Obesity and diabetes are associated with disability in women with hand osteoarthritis. Results from the EpiReumaPt nationwide study

Cruz M[1], Rodrigues AM[2], Dias S[2], Sepriano A[3], Canhão H[4], Gouveia N[5], Ramiro S[6], Branco JC[7]

ACTA REUMATOL PORT. 2021;46:208-217

ABSTRACT

Background: Hand osteoarthritis (HOA) is a highly prevalent rheumatic disease that predominates in females and causes pain and loss of functional capacity. Obesity and metabolic syndrome have been previously suggested to associate with the severity of HOA, but clarity on these associations is yet to be achieved.
Objective: Test the association between obesity and other components of the metabolic syndrome and disability in women with hand osteoarthritis (HOA).
Design: Individuals from EpiReumaPt epidemiological community-based study (2011-2013) are representative of the Portuguese population. Women with diagnosis of primary HOA were included.
Primary outcome: hand functional status, assessed by Cochin questionnaire.
Secondary outcomes: hand pain, assessed by visual analogue scale and tender hand joint count (THJ).
Explanatory variables: obesity, diabetes mellitus, arterial hypertension and hypercholesterolemia. Possible associations between obesity and the other components of metabolic syndrome with Cochin score, hand pain and THJ were tested in a multivariable linear regression model.
Potential confounders considered: age, education level and countrywide distribution.
Results: 473 women with primary HOA were included. Forty percent were overweight and 29% obese. Ninety-three (19.8%) participants had diabetes, 261 (55.8%) reported hypertension and 261 (55.9%) hypercholesterolemia. Mean Cochin score was 15.5±14.8, mean pain VAS was 4.7±2.6 and mean THJ 1.4±3. In the multivariable analysis, obesity (β 4.6 CI 0.7;8.5) and diabetes (β 4.0 CI 0.4;7.6) were found to significantly associate with HOA functional disability. In addition, diabetes, but not obesity, associated with hand pain. There was no association between obesity or diabetes with THJ.
Conclusion: In a Portuguese female population with primary HOA, obesity and diabetes mellitus independently associated with a worse hand functional status. These data add to evidence suggesting a role of metabolic factors in the severity of HOA.

Keywords: Cochin; Metabolic Syndrome; Obesity; Hand osteoarthritis; Severity.

1 NOVA Medical School; Reumatologia / Faculdade de Ciências Médicas de Lisboa; Hospital CUF Descobertas, Lisboa
2 EpiDoc Unit, CEDOC; Comprehensive Health Research Centre / NOVA Medical School, Lisboa
3 NOVA Medical School; Rheumatology / NOVA Medical School, Lisboa; Leiden University Medical Centre, Leiden, Netherlands
4 EpiDoc Unit, CEDOC; Comprehensive Health Research Centre; Reumatologia / NOVA Medical School, Lisboa; CHULC, Hospital Curry Cabral, Lisboa
5 NOVA Clinical Research Unit / NOVA Medical School, Lisboa
6 Rheumatology; Rheumatology / Leiden University Medical Centre, Leiden, Netherlands; Zuyderland Medical Centre, Heerlen, Netherlands; NOVA Medical School, Lisboa
7 EpiDoc Unit, CEDOC; Comprehensive Health Research Centre; Reumatologia / NOVA Medical School, Lisboa; CHLO, Hospital Egas Moniz, Lisboa

INTRODUCTION

BACKGROUND RATIONALE

Osteoarthritis (OA) is the most frequent articular disease[1]. According to the World Health Organization (WHO), the prevalence of OA is increasing due to population ageing and the increase in related factors, such as obesity[1]. According to the United Nations, by 2050 people aged over 60 will account for more than 20% of the world's population. Of that 20%, a conservative estimate of 15% will have symptomatic OA, and one-third of these people will be severely disabled[2]. Hands are frequently affected by this disease[3,4] and the clinical and functional severity spectrum is wide in this lo-

cation[5]. HOA predominates in women[6] and begins frequently in the peri-menopause. It is responsible for articular pain, stiffness and swelling in an additive pattern[7]and also limitation of function[8], sometimes as severe as in rheumatoid arthritis[5,9-11]. HOA has an estimated prevalence of 8.7% in the Portuguese population, with a relevant difference between women (13.8%) and men (3.2%)[12].

Different definitions of metabolic syndrome have been proposed[13-16]. To harmonize the different existing criteria, it has been suggested, in 2009, that metabolic syndrome comprises the presence of at least 3 of the following components: obesity (defined as elevated waist circumference), elevated triglycerides, reduced high density lipoprotein (HDL), elevated blood pressure and elevated fasting plasma glucose[17]. These metabolic factors, especially obesity, have been found to associate with HOA incidence and progression[1,18-22]. Hands are a good anatomical site to study the systemic association of metabolic syndrome with OA, because the mechanical overloading aspect is absent in these joints[20].

Robust evidence supports that some factors, such as insulin resistance and production of abnormal adipocytokines from adipose tissues (leptin, adiponectin, interleukin (IL) 1, IL6)[23], may play a role in the etiology of OA chronic inflammation[24,25]. Fat mass is the cornerstone of this inflammation, but diabetes, dyslipidemia and hypertension are involved in metabolic inflammation and can be implicated in OA pathogenesis[25]. Specifically, adipokines contribute to the low-grade inflammatory state of obese patients and may directly affect cartilage homeostasis[26]. Chondrocytes are insulin-sensitive cells; with high glucose concentrations, chondrocytes lose their responsiveness to insulin growth factor 1 (IGF-1), limiting anabolic processes of cartilage[27]. Hyperglicaemia has been associated with elevated reactive oxygen species and advanced glycation end-products that can lead to low-grade inflammation and oxidative stress, which can damage chondrocytes[25,28]. Since OA is associated with hypertension and atherosclerosis, compromised vascularization of the subchondral bone may be responsible for OA progression[29]. The subchondral ischemia theory proposes that hypertension induces narrowing of blood vessels over time, reducing blood flow in small subchondral vessels[30].

Older age and the presence of erosive disease have been, inconstantly, found to associate with increased pain and dysfunction in HOA[31,32]. However, the role of obesity and other components of the metabolic syndrome in pain and function in HOA is less clear, with few studies examining metabolic factors independently[33].

It is estimated that 1.3 billion people worldwide will be overweight and 573 million will be obese by 2030[34]. There is currently no pharmacological therapy proved to modified the course of HOA, or any other localization. However, interventions targeting modifiable factors, such as obesity and other components of metabolic syndrome may be beneficial, provided these are proved to associate with worse clinical outcomes.

OBJECTIVE

The aim of this study was to test the association between obesity and other components of the metabolic syndrome with HOA disability and pain.

METHODS

STUDY DESIGN

This cross-sectional observational study was conducted using the database of EpiReumaPt.

EpiReumaPt was a national, cross-sectional and community-based study, with the aim of estimating the prevalence of different rheumatic and musculoskeletal diseases (RMDs) in the adult Portuguese population and to assess the burden of RMDs by determining their impact on quality of life, physical function and mental health[12]. The study population were adults living in Portugal mainland and the islands (Azores and Madeira). Participants were selected and the study was realized in a three-stage approach, between September 2011 and December 2013. In a first step, face-to-face interviews took place, and a structured questionnaire using a Computer-Assisted Personal Interview (CAPI) system was used to collect sociodemographic variables, health related data and a screening questionnaire to access RMDs. In the second phase, all participants who screened positive for at least one rheumatic disease plus 20% of individuals with no rheumatic or musculoskeletal symptoms were evaluated by Rheumatologists in the field. Finally, a team of three Rheumatologists revised all data and confirmed the diagnoses, according to validated criteria. EpiReumaPt was designed to obtain a representative sample of the Portuguese population and the analysis to estimate the prevalence of different RMDs took into account extrapolation weights and crossing with some variables

(region, size of locality, gender and age), in a process described elsewhere[35].

STUDY POPULATION

INCLUSION AND EXCLUSION CRITEIRA

In this study we included adult women with a Rheumatologist's diagnosis of HOA defined in the second and third phases of EpiReumaPt. In addition, to be included, patients had to fulfil the ACR classification criteria.

When there was a concomitant diagnosis of rheumatoid arthritis (RA), spondyloarthritis (SpA), gout or other crystal-related arthropathies, patients were excluded. This intended to have a population of primary HOA, excluding disability that could be caused by other rheumatic diseases affecting the hands.

HAND OA ACR DEFINITION

A patient may be classified as having HOA if there is hand pain, aching or stiffness for most days of prior month and at least three of the following criteria: 1. Hard tissue enlargement in at least 2 of 10 selected hand joints (second and third distal interphalangeal - DIP, second and third proximal interphalangeal - PIP and trapezometacarpal -TMC on both hands); 2. Bone swelling in at least two DIP; 3. Fewer than 3 swollen metacarpophalangeal (MCP) joints; 4. Deformity of at least 2 of 10 selected joints[36].

OUTCOME DEFINITION AND ASSESSMENT

Since there is no core set for HOA disability assessment, our evaluation was based on a functional (Cochin functional questionnaire) and two symptomatic measures (hand pain in a visual analogue scale – VAS and the count of tender hand joints – THJ, evaluated by Rheumatologists).

PRIMARY OUTCOME: COCHIN SCORE

To evaluate functional severity we used Cochin questionnaire, a functional disability scale created for rheumatoid hand[37] and later validated to assess functional impairment in HOA[38]. This questionnaire includes 18 questions divided in 5 groups. Each question is scored from 0 to 5, so minimum total score is 0 and maximum is 90, with higher scores meaning poorer function.

SECONDARY OUTCOMES: HAND PAIN AND THJ COUNT

The 10 cm visual analogic scale (VAS) was used for right- and left-hand pain in the last 48 hours. We considered in the analysis pain in the most symptomatic hand, as a continuous variable. For the tender hand joint (THJ) score, 18 joints were evaluated by Rheumatologists: bilateral four DIP, bilateral four PIP and bilateral pollicis IP joints. We used THJ as a binary variable: 0 or ≥ 1 joints.

COVARIATES OF INTEREST – DEFINITION AND ASSESSMENT

MAIN VARIABLE OF INTEREST - BMI

Body mass index (BMI) is a measure to indicate nutritional status in adults. BMI categories were considered according to the WHO definition[39], as follows: < 18.5: underweight; 18.5-24.99: normal; 25-29.99: overweight; ≥ 30: obesity. BMI was calculated from self-reported height and weight. In this study, obesity was defined by BMI, as waist circumference was not measured.

OTHER VARIABLES OF INTEREST - OTHER METABOLIC SYNDROME COMPONENTS

Self-reported diagnosis of diabetes mellitus, arterial hypertension and hypercholesterolemia were used as metabolic syndrome components, obtained during the general questionnaire in EpiReumaPt study.

OTHER COVARIATES OF INTEREST AND POTENTIAL CONFOUNDERS

Considering women with primary HOA, demographic self-reported data were recorded: age, countrywide distribution and education. Age was analyzed as a categorical variable. Geographical distribution of HOA was considered according to the Portuguese Nomenclature of Territorial Units for Statistics (NUTs II: in mainland: North, Centre, Lisbon and Tejo valley, South (Alentejo and Algarve); in the islands: Madeira, Azores). Education level was analysed as a categorical variable, defined in 5 intervals: < 4 years (incomplete first degree); 4 years (from complete first degree – 4 years to incomplete second degree – less than 9 years); 9 years (complete second degree); 10-12 years (incomplete to complete third degree); > 12 years.

Age, education and NUTs were considered in the analysis as potential confounders.

STATISTICAL ANALYSIS

The investigators had access to the whole EpiReumaPt database.

In descriptive analysis, continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as count/percentages. Linear regression models were used to assess the factors associated with Cochin score and secondary outcomes in separate models. All the associated factors at a significance level, $p < 0.2$, on unadjusted (univariable) linear regression analysis were further examined in multivariable linear regression. The final model was achieved by eliminating factors one by one with $p < 0.10$. All analyses were performed using STATA IC version 14.

ETHIC ISSUES

All participants signed an informed consent in EpiReumaPt study, which was performed according to the principles of Helsinki Declaration, reviewed and approved by competent Portuguese authorities: NOVA Medical School Ethics Committee and National Committee for Data Protection, besides the Ethical Committees of Regional Health Authorities. All participants received clear information in lay terms about the research being undertaken, and they were given the opportunity to ask questions and enough time to decide whether to participate in the study and only after they signed the consent form.

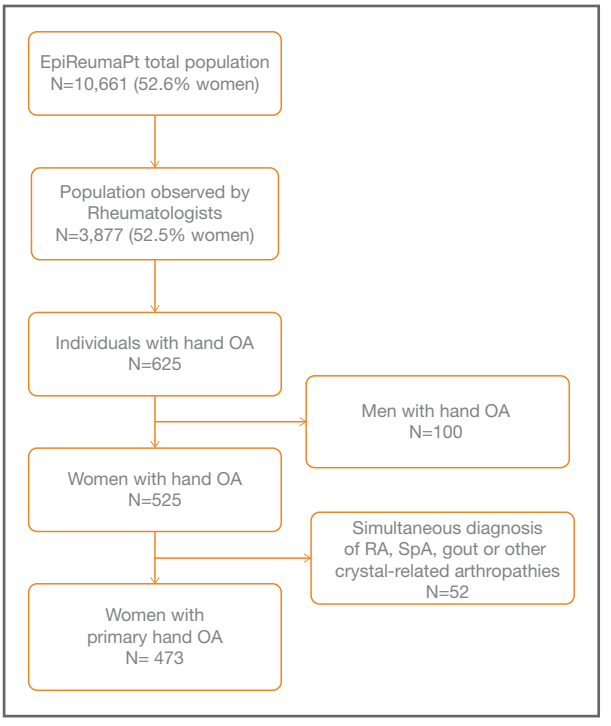

FIGURE 1. Population flowchart.
OA: osteoarthritis; RA: rheumatoid arthritis; SpA: spondyloarthritis

RESULTS

PARTICIPANTS

From the 10,661 individuals interviewed in EpiReumaPt, 3,877 participants were observed by Rheumatologists in the field. Of these, 625 were diagnosed with HOA, of which 525 were women. After excluding simultaneous diagnosis of RA, SpA, gout and other crystal-related arthropathy, 473 women were diagnosed as primary HOA, which gives a weighted national prevalence of 6.6% - Figure 1.

DESCRIPTIVE ANALYSIS

Table I shows the population characteristics. The geographic distribution of this primary HOA female population is shown on the table.

Minimal age found was 36 years old and maximum age was 91 years old. 69.6% women had 8 or less years of education and only 10.8% had more than 12 years of education.

TABLE I. POPULATION CHARACTERISTICS

	Frequency (%)
Age (years old)	
36-45	7 (1.5)
46-55	67 (14.2)
56-65	142 (30)
66-75	152 (32.1)
76-85	95 (20.1)
≥ 86	10 (2.1)
Education level (years)	
<4	78 (16.5)
4-8	251 (53.1)
9	55 (11.6)
10-12	35 (7.4)
> 12	51 (10.8)
No answer	3 (0.6)
BMI (n=444)	
Underweight (<18.5)	5 (1.1)
Normal (18,5-24.99)	132 (29.7)
Overweight (25-29.99)	179 (40.3)
Obese (≥30)	128 (28.8)
Overweight and obese	307 (69.2)
Diabetes mellitus (n=470)	93 (19.8)
Arterial hypertension (n=468)	261 (55.8)
Hypercholesterolemia (n=467)	261 (55.9)

BMI: body mass index

The BMI distribution of women with primary HOA is shown also on table 1: 1.1% were underweight,

TABLE I. DEMOGRAPHIC AND CLINICAL FEATURES OF THE PATIENTS WITH JH AND CONTROL GROUP

Parameters	Patients with JH (n=113)	Control subjects (n=995)	p value
Age, mean ± SD, years	9.3 ± 3.1	9.1 ± 4.3	0.70
Age groups, n (%)			
<9 years	71 (62.8)	597 (60)	0.55
9-17 years	42 (37.2)	398 (40)	
Gender, female, n, (%)	51.3	51.9	0.90
Acute malnutrition, n (%)	5 (4.4)	45 (4.5)	0.90
Chronic malnutrition, n (%)	17 (15)	115 (11.2)	0.27
Obesity, n (%)	19 (16.8)	124 (12.5)	0.19
Accompanying gastrointestinal symptoms, n (%)			
Chronic abdominal pain	17 (15)	112 (11.3)	0.23
Chronic dyspepsia	12 (10.6)	67 (10.1)	0.90
Functional constipation	18 (15.9)	113 (11.4)	0.15

TABLE II. UNIVARIABLE AND MULTIVARIABLE ANALYSIS - HAND FUNCTION

	Univariable			Multivariable		
Cochin	β	95% CI	p-value	β	95% CI	p-value
BMI (Ref: normal weight)						
Underweight	-4.6	-17.5; 8.4	0.488	-1.2	-13.9; 11.4	0.847
Excess weight	2.7	-0.7; 6.1	0.124	2.4	-1.0; 5.8	0.161
Obesity	5.8	2.2; 9.5	0.002	4.6	0.7; 8.5	0.021
Age (Ref: 36-46)						
46-56	-5.9	-20.6; 8.9	0.435	-7.3	-21.5; 7.0	0.316
56-66	-1.3	-15.9; 13.2	0.858	-5.1	-19.1; 9.0	0.481
66-76	-1.9	-16.4; 12.6	0.799	-7.3	-21.5; 6.9	0.311
76-86	0.4	-14.3; 15.0	0.960	-5.3	-19.5; 9.0	0.470
> 86	13.6	-3.7; 30.8	0.122	8.3	-9.3; 26.0	0.355
Education (Ref: <4y)						
4-9	-3.7	-7.2; -0.2	0.036	-3.4	-7.4; 0.5	0.089
9	-8.2	-14.5; -2.0	0.010	-7.6	-14.2; -0.9	0.026
10-12	-9.6	-15.2; -3.9	0.001	-9.4	-15.6; -3.3	0.003
> 12	-10.7	-15.9; -5.6	<0.001	-8.6	-14.4; -2.8	0.004
NUTS (Ref: Lisbon)						
North	-2.3	-6.4; 1.8	0.267	-4.9	-9.0; -0.7	0.022
Centre	-3.7	-7.7; 0.3	0.076	-5.9	-10.0; -1.8	0.005
Alentejo	-0.6	-6.6; 5.4	0.854	-2.9	-9.1; 3.3	0.360
Algarve	-0.9	-7.7; 5.9	0.784	-2.1	-8.8; 4.5	0.532
Azores	-2.4	-8.0; 3.3	0.409	-5.7	-11.4; -0.0	0.049
Madeira	-5.4	-10.8; -0.0	0.048	-7.9	-13.2; -2.6	0.004
Diabetes	5.8	2.4; 9.3	0.001	4.0	0.4; 7.6	0.029
Hypercholesterolemia	3.9	1.1; 6.7	0.006	#	#	#
Hypertension	3.5	0.7; 6.3	0.014	#	#	#

BMI: body mass index. NUTS: Nomenclature of Territorial Units for Statistics
#not included in the multivariable model, because there was no significant association

TABLE III. UNIVARIABLE AND MULTIVARIABLE ANALYSIS - HAND PAIN

	Univariable			Multivariable		
Hand pain	**β**	**95% CI**	**p-value**	**β**	**95% CI**	**p-value**
BMI (Ref: normal weight)						
Underweight	-0.3	-2.7; 2.0	0.772	-0.3	-2.6; 2.1	0.825
Excess weight	0.6	-0.0; 1.2	0.065	0.4	-0.2; 1.1	0.162
Obesity	1.0	0.3; 1.7	0.004	0.6	-0.1; 1.3	0.096
Age (Ref: 36-46)						
46-56	-0.5	-3.2; 2.2	0.709	-0.6	-3.2; 2.1	0.679
56-66	0.1	-2.5; 2.7	0.941	-0.3	-2.9; 2.3	0.840
66-76	-0.5	-3.2; 2.1	0.689	-1.1	-3.7; 1.5	0.402
76-86	-0.6	-3.2; 2.1	0.663	-1.0	-3.6; 1.6	0.458
> 86	0.3	-2.8; 3.4	0.833	-1.1	-4.4; 2.1	0.487
Education (Ref: <4y)						
4-9	0.0	-0.6; 0.7	0.882	-0.4	-1.1; 0.4	0.350
9	0.5	-0.7; 1.6	0.424	-0.0	-1.3; 1.2	0.973
10-12	-1.0	-2.0; 0.1	0.071	-1.6	-2.7; -0.4	0.007
> 12	-1.1	-2.1; -0.2	0.020	-1.3	-2.4; -0.3	0.015
NUTS (Ref: Lisbon)						
North	-0.5	-1.2; 0.3	0.221	-0.8	-1.6; 0.0	0.050
Centre	-0.9	-1.7; -0.2	0.012	-1.1	-1.8; -0.3	0.006
Alentejo	0.7	-0.4; 1.7	0.223	0.5	-0.7; 1.6	0.406
Algarve	-0.2	-1.4; 1.0	0.762	-0.2	-1.4; 1.0	0.747
Azores	-0.3	-1.3; 0.7	0.564	-0.9	-1.9; 0.2	0.102
Madeira	-0.9	-1.9; 0.1	0.063	-1.2	-2.2; -0.3	0.014
Diabetes	0.8	0.2; 1.4	0.011	0.7	3.2; 8.8	0.038
Hypercholesterolemia	0.5	-0.0; 1.0	0.075	#	#	#
Hypertension	0.2	-0.3; 0.8	0.337	#	#	#

BMI: body mass index. NUTS: Nomenclature of Territorial Units for Statistics
not included in the multivariable model, because there was no significant association

29.7% had normal weight, 40.3% were overweight and 28.8% obese. Ninety-three/470 (19.8%) of these women had diabetes, 261/468 (55.8%) had hypertension and 261/467 (55.9%) had hypercholesterolemia.

Mean Cochin score was 15.5 ± 14.8 SD. Mean VAS was 4.7 ± 2.6 SD. Mean THJ was 1.4± 3.0 SD. Sixty-nine percent participants had no tender joints and 31% had 1 to 18 tender joints.

ASSOCIATIONS BETWEEN METABOLIC SYNDROME AND HOA FUNCTION

In the univariable analysis, obesity and diabetes were associated with worse hand function. Hypercholesterolemia and hypertension were also associated with worse hand function.

In the multivariable linear regression model, arterial hypertension and hypercholesterolemia had no significant association with worse function, so we kept only diabetes and BMI in the final model. The multivariable analysis showed association between obesity (β 4.6 CI 0.7;8.5) and diabetes (β 4.0 CI 0.4;7.6) and worse hand function - Table II.

ASSOCIATIONS BETWEEN METABOLIC SYNDROME AND HAND PAIN

In the univariable analysis, obesity and diabetes associated with worse hand pain and hypercholesterolemia and hypertension did not. In the multivariable analysis, only diabetes associated with worse hand pain (β 0.7 CI 3.2;8.8) – Table III.

ASSOCIATIONS BETWEEN METABOLIC SYNDROME AND TENDER HAND JOINTS

In the univariable and multivariable analysis, we found

TABLE IV. UNIVARIABLE AND MULTIVARIABLE ANALYSIS - TENDER HAND JOINT COUNT

	Univariable			Multivariable		
THJ	β	95% CI	p-value	β	95% CI	p-value
BMI (Ref: normal weight)						
Underweight	-0.2	-3.5; 3.2	0.929	0.4	-3.1; 3.9	0.811
Excess weight	0.2	-0.6; 1.1	0.576	0.2	-0.7; 1.0	0.737
Obesity	0.0	-0.9; 0.9	0.976	0.0	-1.1; 1.1	0.994
Age (Ref: 36-46)						
46-56	0.7	-5.3; 6.7	0.819	0.9	-5.2; 7.0	0.769
56-66	1.3	-4.6; 7.3	0.661	1.5	-4.6; 7.5	0.635
66-76	1.4	-4.6; 7.3	0.654	1.0	-5.1; 7.0	0.753
76-86	1.6	-4.4; 7.5	0.606	1.3	-4.8; 7.4	0.677
> 86	3.1	-3.2; 9.5	0.328	3.4	-3.2; 9.9	0.314
Education (Ref: <4y)						
4-9	-1.1	-2.1; -0.2	0.017	-0.8	-1.9; 0.3	0.155
9	-0.2	-1.8; 1.5	0.824	0.2	-1.6; 2.0	0.824
10-12	-1.3	-2.8; 0.1	0.075	-1.0	-2.6; 0.6	0.229
> 12	-1.5	-2.9; -0.2	0.027	-1.1	-2.8; 0.5	0.176
NUTS (Ref: Lisbon)						
North	-1.0	-2.1; 0.2	0.116	-0.9	-2.1; 0.4	0.182
Centre	0.2	-0.8; 1.1	0.683	-0.2	-1.2; 0.9	0.769
Alentejo	0.6	-1.0; 2.2	0.468	0.4	-1.3; 2.2	0.646
Algarve	1.0	-0.6; 2.6	0.216	1.0	-0.6; 2.6	0.232
Azores	-1.3	-2.3; 0.3	0.107	-1.3	-2.9; 0.3	0.102
Madeira	0.5	-0.9; 1.8	0.486	-0.2	-1.6; 1.2	0.750
Diabetes	0.5	-0.4; 1.4	0.279	0.3	-0.6; 1.3	0.482
Hypercholesterolemia	0.2	-0.6; 0.9	0.634	0.021	-0.7; 0.8	0.957
Hypertension	-0.2	-0.9; 0.6	0.687	-0.012	-0.8; 0.8	0.976

BMI: body mass index. THJ: tender hand joint count. NUTS: Nomenclature of Territorial Units for Statistics

no association between any of the metabolic syndrome components and the number of tender hand joints – Table IV.

DISCUSSION

This study, in a nationwide community-based population of women with primary HOA, showed that obesity and diabetes mellitus independently associate with hand disability. Diabetes was also independently associated with more pain.

In our population, representative of Portuguese women, 40.3% of women with primary HOA were overweight and 28.8% obese (69% population had high weight). This compares to the lower percentage of the total female population in EpiReumaPt that were overweight (31.8%) and obese (19.1%)[12]. The prevalence of the other metabolic syndrome components in EpiReumaPt was more than half of the prevalence in our primary HOA female population: diabetes prevalence was 8.3%, hypertension 23.1% and hypercholesterolemia 24.4%[12]. Diabetes was less prevalent in our population (20%) than hypertension (56%) and hypercholesterolemia (56%), but showed the strongest association with poor function and with more pain in HOA. It is possible that pathogenic pathways related to insulin resistance, or even other related to diabetes mellitus, not considered in this population, such as neuropathy, and fat accumulation have more weight in HOA clinical severity, than those related to other mechanisms, namely ischemia.

Although the majority of these women had no tender hand joints at the time of observation and few had

many tender joints, mean VAS in this population was 4.7 cm. One hypothesis to explain this symptom discrepancy is that pain referred by this population may be related to hand function and mobility and not so much felt in resting joints. It may also be related with peripheral or central sensitization of pain, recognized in individuals with HOA and higher self-reported levels of pain[40].

The majority of studies are cross-sectional and search for HOA incidence or prevalence association with metabolic syndrome factors, and we didn t find any that looked for association between HOA clinical severity and metabolic syndrome factors. Besides, the few studies that associate metabolic syndrome factors and HOA severity relate to radiographic HOA, not dysfunction[41,42].

In a systematic review published in 2010, 64% of the studies showed moderate association between HOA and excess weight, with a moderate level of evidence of that association[17]. In a longitudinal 5-year study published in 2016, HOA occurred more frequently in obese people, but the association was stronger in knee OA[19]. A cross-sectional analysis of the Netherlands Epidemiology of Obesity study in which different obesity measures were considered, showed that fat percentage and waist-to-hip ratio were associated with HOA in men and women, but only visceral adipose tissue was associated with HOA in men, not women[43].

Some authors found no association between HOA incidence and obesity. A large population-based case-control study from the UK didn't find association between diabetes and increased risk of HOA[44] and a large population evaluation showed no association between HOA and obesity, in the cross-sectional analysis, nor association with erosive progression, in the longitudinal follow-up[45].

A recent systematic literature review concluded that knee and hip OA are not associated with metabolic syndrome, but it is not possible to conclude as for hand OA, due to insufficient data[32].

Strengths and limitations of our study should be considered. One strength of the study is the choice of a national representative community-based population, such as the one evaluated by EpiReumaPt, which can capture an enlarged range of disease severity, avoiding a selection bias that would be likely to occur if individuals were chosen from the health system (for instance, in hospital consultations). To our knowledge, this is the first study to characterize primary HOA in a wide Portuguese population. Another strength is that HOA cases are defined by a Rheumatologist observation in the field and ACR classification criteria, instead of a self-report.

One limitation of the study is its cross-sectional setting. The individual actual BMI category may not be representative of initial BMI, when HOA developed. So, it may be difficult to assume an association between obesity or overweight with actual HOA severity, depending on disease duration. Actual BMI may also be the consequence of less mobility, related to disease severity, not only in hands, which wasn t evaluated in this study. Also radiographic evaluation could have helped to establish an association between BMI, diabetes and the other factors with distinct radiographic patterns and severity, besides clinical severity.

CONCLUSION

In a nationwide community-based population, representative of the Portuguese population, obesity and diabetes mellitus independently associated with hand disability in women with primary HOA. Arterial hypertension and hypercholesterolemia had no significant association with HOA functional severity. Diabetes was also associated with higher levels of hand pain. These findings support the notion that metabolic syndrome, or at least some of its components, is associated with more severity in HOA patients. Our study suggests that metabolic syndrome prevention and control may improve hand function and provide symptom relief in HOA patients.

CORRESPONDENCE TO
Margarida Cruz
Rua do Bairro, nº5 A,
2500-068 Caldas da Rainha
E-mail: cmargaridamoccruz@gmail.com

REFERENCES

1. Kaplan W, Wirtz VJ, Mantel-Teeuwisse A, Stolk P, Duthey B, Laing R. Priority Medicines for Europe and the World "A Public Health Approach to Innovation – 2013 update", 126-128; Geneva: WHO Press; 2013. Wittenauer R, Smith L, Aden K. Background Paper 6.12 Osteoarthritis. Available from: https://www.who.int/ medicines/areas/priority_medicines/Ch6_12Osteo.pdf
2. United Nations. World Population to 2300. Available at: http://www.un.org/esa/population/publications/…/WorldPop2300final.pdf
3. Van Saase JL, van Romunde LK, Cats A, Vandenbroucke JP, Valkenburg HA. Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. Ann Rheum Dis 1989; 48: 271-280

4. Pereira D, Peleteiro B, Araújo J, Branco J, Santos RA, Ramos E. The effect of osteoarthritis definition on prevalence and incidence estimates: a systematic review. Osteoarthritis and Cartilage 2011; 19:1270-1285
5. Kloppenburg M, Kwok WY. Hand osteoarthritis – a heterogeneous disorder. Nat Rev Rheumatol 2011; 8: 22-31
6. Bijsterbosch J, Watt I, Meulenbert I, Rosendaal FR, Huizinga TWJ, Kloppenburg M. Clinical and radiographic disease course of hand osteoarthritis and determinants of outcome after 6 years. Ann Rheum Dis 2011; 70 (1): 68-73
7. Poiraudeau S, Lefèvre-Colau MM, Chevalier X, Chevalier X, Conrozier T, Flippo RM, Lioté F, Noel E et al. Reliability, validity and sensitivity to change of the hand functional disability scale in hand osteoarthritis. Osteoarthritis Cartilage 2001; 9:570-577
8. Kwok WY, Vileland TPMV, Rosendaal FR Huizinga TWJ, Kloppenburg M. Limitations in daily activities are the major determinant of reduced health-related quality of life in patients with hand osteoarthritis. Ann Rheum Dis 2011; 70: 334-336
9. Slatkowsky-Christensen B, Mowinckel P, Loge JH, Kvien TK. Health-related quality of life in women with symptomatic hand osteoarthritis: a comparison with rheumatoid arthritis patients, healthy controls and normative data. Arthritis Rheum 2007; 57: 1404-1409
10. Wittoek R, Cruyssen BV, Verbruggen G. Predictors of functional impairment and pain in erosive osteoarthritis of the interphalangeal joints. Comparison with controlled inflammatory arthritis. Arthritis Rheum 2012; 64(5): 1430-1436
11. Michon M, Maheu E, Berenbaum F. Assessing health-related quality of life in hand osteoarthritis: a literature review. Ann Rheum Dis 2011; 70: 921-928
12. Branco JC, Rodrigues AM, Gouveia N Eusébio M, Ramiro S, Machado PM et al. Prevalence of rheumatic and musculoskeletal diseases and their impact on health-related quality of life, physical function and mental health in Portugal: results from EpiReumaPt– a national health survey. RMD Open 2016; 2(1): e000166
13. Engin A. The definition and prevalence of obesity and metabolic syndrome. Adv Exp Med Biol 2017; 960: 1-17
14. Grundy SM, Cleeman JI, Daniels SR Donato KA, Eckel RH, Franklin BA et al. Diagnosis and Management of the Metabolic Syndrome: an American Heart Association/National Heart, Lung and Blood Institute Scientific Statement: Circulation 2005; 112: 2735-2752
15. Zimmet P, Magliano D, Matsuzawa Y, Alberti G, Shaw J. The Metabolic Syndrome: A Global Public Health Problem and a New Definition. J Atheroscler Thromb 2005; 12: 295-300
16. Yamagishi K, Iso H. The criteria for metabolic syndrome and the national health screening and education system in Japan. Epidemiol Health 2017; 39: e2017003
17. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA et al. Harmonizing the metabolic syndrome: a joint interin statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009; 120: 1640-1645
18. Yusuf E, Nelissen RG, Ioan-Facsinay, A Stojanovic-Susulic V, DeGroot J, van Osch G et al. Association between weight or body mass index and hand osteoarthritis: a systematic review. Ann Rheum Dis 2010. 69: 761-765
19. Reyes C, Leyland KM, Peat G et al. Association Between overweight and obesity and risk of clinically diagnosed knee, hip and hand osteoarthritis: a population-based cohort study; Arthritis Rheum 2016; 68(8): 1869-1875
20. Visser AW, Mutsert R, le Cessie S, den Heijer M, Rosendaal FR, Kloppenburg M, NEO Study Group. The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study. Ann Rheum Dis 2014; 0: 1-6
21. Zhuo Q, Yang W, Chen J, Wang Y. Metabolic syndrome meets osteoarthritis. Nat Rev Rheumatol 2012; 8: 729-737
22. Haugen IK, Magnusson K, Turkiewicz A, Englund M. The prevalence, incidence and progression of hand osteoarthritis in relation to body mass index, smoking and alcohol consumption. J Rheumatol 2017; 44(9): 1402-1409
23. Li S, Felson D. What is the evidence to support the association between metabolic syndrome and osteoarthritis? – A systematic review. Arthritis Care Res (Hoboken); 2018 Jul 12. doi: 10.1002/acr.23698. [Epub ahead of print]
24. Hotamisligil GS. Inflammation and Metabolic Disorders. Nature 2006; 444: 860-867
25. Courties A, Gualillo O, Berembaum F Sellam J. Metabolic Stress-Induced Joint Inflammation and Osteoarthritis. Osteoarthritis Cartilage 2015; 23: 1955-1965
26. Goldring MB, Otero M. Inflammation in Osteoarthritis. Curr Opinion Rheumatol 2011; 23: 471-478
27. Rosa SC, Rufino AT, Judas F, Tenreiro C, Lopes MC, Mendes AF. Expression and Function of the Insulin Receptor in Normal and Osteoarthritic Human Chondrocytes: Modulation of Anabolic Gene Expression, Glucose Transport and GLUT-1 Content by Insulin. Osteoarthritis Cartilage 2011;19: 719-727
28. Laiguillon MC, Courties A, Houard X Auclair M, Sautet A, Capeau J et al. Characterization of Diabetic Osteoarthritic Cartilage and Role of High Glucose Environment on Chondrocyte Activation: Toward Pathophysiological Delineation of Diabetes Mellitus-Related Osteoarthritis. Osteoarthritis Cartilage 2015; 23: 1513-1522
29. Conaghan PG, Vanharanta H, Dieppe PA. Is Progressive Osteoarthritis an Atheromatous Vascular Disease? Ann Rheum Dis 2015: 64: 1539-1541
30. Findlay DM. Vascular Pathology and Osteoarthritis. Rheumatology Oxford 2007: 46: 1763-1768
31. Bijsterbosch J, Watt I, Meulenbelt I Rosendaal FR, Huizinga TWJ, Kloppenburg M. Clinical burden of erosive hand osteoarthritis and its relationship to nodes. Ann Rheum Dis 2010; 69: 1784-1788
32. Sayer AA, Poole J, Cox V Kuh D, Hardy R, Wadsworth M et al. Weight from birth to 53 years: a longitudinal study of the influence on clinical hand osteoarthritis. Arthritis Rheum 2003; 48: 1030-1033
33. Magnusson K, Slatkowsky-Christensen B, van der Heijde D, Kvien TK, Hagen KB, Haugen IK. Body Mass Index and Progressive Hand Osteoarthritis: Data From the Oslo Hand Osteoarthritis Cohort. Scand J Rheumatol 2015; 44: 331-336
34. Kelly T, Yang W, Chen CS, Reynolds K, He J. Global burden of obesity in 2005 and projections to 2030. Int J Obes (Lond) 2008; 32: 1431-1437
35. Rodrigues AM, Gouveia N, da Costa LP, Eusébio M, Ramiro S, Machado P et al. EpiReumaPt- the study of rheumatic and musculoskeletal diseases in Portugal: a detailed view of the methodology. Acta Reumatol Port 2015;40:110–24

36. Altman R, Alarcon G, Appelrouth D Bloch D, Borenstein D, Brandt K et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis Rheum1990; 33: 1601-1610
37. Duruoz MT, Poiraudeau S, Fermanian J Menkes CJ, Amor B, Dougados M et al. Development and validation of a rheumatoid hand functional disability scale that assesses functional handicap. J Rheumatol 1996; 23 (7): 1167-1172
38. Poiraudeau S, Chevalier X, Conrozier T, Flippo RM, Lioté F, Noel E et al. Reliability, validity and sensitivity to change of the Cochin hand functional disability scale in hand osteoarthritis. Osteoarthritis Cartilage 2001; 9: 570-577
39. www.who.euro.int – nutrition- BMI
40. Pettersen TS, Neogi T, Magnusson K. Peripheral and Central Sensitization of Pain in Individuals With Hand Osteoarthritis and Associations With Self-Reported Pain Severity. Arthritis Rheumatol 2019; 71: 1070-1077
41. Marshall M, Peat G, Nicholls E Myers HL, Mamas MA, van der Windt DA. Metabolic Risk Factors and the Incidence and Progression of Radiographic Hand Osteoarthritis: A Population-Based Cohort Study. Scand J Rheumatol 2019; 48: 52-63
42. Massengale M, Lu B, Pan JJ, Katz JN, Solomon DH. Adipokine Hormones and Hand Osteoarthritis: Radiographic Severity and Pain. PLOS One 2012; 7: e47860 e47860
43. Visser AW, Ioan-Facsinay A, Mutsert R Widya RL, Loef M, de Roos A et al. Adiposity and hand osteoarthritis: the Netherlands Epidemiology of Obesity study. Arthritis Research & Therapy 2014; 16: R19
44. Frey N, Hugle T, Jick SS, Meier CR, Spoendlin. Type II Diabetes Mellitus and Incident Osteoarthritis of the Hand: A Population-Based Case-Control Analysis. Osteoarthritis Cartilage 2016; 24: 1535-1540
45. Magnusson K, Osteras N, Haugen IK Mowinckel P, Nordsletten L, Natvig B et al. No strong relationship between body mass index and clinical hand osteoarthritis – results from a population-based case-control study. Scand J Rheumatol 2014; 43: 409--415