randomized Clinical Trial
Bakilan et al., 2016	The Eurasian Journal of Medicine	39	45 - 70 anos F: 36 M: 3	Moderate to Severe (KLS 2 e 3)	90 days	Mono-Blind Randomized Controlled Clinical Trial
Lugo et al., 2016	Nutrition Journal	191 (Nf = 164)	40 - 75 years old F: 96 M: 89	Moderate to Severe (KLS 2 e 3)	180 days	Double-blind and placebo-controlled randomized clinical trial
Mehra et al., 2019	International Journal of Research in Orthopaedics	291 (Nf = 226)	28 - 79 years old (average 56.2 +/- 8.7) F: 53,3% (155) M: 46,7% (136)	Not specified (Clinical or radiographic gonarthrosis)	90 days	Non-Interventional Multicenter Real Life Study

Table 2: Characteristics of the intervention and control groups

Author/Year	Intervention group	Control group	Groups	Outcome				
				WOMAC				VAS
Crowley et al., 2009	UC-II: 40mg/day (10mg/day of UC-II bioactive) (N = 26)	G+C: 1.500mg/day + 1.200mg/day (N = 26)	UC-II	33% reduction				40% reduction
			G+C	14% reduction				15% reduction
Bakilan et al., 2016	UC-II + AC: 10mg/day (UC-II native) + 1500mg/day (N = 20)	AC: 1500mg/day (N = 19)		WOMAC-pain	WOMAC-stiffness	WOMAC-function	WOMAC-total	VAS - rest / VAS-walking
			UC-II + AC	T0: 12 T90: 9	T0: 4,5 T90: 4	T0: 37 T90: 31	T0: 53,5 T90: 44	T0: 4 / T0: 6 T90: 2 / T90: 3
			AC	T0: 9 T90: 11	T0: 5 T90: 5	T0: 33 T90: 35	T0: 50 T90: 52	T0: 3 / T0:3 T90: 3 / T90: 90
Lugo et al., 2016	UC-II: 40mg/day (N = 63)	G+C 1.500mg/day + 1200mg/day (N = 65) Placebo (N = 58)		WOMAC-pain	WOMAC-stiffness	WOMAC-function	WOMAC-total	VAS - rest / VAS-walking
			UC-II	T0: -3,88 Tf -24	T0: -4,24 Tf: -23,8	T0: -3,91 Tf: - 22,5	-551	Tf: -22,6
			G+C	T0: -4,57 Tf: -19,2	T0: -4,22 Tf: -19,4	T0: - 4,14 T90: - 18,8	-454	Tf: -17,0
			Placebo	T0: -3,21 Tf: -17,0	T0: -3,42 Tf: -17,8	T0: -3,17 T90: -17,3	-414	Tf: - 18,4
Mehra et al., 2019	UC-II initial (UCII-i)	UC-II final (UCII-f)	UCII-i UCII-f		59,7 +/- 19,6 - 20,7 +/- 12,6			6,5 +/- 1,4 - 3.3 +/- 1,8

Figure 2: Forest Plot WOMAC and VAS scores

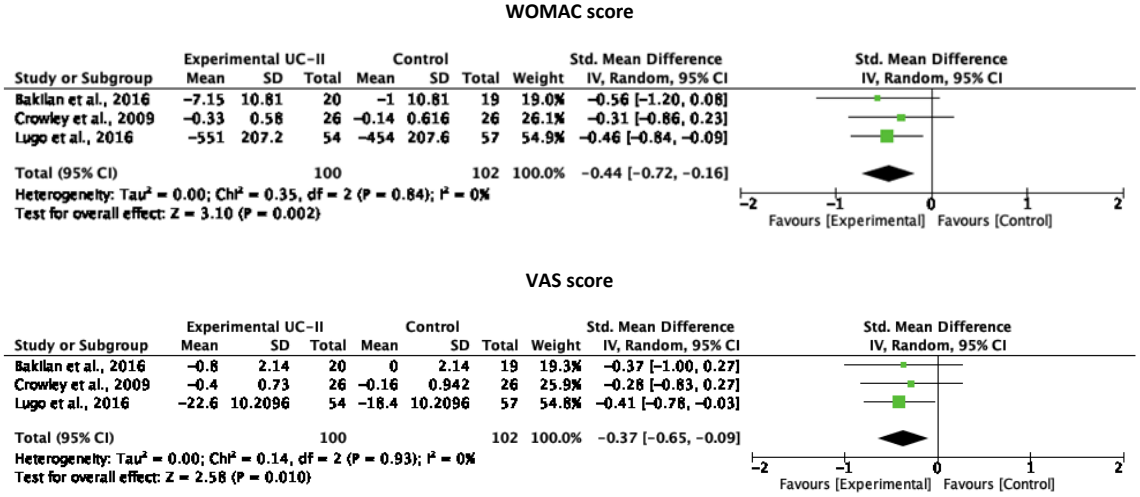

Figure 3: Funnel Plot WOMAC and VAS scores