



ASSOCIATION BETWEEN KNEE OSTEOARTHRITIS AND METABOLIC SYNDROME: A SYSTEMATIC REVIEW

Associação entre osteoartrite de joelho e síndrome metabólica: uma revisão sistemática

Asociación entre osteoartritis de rodilla y síndrome metabólico: una revisión sistemática

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ABSTRACT

Objective: To identify possible associations between knee osteoarthritis (KO) and metabolic syndrome (MS). **Methods:** A systematic review was carried out between 2012 and 2017 on the Virtual Health Library (VHL), SciELO, Cochrane and Embase databases to search for publications in Portuguese and/or English using the descriptors "osteoarthritis" and "metabolic syndrome" in both languages. Methodological quality was assessed using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) Statement. Seven articles with high methodological quality were selected. **Results:** The data point to the association between symptomatic KO and systemic arterial hypertension, dyslipidemia and number of accumulated factors, with increased severity and progression of symptoms in women. However, the association between the pre-inflammatory stage of MS and KO has not yet been fully clarified. **Conclusion:** The findings suggest that a better understanding of the actions of the metabolic pathways involved in KO could open a new avenue for the treatment of these patients.

Descriptors: Osteoarthritis; Metabolic Syndrome; Obesity; Hypertension.

RESUMO

Objetivo: Identificar as possíveis associações entre osteoartrite de joelho (OA) e síndrome metabólica (SM). **Métodos:** Revisão sistemática de literatura, ocorrida entre os anos de 2012 e 2017, nas bases: Biblioteca Virtual em Saúde (BVS), SciELO, Cochrane e Embase; em português e/ou inglês, com os descritores "osteoartrite" e "síndrome metabólica" em ambas as línguas. Para avaliação da qualidade metodológica, utilizou-se a Declaração STROBE (Strengthening the Reporting of Observational Studies in Epidemiology). Selecionaram-se sete artigos, todos com qualidade metodológica alta. **Resultados:** Os dados apontam para associação entre OA sintomática e hipertensão arterial sistêmica, dislipidemia e o número de fatores acumulados, com aumento da gravidade e progressão dos sintomas em mulheres. Entretanto, ainda não se esclareceu por completo a associação entre o estado pré-inflamatório da SM e a OA. **Conclusão:** Os resultados encontrados sugerem que uma melhor compreensão das ações das vias metabólicas envolvidas com a osteoartrite de joelho poderia abrir uma nova avenida terapêutica a esses pacientes.

Descritores: Osteoartrite; Síndrome Metabólica; Obesidade; Hipertensão.

RESUMEN

Objetivo: Identificar las posibles asociaciones entre la osteoartritis de rodilla (OA) y el síndrome metabólico (SM). **Métodos:** Revisión sistemática de la literatura entre los años de 2012 y 2017 en las bases de datos Biblioteca Virtual de Salud (BVS), SciELO, Cochrane y Embase; en portugués y/o inglés con los descriptores "osteoartritis" y "síndrome metabólico" en ambos los idiomas. Para la evaluación de la calidad metodológica se utilizó la Declaración STROBE (Strengthening the Reporting of



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Observational Studies in Epidemiology). Se han seleccionado siete artículos y todos con alta calidad metodológica. **Resultados:** Los datos señalan la asociación entre la OA sintomática y la hipertensión arterial sistémica, la dislipidemia y el número de factores acumulados, con el aumento de la severidad y la progresión de los síntomas en mujeres. Sin embargo, todavía no se ha aclarado por completo la asociación entre el estado pre-inflamatorio del SM y la AO. **Conclusión:** Los resultados encontrados sugieren que una mejor comprensión de las acciones de las vías metabólicas de la osteoartritis de rodilla puede ser una nueva opción terapéutica para esos pacientes.

Descriptor: Osteoartritis; Síndrome Metabólico; Obesidad; Hipertensión.

INTRODUCTION

Osteoarthritis (OA) is a musculoskeletal condition that affects millions of people and is the leading cause of disability in people aged over 40 years worldwide⁽¹⁻³⁾. It is the main cause of physical disability and it causes pain, stiffness and limitations in activities of daily living (ADL)⁽³⁻⁵⁾. Its incidence increases with advancing age: about 40% of adults over 70 years of age have knee OA and 80% of those with the disease have some type of movement limitation⁽⁵⁾.

Despite being historically seen as a wearing disease, it is currently considered a low-grade inflammatory disease resulting from the loss of balance between cellular degradation and repair within the cartilage by chondrocytes⁽⁶⁾. Its pathogenesis and progression seem to be the result of the complex and dynamic interaction of mechanics and cellular and systemic molecular factors⁽⁷⁻⁹⁾.

Due to its heterogeneity, it is subdivided into phenotypic subgroups⁽⁹⁾ that, despite presenting important causal differences, probably share common elements, such as aging, biomechanical factors and metabolic alterations^(9,10).

In the 20th century, the metabolic syndrome (MS) increased dramatically due to changes in the population's lifestyle (increased calorie intake and sedentary behavior)⁽¹⁰⁾. The World Health Organization (WHO)⁽¹¹⁾ defined MS as a change in glucose metabolism and/or insulin resistance associated with systemic arterial hypertension (SAH), an increase in plasma triglycerides and/or a decrease in High Density Lipoprotein (HDL) cholesterol and central or abdominal obesity; however, there is still no single definition. It affects mainly people over 45 years of age and it is present in 10 to 30% of the world population and prevalent in 59% of patients with OA⁽¹⁾. Moreover, individuals with OA and MS concomitantly present more severe and early symptoms than the general population⁽²⁾.

The association between diabetes mellitus (DM) and OA was first described in 1961⁽¹²⁾, but the first large study that explored this association was carried out only in 2007⁽¹³⁾. The authors demonstrated that patients with type 2 DM had a two-fold higher rate of knee or hip arthroplasty due to OA than non-diabetic subjects. They also found that diabetic patients had higher levels of synovial inflammation and pain⁽¹³⁾.

Thereafter, a new subtype of OA was proposed: the metabolic OA⁽¹⁴⁾. The involvement of metabolic factors in the etiology of OA is supported by epidemiological studies and experimental data⁽¹⁵⁾. Both in vivo and in vitro findings have shown that inflammatory mediators derived from adipose tissue, hyperglycemia, dyslipidemia and chronic low-grade inflammation have a direct deleterious effect on cartilage metabolism^(1-3,10,15).

Given the risk of functional impairment caused by OA, the cardiovascular risk and the high morbidity and mortality rates of MS are currently seen as obstacles to quality of life and a major public health issue⁽⁸⁻¹⁰⁾. Changes in life habits and regular physical activity, among other healthy attitudes, lead to the prevention of new symptoms, delayed aggravation of existing symptoms and reduction of health risk^(16,17). Thus, the control of the signs and symptoms of OA and MS are essential in promoting a healthy life⁽¹⁸⁾.

Understanding the mechanisms of the association between metabolic factors and knee OA and the way they harm the human body is critical for the development and targeting of more specific and effective therapies for symptom prevention and health promotion. Thus, this study aimed to identify possible associations between knee osteoarthritis and metabolic syndrome.

METHODS

The present study is a systematic review of studies indexed in the free access electronic databases of Virtual Health Library (VHL), Scielo, Cochrane and Embase. Aiming to select the most recent studies and respect the original research schedule, only studies published between January 2012 and April 2017 were analyzed.

The search for studies was carried out using the descriptors osteoarthritis (*osteoartrite*) and metabolic syndrome (*síndrome metabólica*) and the connector “and” (*‘e’*). Inclusion criteria were: full texts of studies published in English and/or Portuguese carried out with human beings. Exclusion criteria were: a) editorials, letter to the reader and/or review studies; b) studies that did not assess the association between OA and MS; c) studies that did not assess isolated knee OA.

The first stage of the study consisted of a survey of the studies found by applying the descriptors in the previously mentioned the databases. In the second stage, the pre-established exclusion criteria were applied, and in the third stage, the titles and abstracts of the studies were analyzed and duplicates and studies that did not meet the inclusion criteria were excluded. The fourth stage consisted of a thorough reading of the full texts and a qualitative analysis of them. The process of selecting, reading and analyzing the articles was conducted in pairs. In case of disagreement between the reviewers, they should discuss the issues in order to determine whether the study should be included.

The methodological quality of the studies was determined according to the Strengthening the Reporting of Observational Studies in Epidemiology or STROBE Statement⁽¹⁹⁾. This statement is a checklist consisting of 22 items with recommendations on what should be included in a more accurate and complete description of studies. Scores of zero (when the item is not addressed) or one (when the item is addressed) are assigned, thus indicating the study’s quality level. The higher the score, the higher the quality of the study. This strategy was used in order to identify the quality of the studies: high quality (above 70% of the score), medium quality (between 50 to 69%) and low quality (below 50%).

RESULTS

After a thorough analysis of the titles and abstracts, seven studies were deemed relevant to the review: Niu et al., 2017⁽²⁰⁾, Yasuda et al., 2017⁽²¹⁾, Eymard et al., 2015⁽²²⁾, Maddah et al., 2015⁽²³⁾, Shin, 2014⁽²⁴⁾, Han et al., 2013⁽²⁵⁾ and Jungmann et al., 2013⁽²⁶⁾.

Figure 1 shows the stages of the study selection process and the number of studies identified, selected, excluded and included in the review.

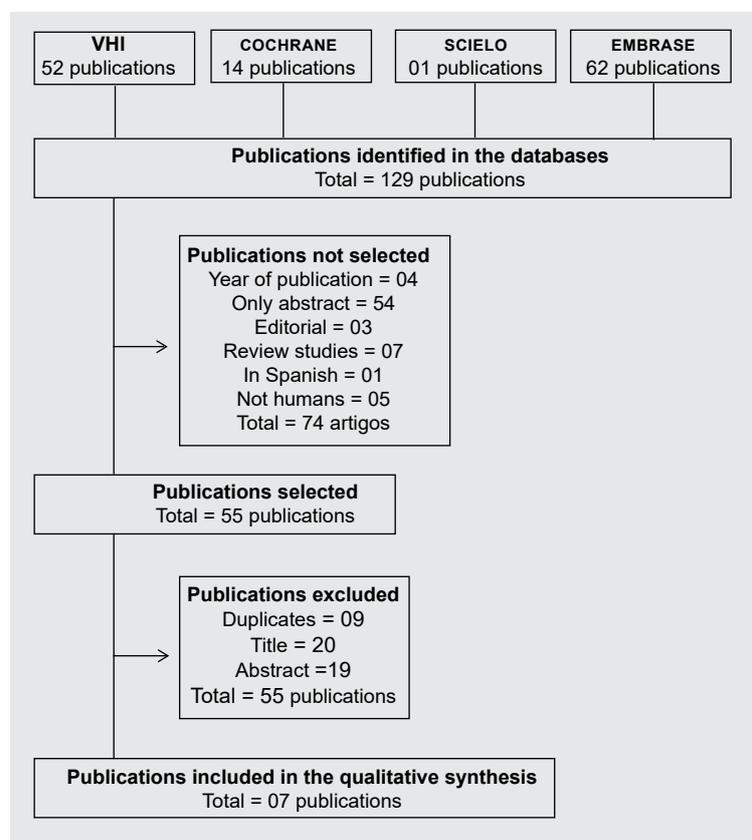


Figure 1 - Flow chart of the study selection stages in the systematic review.

The systematic review consisted of the analysis of the seven studies that assessed the association between knee OA and MS. Details on sample composition, research locale, OA diagnostic criteria and MS diagnostic criteria in each study are presented in Chart I.

Chart I - Characterization of the analyzed studies.

Author	Sample	Age / Mean	Study / Locale	OA	MS
Niu et al. 2017 ⁽²⁰⁾	991 subjects	> 40 years 54.2	Framingham USA	KL \geq 2	NCEP ATP III
Yasuda et al. 2017 ⁽²¹⁾	119 women	45-88 years 69.0	Japan	KL \geq 2	Examination Committee of Criteria for Metabolic Syndrome in Japan
Eymard et al. 2015 ⁽²²⁾	559 patients	> 50 years 62.8	SEKIOIA Study 18 countries	JSW (annual mean)	NCEP ATP III *Self-report
Maddah et al. 2015 ⁽²³⁾	625 subjects	> 18 years Men 55.4 Women 54.4	Iran	KL \geq 2	NCEP ATP III
Shin 2014 ⁽²⁴⁾	2,363 subjects	\geq 50 years 63.4	KNHANES Study Korea	KL \geq 2	NCEP ATP III
Han et al. 2013 ⁽²⁵⁾	2,234 subjects	40- 91 years With OA 64.5 Without OA 53.2	KNHANES Study Korea	Self-report	NCEP ATP III
Jungmann et al 2013 ⁽²⁶⁾	403 subjects	45-60 years Men 52.0 Women 52.2	The Osteoarthritis Initiative Multicenter/ USA	KL \geq 2	NCEP ATP III *Self-report

OA: Osteoarthritis; MS: Metabolic Syndrome; USA: United States of America; KL: Kellgren-Lawrence; SEKIOIA: Strontium Ranelate in Knee Osteoarthritis; JSW: Joint Space Width; KNHANES: Korean National Health and Nutrition Examination Survey; NCEP ATP III: National Cholesterol Education Program-Adult Treatment Panel III

All the studies are observational: three are longitudinal^(20,22,26) and four are cross-sectional^(21,23-25). In addition, two are multicenter studies^(22,25), six were carried out with individuals of both sexes^(20,22-26) and one was carried out with women only⁽²¹⁾.

As for the year of publication, two studies were published in 2017^(20,21), two in 2015^(22,23), one in 2014⁽²⁴⁾ and two in 2013^(25,26). No publications in 2012 and in 2016 could be included in this review.

With regard to age, one study was carried out with individuals aged over 18 years⁽²³⁾, two included individuals aged over 40 years^(20,25), two included individuals aged over 45 years^(21,26) and two were carried out with individuals aged over 50 years^(22,24). Only one of the studies had set a maximum age limit⁽²⁶⁾ – 60 years – and none of them was exclusively carried out with older adults. In one study, the mean age of the subjects was over 65 years⁽²¹⁾.

As for sample composition, one study assessed individuals admitted for elective knee surgery⁽²¹⁾, two assessed outpatients with symptomatic OA^(22,23), four studies assessed individuals in the community^(20,24-26) and no study assessed institutionalized individuals.

MS was defined based on the NCEP ATP III in six studies^(20,22-26); however, two of them used self-report for some of the metabolic factors^(22,26), such as diabetes and triglycerides. One study used other diagnostic criteria recommended by the Examination Committee of Criteria for Metabolic Syndrome of Japan⁽²¹⁾.

For the diagnosis of OA, five studies used the KL \geq 2 scale^(20,12,23,24,26), one used joint space measurement⁽²²⁾ and one used self-report⁽²⁵⁾.

All the studies obtained a STROBE⁽¹⁹⁾ score between 16 and 22, which indicates a high quality percentage (between 72.72% and 100%). The items that received no scores were related to the lack of description of the key elements of the study design, the description of the relevant context, places and dates, measures taken to avoid bias, discrimination of participants in each phase of the study, specification of confounding factors, a summary of the main objectives and limitations of the study in the discussion, the possibility of generalizability of results, and the lack of description of research funding.

DISCUSSION

For 57% of the researchers, knee OA prevails in women and older people^(20,23-25). For 29% of the researchers, people with OA have a higher body mass index (BMI)^(20,23), increased WC, higher systolic blood pressure (SBP) levels, higher LDL levels^(23,25), higher smoking rates, lower weight, decreased height, lower drinking rates and lower levels of physical activity^(20,25). For 14% of the researchers, people with OA have lower levels of education⁽²⁰⁾.

With regard to MS: 29% of the studies reported that its prevalence is higher in men and that it increases with advancing age^(23,25); 14% of the studies showed that WC measure is associated with a higher prevalence of OA in women⁽²⁵⁾ and that having MS increases the odds of developing OA⁽²⁴⁾ in both sexes by 49%.

As for isolated metabolic factors: 29% of the studies found a significant association between type 2 DM and knee joint space reduction^(22,26). However, 50% of the studies state that such association occurs only in men⁽²²⁾ and the other 50% state it occurs in both sexes⁽²⁶⁾.

The accumulation of metabolic factors, regardless of BMI, was associated with a greater deterioration of articular cartilage in 14% of the publications⁽²⁶⁾. The authors suggest a negative metabolic interference in the biochemical composition of the cartilage. On the other hand, 43% of the publications found no associations between the metabolic components⁽²⁰⁻²²⁾ – whether isolated or accumulated – and radiographic knee OA after adjusting for confounding variables.

Both isolated factors and MS are associated with knee OA, but not regardless of BMI and body weight⁽²⁰⁻²²⁾. A recent systematic review on the subject found no such an association⁽²⁷⁾. In this study, the researchers reported that after adjusting for BMI or body weight the association between MS and radiographic knee OA did not remain significant in the studies analyzed.

With regard to MS and symptomatic OA, there was a significant association of hypertension, dyslipidemia and number of accumulated factors with increased severity and progression of symptoms in women in 14% of the studies⁽¹⁸⁾ even after adjusting for BMI and age. In that case, the authors pointed out that the accumulation of metabolic components is associated with increased pain intensity, regardless of age, sex and weight⁽¹⁸⁾.

Some differences in the results of the studies are possibly due to the heterogeneity of the samples – age, sex and different health conditions – and the lack of standardization (and even some adaptations) of the diagnostic criteria. Authors also found conflicting and insufficient data to establish a definitive conclusion about such an association. In addition, they suggest that further studies use more robust samples to focus on the early stages of disease and on the manifestations of metabolic components throughout life⁽²⁷⁾.

Including information on healthy diet and exercise may reduce additional costs for the management of OA symptomatology^(21,26). Preventive measures and changes in lifestyle have been highlighted as health providers. The Mediterranean diet is associated not only with a lower prevalence of knee OA^(10,28) and cardiovascular disease (CVD)⁽²⁹⁾, but also with better quality of life, lower levels of pain and functional disability, and lower rates of depression in patients with knee OA⁽³⁰⁾.

The monitoring and prevention of MS through intervention actions delivered by the health sector and specific programs of the Unified Health System aimed at reducing risk factors and promoting obesity control and regular physical activity to improve lipid and glycemic profile and control blood pressure levels should be considered⁽³¹⁾.

It is quite beneficial to educate and encourage society to remain healthy, including those individuals without symptoms in a preventive way. However, it is important to emphasize that the effectiveness of health promotion programs depends, among other factors, on contextual behaviors and situational factors, such as levels of pain, self-efficacy and awareness of recommendation⁽³²⁾. Thus, providers and facilitators of these programs should consider the salience of these factors for self-management and health promotion.

Longitudinal studies with standardized criteria that seek to assess the specific impact of chronic metabolic and hyperglycemic components on OA progression are interesting and should be encouraged.

CONCLUSION

It is concluded that a better understanding of the actions of the metabolic pathways involved in the onset and progression of OA may open a new avenue for therapy focused on glycemic balance and, together with health promotion programs, promote a healthier life for these patients.

CONFLICTS OF INTEREST

There are no conflicts of interest in this study.

CONTRIBUTIONS

Maura Fernandes Franco contributed to the study conception and design; acquisition, analysis and interpretation of data; writing and/or revision of the manuscript; **Daniel Vicentini de Oliveira** contributed to the analysis and interpretation of data; **Arlete Maria Valente Coimbra** contributed to the study conception and design; revision of the manuscript.

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