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Original article

Prevalence of ischemic heart disease and associated factors in patients with rheumatoid arthritis in Southern Brazil

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ABSTRACT

Objective: To estimate the prevalence of ischemic heart disease and associated factors in patients with rheumatoid arthritis.

Methods: A cross-sectional study using the American College of Rheumatology diagnostic criteria in order to select patients seen at primary or secondary health care units in Blumenau, Santa Catarina, Southern Brazil, in 2014. The presence of ischemic heart disease was defined as an acute myocardial infarction with percutaneous coronary intervention or coronary artery bypass graft surgery that has occurred after diagnosis. Fischer's exact test, Wald's linear trend test, and multivariate logistic regression analysis were used to test the associations.

Results: Among 296 patients (83.1% female) with a mean age of 56.6 years and a mean rheumatoid arthritis duration of 11.3 years, 13 reported having acute myocardial infarction requiring a percutaneous or surgical reperfusion procedure, a prevalence of 4.4% (95% CI 2.0–6.7). Diabetes Mellitus (odds ratio [OR] 4.9 [95% CI 1.6–13.8]) and disease duration >10 years (OR 8.2 [95% CI 1.8–39.7]) were the only factors associated with an ischemic disease that remained in the final model, after the multivariate analysis.

Conclusion: The prevalence of acute myocardial infarction was similar to that observed in other studies. Among the traditional risk factors, Diabetes Mellitus, and among the factors related to rheumatoid arthritis, disease duration, were the variables associated with comorbidity.

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Prevalência de doença isquêmica cardíaca e fatores associados em pacientes com artrite reumatoide no Sul do Brasil

Palavras-chave:
Artrite reumatoide
Doença cardiovascular
Infarto agudo do miocárdio
Prevalência

RESUMO

Objetivo: Estimar a prevalência da doença isquêmica cardíaca e os fatores associados em pacientes com artrite reumatoide.

Métodos: Estudo transversal que usou o critério diagnóstico do Colégio Americano de Reumatologia para selecionar pacientes atendidos nas unidades de saúde da atenção primária ou secundária em Blumenau, Santa Catarina, sul do Brasil, em 2014. A presença de doença cardíaca isquêmica foi definida com infarto agudo do miocárdio com intervenção coronariana percutânea ou cirurgia de revascularização do miocárdio que tenha ocorrido depois do diagnóstico. Para testar as associações usou-se o teste exato de Fischer, o teste de tendência linear de Wald e a análise de regressão logística multivariada.

Resultados: Entre 296 pacientes, 83,1% de mulheres, com média de 56,6 anos, tempo médio de artrite reumatoide de 11,3 anos, 13 relatam ter tido infarto agudo do miocárdio que necessitou de procedimento de reperfusão percutânea ou cirúrgica, prevalência de 4,4% (IC 95% 2,0-6,7). O *diabetes melittus* (razão de chance de 4,9 [IC 95% 1,6-13,8]) e o tempo de doença maior do que 10 anos (razão de chance de 8,2 [IC 95% 1,8-39,7]) foram os únicos fatores associados com a doença isquêmica que permaneceram no modelo final após análise multivariada.

Conclusão: A prevalência de infarto agudo do miocárdio foi semelhante com a observada em outros estudos. Entre os fatores de risco tradicionais e entre os fatores relacionados à artrite reumatoide, o *diabetes melittus* e o tempo de doença foram as variáveis associadas à comorbidade.

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory autoimmune disease characterized by the involvement of the synovial membrane of peripheral joints leading to destruction and functional limitation.[1] The prevalence of RA varies from 0.24 to 1% of the adult population, with a predominance of women and a higher incidence in the 30–50-year age group.[2–4] In Brazil, two studies were published. The first study shows a variation from 0.2 to 1%, depending on the region of this country,[5] and the other establishes a prevalence of 0.46%.[6]

Studies point to an increased risk of cardiovascular disease (CVD) in patients with RA compared to the general population.[7–9] CVD exerts a great impact and represents an important morbidity in patients with RA, and acute myocardial infarction (MI) is considered to be the most common event.[9,10] Studies conducted in different countries indicate that the prevalence can vary from 1 to 17%.[10–12]

The greatest number of cardiac ischemic events in RA patients is not entirely explained by the presence of traditional risk factors alone.[10] A study in Sweden with two cohorts of RA patients demonstrated that there is no increase in the occurrence of ischemic heart disease prior to the rheumatologic diagnosis.[13] On the other hand, soon after the onset of the disease[14] and along its course,[15] RA plays an important role in the onset of MI, above all in patients with an accumulation of severity markers.[10] Thus, RA was considered as an independent risk factor for the occurrence of coronary artery disease.[16,17]

Despite the important advances in diagnosis and available treatments, there remains a high CVD morbidity.[10] This is due to the combination of the characteristics of a chronic inflammatory disease, which are predisposing factors to the development of comorbidities; of the drugs used in treatment, for example, glucocorticoids[11]; to an increased prevalence of traditional risk factors over the duration of disease[18,19]; and to the persistent activity of the disease in its most aggressive periods.[7]

The present study aimed to estimate the self-reported prevalence of coronary ischemic events and to identify the possible associated factors in patients with RA in Blumenau, Santa Catarina, Southern Brazil, in 2014.

Materials and methods

This is a cross-sectional, population-based study conducted between July 2014 and January 2015 with men and women aged 20 years and older with rheumatoid arthritis according to the American College of Rheumatology (1987) criteria, residents in the municipality of Blumenau, Southern Brazil. In 2010, Blumenau had a municipal human development index (IDH-M) = 0.806, ranking 25th among all Brazilian municipalities.[20] According to the national census conducted also in the year of 2010, the number of people pertaining to the age group of this study corresponded to 221,839 inhabitants, equivalent to 71.7% of the total population of the municipality.[21]

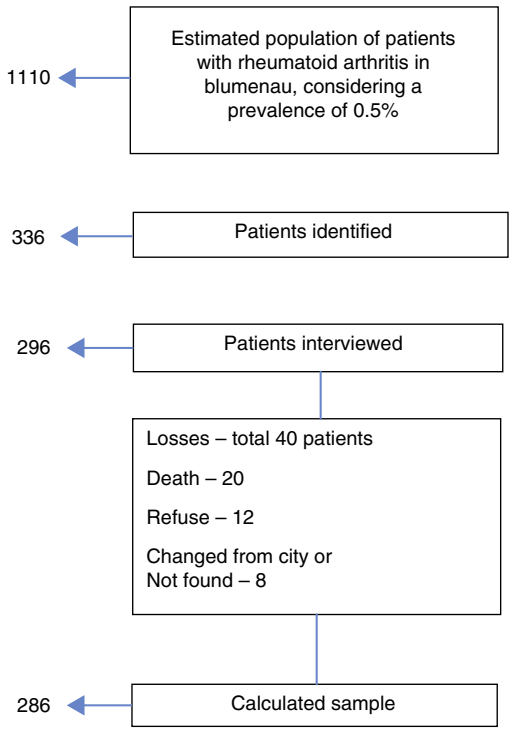

Fig. 1 – Diagram.

To calculate the sample size, the formula for estimating the prevalence for a simple random sample was applied. The following parameters were considered: prevalence of RA = 0.5% (1110 patients), prevalence of exposure and unknown outcome = 50%, sampling error = 5%, and confidence level of 95%. The sample size calculated was of 286 individuals. The sample collection process was carried out by reviewing medical records in the basic health units and in the medical specialty outpatient clinic, as well as by identifying patients in the waiting room at the high-cost drug dispensing pharmacy from the city (Fig. 1).

Households visited at least twice without the interviewer meeting the person, including a weekend visit and another nighttime visit, or in the case of a change of address, or even in cases of refusal on two occasions, were considered as "losses".

The team was composed of 8 medical students from the medical school of the Fundação Universidade Regional de Blumenau (FURB), previously trained to carry out a pre-structured interview and, if necessary, to conduct the interview by telephone in another occasion, and also by a local professor supervisor. Quality control was performed in 20% of the respondents when they were interviewed for a second time, through the application of a short questionnaire.

The dependent variable was the presence of a positive history of a coronary ischemic event after a diagnosis of rheumatoid arthritis, defined by an acute myocardial infarction diagnosed by the physician and requiring cardiac catheterization for angioplasty or stent implantation, or a coronary artery bypass graft surgery.

The independent variables were defined as (a) demographic variables: gender, age in completed years, categorized in a group of 20–59 years for adults and of 60 years or more for the elderly; (b) traditional cardiovascular risk factors reported in the interview: previous diagnosis of hypertension, diabetes mellitus or dyslipidemia, or use of medications for such diseases; previous or current smoking; prior and current practice of leisure-time physical activity; positive family history for heart attack or cardiac catheterization at any age (mother, father, brothers or sisters); dichotomous categorization; current body mass index – BMI (kg/m^2) according to weight and height and categorized according to the World Health Organization recommendations (low/normal weight $\leq$24.9 kg/m^2, overweight 25–29.9 kg/m^2, and obesity $\geq$30 kg/m^2); and (c) RA-related variables: disease duration in years and presence of rheumatoid factor, both categorized respectively between 0–10 or 11 or more years of disease, and rheumatoid factor <60 (negative or low titer) or >60 (high titers).

The data were entered in a system developed for this study with their output in the Excel® table format; subsequently, the final file was exported to the Stata 10.0 program (Stata Corp., College Station, United States). The variables of interest were analyzed for their distributions; for this end, mean, standard deviation and median were used for continuous variables, and frequency and percentage were used for categorical variables. To test the association between history of a coronary ischemic event and independent variables, the Fisher's exact test and, where appropriate, the Wald's linear trend test were used. After that, a multivariate logistic regression analysis was performed, aiming to verify the association of the factors studied with the dependent variable, with estimates of gross and adjusted odds ratios (OR) and of the respective 95% confidence intervals.

For the entry into the final multivariate model, all the variables with a p-value < 0.20 in the univariate analysis were taken into account. Those variables that maintained a p-value $\leq$ 0.05 or which were adjusted to the final model remained in the multivariate regression model. For the inclusion of the variables in the logistic regression model, the investigators opted sequentially by the inclusion, in the first place, of the demographic variables; then, the traditional risk factors for coronary artery disease, and finally the variables related to the disease were included. This research was submitted to the Research Ethics Committee of the Universidade de São Paulo (USP) and FURB (protocols 339/13 and 133/12, respectively), having obtained approval. All participants in this study signed an informed consent form.

Results

On the whole, 296 RA patients were interviewed. The majority were women (83.1%) and adults (60.8%), with a mean age of 56.6 ± 11.7 years, ranging from 25 to 91 years, and with disease duration of 11.3 ± 9.2 years, ranging from 1 to 51 years. The mean BMI was 26.4 ± 4.7 kg/m^2. The prevalence of MI with a percutaneous or surgical reperfusion procedure was 4.4% (95% CI 2.0–6.7). In the descriptive analysis, the most prevalent demographic variables were female gender and age $\geq$60 years. The majority of cases were related to the presence of traditional risk factors, with greater relevance among diabetic participants (14.7%). Regarding the characteristics

Table 1 – Description of the sample and prevalence of acute myocardial infarction according to the independent variables in patients with rheumatoid arthritis. Blumenau, Santa Catarina, Brazil, 2014.

Variables	Sample		Acute myocardial infarction		*p*-Value
	n	%	Prevalence (%)	CI 95%	
Total	296	100.0	4.4	(2.0–6.7)	
Gender (n = 296)					0.619[a]
Male	50	16.9	4.0	(1.5–9.5)	
Female	246	83.1	4.4	(1.8–7.0)	
Age in years (n = 296)					0.400[a]
20–59 (adults)	180	60.8	3.8	(1.0–6.7)	
≥60 (elderly)	116	39.2	5.1	(1.1–9.2)	
Hypertension (n = 296)					0.017[a]
No	164	55.4	1.8	(0.2–3.8)	
Yes	132	44.6	7.5	(3.0–12.5)	
Diabetes Mellitus (n = 296)					0.010[a]
No	262	88.5	3.0	(0.9–5.1)	
Yes	34	11.5	14.7	(2.5–26.8)	
Dyslipidemia (n = 296)					0.071[a]
No	223	75.3	3.1	(0.8–5.4)	
Yes	73	24.7	8.2	(1.8–14.5)	
Body mass index (kg/m^2) (n = 296)					0.364[b]
≤24.9	113	38.1	3.5	(0.8–6.9)	
25–29.9	124	41.9	4.0	(0.5–7.5)	
≥30	59	20	6.7	(0.1–13.2)	
Smoking (n = 296)					0.053[a]
Never smoked	167	56.4	2.3	(0.5–4.7)	
Previous and/or current smokers	129	43.6	6.9	(2.5–11.4)	
Physical leisure activity (n = 288)					0.214[a]
Never practiced	114	39.6	3.4	(0.7–6.1)	
Practiced and/or practices	174	60.4	6.1	(1.6–10.5)	
Positive family history (n = 296)					0.136[a]
No	169	57.1	2.9	(0.3–5.5)	
Yes	127	42.9	6.2	(2.0–10.5)	
Disease duration (n = 296)					0.001[a]
0–10 years	175	59.1	1.1	(0.4–2.7)	
≥11 years	121	40.9	9.0	(3.9–14.2)	
Presence of rheumatoid factor (n = 266)					0.603[a]
0–60 (negative, or low titers)	164	61.6	4.8	(1.5–8.2)	
≥61 (high titers)	102	38.4	4.9	(0.6–9.1)	

[a] Fischer's exact test.
[b] Wald's linear trend test.

related to RA, duration of disease over 10 years was the only variable to demonstrate a statistically significant association (Table 1).

In the gross analysis, it was verified that the dependent variable presented a tendency of association with dyslipidemia and smoking; on the other hand, significance was observed with hypertension, diabetes mellitus, and disease duration. In the adjusted analysis, the variable hypertension lost the power of association; thus, it was suppressed from the final model, composed of diabetes mellitus and disease duration. These two variables presented, respectively, 3.5- and 8.2-fold increases in the chance of showing the outcome, compared to non-diabetic patients with less than 10 years of disease (Table 2). Together, these two variables established a coefficient of determination of 17%.

Discussion

The study identified a greater chance of MI defined by cardiac catheterization for angioplasty or stent implantation or for coronary artery bypass grafting in RA patients with diabetes mellitus and over 10 years of disease.

In Brazil, this is the first study to establish the prevalence of MI (4.4%) in this population. Previous studies have shown that European countries have a prevalence between 2% (United Kingdom) and 7% (Germany and the Netherlands)[11]; from 1% (Morocco) to 3% (Egypt) in African countries[11]; from 2% (Taiwan) to 5% (Japan and Russia) in Asian countries[11,22]; from 3.7 to 5% in North America (United States)[10,11]; and finally from 2% (Argentina and Venezuela) to 7% (Uruguay) in Latin America.[11,23] On the other hand, a review of the literature for

Table 2 – Gross and adjusted logistic regression analysis of patients with acute myocardial infarction and independent variables in patients with rheumatoid arthritis. Blumenau, Santa Catarina, Brazil, 2014.

Variables		Gross analysis			Adjusted analysis	
Total	OR	CI 95%	*p*-Value	OR	CI 95%	*p*-Value
Gender			0.882[a]			0.864
Male	1.0			1.0		
Female	1.1	(0.2–5.2)		1.0	(0.4–2.3)	
Age in years			0.600[a]			0.595
20–59 (adults)	1.0			1.0		
≥60 (elderly)	1.3	(0.4–4.1)		1.3	(0.4–4.1)	
Hypertension			0.027			0.116[b]
No	1.0			1.0		
Yes	4.3	(1.1–16.3)		3.0	(0.7–12.4)	
Diabetes Mellitus			0.005			0.006
No	1.0			1.0		
Yes	5.4	(1.6–17.8)		3.5	(1.7–21.2)	
Dyslipidemia			0.076			0.379[b]
No	1.0			1.0		
Yes	2.7	(0.8–8.5)		1.7	(0.5–6.0)	
Body mass index (kg/m²)			0.367[a]			0.846
≤24.9	1.0			1.0		
25–29.9	1.1	(0.2–4.3)		1.0	(0.2–3.6)	
≥30	1.9	(0.4–8.2)		1.1	(0.2–5.4)	
Smoking						
Never smoked	1.0		0.068	1.0		0.108[b]
Previous and/or current smokers	3.5	(0.9–10.1)		2.7	(0.8–9.1)	
Physical leisure activity			0.288[a]			0.399
Never practiced	1.0			1.0		
Practiced and/or practices	1.8	(0.5–5.5)		1.6	(0.5–5.0)	
Positive family history			0.175			0.221[b]
No	1.0			1.0		
Yes	2.2	(0.7–6.9)		2.0	(0.6–6.5)	
Disease duration			0.005			0.005
0–10 years	1.0			1.0		
≥11 years	8.6	(1.8–39.7)		8.2	(1.9–43.6)	
Presence of rheumatoid factor			0.993[a]			0.946
0–60 (negative, or low titers)	1.0			1.0		
≥61 (high titers)	1.0	(0.3–3.1)		1.0	(0.2–3.2)	

[a] Excluded from the multiple analysis ($p > 0.20$).
[b] Excluded from the final model ($p > 0.05$).

CVD limited to Latin American countries found a more important prevalence (9%) of coronary artery disease.[24] In Oceania, a study using the hospital database of the city of Christchurch established a prevalence of 8.3%.[15]

The CORONNA[10] study found a significant difference in the risk of ischemic events among women (RR 3.1) *versus* men (RR 6.5). The sample consisted of 75% of women, which differs from our study, with 83% of women. This could explain the difference in results between genders. The age factor showed a tendency of greater chance among the elderly, but without significance. In this study, results were obtained that were common to those in the QUEST-RA study,[12] which, after the multivariate analysis for MI, showed no difference in relation to age.

Among the traditional risk factors, patients with a history of hypertension or dyslipidemia did not show a greater chance of MI because, after the analysis adjusted for gender and age in the final model, they lost an association with outcome, although this association was pointed out by other international studies.[25,26]

Diabetes mellitus presents a direct association with an ischemic event, a finding also observed in other studies.[12,25] A systemic review and meta-analysis on the impact of cardiovascular risk factors for MI in patients with RA performed in 2014 indicated that diabetic individuals demonstrated a propensity 1.9 times higher *versus* non-diabetic patients,[26] while in the present study a 3.5 times higher chance was found.

Other studies have confirmed that the risk factors obesity and physical activity were not associated with ischemic cardiac morbidity.[8,12,27] In a French hospital, smoking was evaluated among patients with RA in association with an ischemic

outcome.[28] The investigators found that there was no association with CVD, a finding in line with the results of our study. There was a prevalence of 43% for positive family history in the sample, but with no statistical significance with the outcome, while two other studies indicated an opposed relationship.[29,30]

Patients with disease duration over 10 years had an 8.2-fold higher chance of MI *versus* patients with a shorter duration of their disease. This association was maintained after the adjusted analysis and remained in the final model. A Japanese study including a follow-up of 571 patients in a university hospital over a decade concluded that disease duration (>10 years) was an independent risk factor for cardiovascular events.[31] This finding results from the longer duration of the inflammatory process for the generation of consequences such as atherosclerosis and endothelial dysfunction.[32] On the other hand, a study conducted in the Netherlands did not indicate a difference in the risk for an ischemic event due to a disease duration of less than or greater than 10 years.[33]

In this study, the value of the rheumatoid factor (RF) in high titers was used as a marker of poor prognosis (RF > 60), because RF is a predictor of cardiovascular disease[34] and also because it could promote instability and rupture of atherosclerotic plaque into the coronary artery.[35] Some studies have shown that the presence of RF in both non-diseased individuals[36] and in patients with RA[37] confers a higher chance of MI. However, the results of this study did not show any association of RF with the outcome, as already indicated in another study.[14]

In the present study, some limitations must be taken into account. The cross-sectional design of the study makes it impossible to determine cause and effect between the exploratory variables and the outcome. Based on the results obtained, the possibility of reverse causality, characteristic in cross-sectional studies, is highlighted. Another factor to consider is the possibility of memory bias in the collection of some information, which is attenuated by the common characteristic of RA being a chronic illness. Finally, the self-reported data on comorbidities have not been confirmed by a physician. On the other hand, health surveys reveal that the information obtained on the prevalence of chronic diseases presents good agreement, when compared to medical records or clinical exams, especially for some chronic diseases such as hypertension and diabetes mellitus (DM).[38,39] It should further be considered that the data related to RA were collected according to the European League Against Rheumatism (EULAR) recommendations for annual detection and monitoring for cardiovascular risk.[40]

This is the first Brazilian study to establish a prevalence of MI among RA patients. Among the traditional risk factors, diabetes mellitus, and among factors related to RA, disease duration, were the associated variables. New population-based studies are needed in order to increase the consistency of information on coronary artery disease in RA patients and also to investigate associated factors in other Brazilian regions.

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Conflicts of interest

The authors declare no conflicts of interest.

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