CSP CADERNOS DE SAÚDE PÚBLICA
REPORTS IN PUBLIC HEALTH

ARTIGO
ARTICLE

Association of metabolic syndrome with inflammatory markers in a sample of community-dwelling older adults

Associação entre síndrome metabólica e marcadores inflamatórios em idosos residentes na comunidade

Asociación entre síndrome metabólico y marcadoresinflamatorios en ancianos residentes en comunidades

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doi: 10.1590/0102-311X00129918

Abstract

The study aimed to identify the cutoff points for inflammatory markers that best discriminate the occurrence of metabolic syndrome in community-dwelling older adults. Baseline data were used from the elderly cohort in the city of Bambuí, Minas Gerais State, Brazil. The target exposure was presence of metabolic syndrome, defined according to the Adult Treatment Panel III *criterion, and the outcomes included the following inflammatory markers: cytokines (IL-1β, IL-6, IL-10, IL-12 e TNF), chemokines (CXCL8, CXCL9, CCL2, CXCL10, and CCL5), and C-reactive protein (CRP). Definition of the cutoff points for the inflammatory markers was based on the* Classification and Regression Tree *(CART) method. The associations between these markers and metabolic syndrome were estimated by logistic regression models, obtaining odds ratios and 95% confidence intervals, considering adjustment for confounding factors. Prevalence of metabolic syndrome was 49.1%, and IL-1β, IL-12, and TNF levels were not associated statistically with this exposure. After adjustment, presence of metabolic syndrome was associated with higher IL-6 and CRP levels and lower CXCL8 and CCL5. Significant associations were also observed with intermediate serum CXCL9 and CXCL10 levels. The combination of markers also showed a significant and consistent association with metabolic syndrome. In addition to demonstrating an association between metabolic syndrome and a wide range of biomarkers (some not previously described in the literature), the results highlight that this association occurs at much lower levels than previously demonstrated, suggesting that metabolic syndrome plays an important role in the inflammatory profile of the older adults.*

Metabolic Syndrome; Inflammation; Biomarkers; Health of the Elderly

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Introduction

Metabolic syndrome is characterized by a series of dysfunctions in the individual's metabolism, such as hyperglycemia, visceral obesity, dyslipidemia, hypertension, and proinflammatory and prothrombotic state [1,2,3]. Although using the same diagnostic criterion, prevalence of metabolic syndrome varies widely between elderly populations (from 25% to 60%), which may be explained by differences in the populations' composition in terms of gender, age bracket, ethnicity, and environmental factors, among others [4,5,6,7,8,9]. Among North Americans without a history of cardiovascular disease, prevalence of metabolic syndrome reached 32.2% in the 50-69-year bracket and 34.6% in individuals 70 years and older [9], while prevalence was 27% in a sample of elderly Italians [7]. Higher levels have been observed in low-income countries, reaching 36% in elderly Mexicans [8], 45-50% in some Brazilian cities [5,6], and 58.1% in China [4]. Furthermore, prevalence of metabolic syndrome has shown a steady increase over time, especially in low and middle-income countries and among the older adults [5,10,11].

Given the accelerated growth of the elderly population in Brazil and the world [12], alongside the phenomenon of "inflammaging" [13], namely the higher degree of inflammation in the elderly population, it is obviously important to elucidate the role of inflammatory state as a component of the metabolic syndrome phenotype in this age group. This inflammatory profile is commonly associated with various noncommunicable diseases (NCDs) and their risk factors, common in the elderly population, as with the features of metabolic syndrome itself (obesity, dyslipidemia, hypertension, and diabetes) [14,15,16,17,18,19,20]. Still, there is no consensus as to the best inflammatory marker or combination of markers that is most consistently associated with metabolic syndrome in this population group [14,21,22,23]. Previous studies among the older adults have only reported a positive association between metabolic syndrome and increased levels of interleukin 6 (IL-6) and C-reactive protein (CRP) [22,24,25,26] but these associations have not been described in other populations [27,28].

This lack of consensus on the association between metabolic syndrome and inflammatory markers may be explained at least partly by the different diagnostic criteria used for definition of the syndrome [3,29] and/or by the different ways of treating inflammatory markers used in the statistical analyses, using continuous measures (generally with log transformation) or categorized measures (using medians, tertiles, quartiles, etc.) [16,17,19,20,30,31,32,33,34], which hinders the identification of a cutoff point based on which one can show significant changes in the prevalence of the target outcomes.

The current study thus aimed to identify cutoff points in a wide range of inflammatory markers that best discriminate the occurrence of metabolic syndrome in community-dwelling older adults. The study also estimated the association between the inflammatory markers, using the cutoff points defined in this study, and the presence of metabolic syndrome, considering adjustment for potential confounding factors.

Methodology

Study population and data collection

The *Bambuí Health and Aging Study* is a prospective population-based cohort study in the city of Bambuí in southwestern Minas Gerais State, Brazil, located 215km from Belo Horizonte. The study's baseline was established in 1997, when the entire resident population 60 years and older (n = 1,742) was identified by a census and invited to participate.

The data were obtained from interviews, physical examination, and blood samples for laboratory tests. The interviews were held in the participants' homes with trained interviewers using a standardized questionnaire. Physical examination and collection of blood samples were done at the project's field clinic (Emmanuel Dias Advanced Studies Health Post) by trained examiners and using standardized instruments, except when the elderly individual was physically unable to attend at the clinic, and in this case the procedures were performed at the participant's home [35].

The cohort's baseline was approved by the Institutional Review Board of the Oswaldo Cruz Foundation, and all the participants signed a free and informed consent form to participate in the study.

Study outcomes: inflammatory markers

To titrate the biomarkers, a 5mL blood sample was drawn by venipuncture using the vacuum blood collection system (Vacutainer, Becton Dickinson, USA) in a tube containing sodium heparin. Participants were instructed to fast for 12 hours before the blood draw, and the samples were centrifuged, refrigerated, and later transferred to the René Rachou Institute, Oswaldo Cruz Foundation, Belo Horizonte, having been stored in a freezer at -80ºC.

The serum levels were subsequently determined for interleukins (IL-1β, IL-6, IL-10, IL-12, and tumor necrosis factor – TNF), chemokines (CXCL8, CXCL9, CCL2, CXCL10, and CCL5), and ultrasensitive CRP (CRP-us). Multiplex flow cytometry (CBA immunoassay kit, Becton Dickinson, USA) was used for quantitative determination of cytokines (human inflammatory kit) and chemokines (human chemokines kit). The CBA inflammatory kit includes beads coupled with the monoclonal antibody (moAb) against cytokines IL-1β, IL-6, TNF, IL-12, and IL-10, and the CBA chemokines kit detects CXCL8, CXCL9, CXCL10, CCL2, and CCL5. Anti-cytokine antibodies were used, labeled with phycoerythrin to indicate the mean fluorescence intensity (MFI). MFI data were obtained with the FACSVerse flow cytometer (Becton Dickinson, USA), and the concentrations in pg/mL were calculated with the BD FCAP Array 3.0 software (Becton Dickinson, USA), based on standard concentration curves expressed in pg/mL. Intra- and inter-assay coefficients of variation were 5-10% and 7-12%, respectively [36]. C-reactive protein was obtained automatically by the immunonephelometric method and expressed in mg/L (BNII, Dade Behring, Germany).

Explanatory variable: metabolic syndrome

Metabolic syndrome was defined according to the criteria of the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATPIII) and recommended by the *Ist Brazilian Consensus on Diagnosis and Treatment of Metabolic Syndrome* (I-DBSM). According to these criteria, metabolic syndrome was defined as the presence of at least three alterations among five components, namely: (a) fasting blood glucose ≥ 110mg/dL; (b) blood pressure ≥ 130/85mmHg; (c) triglycerides ≥ 150mg/dL; (d) HDL-cholesterol < 40mg/dL in men and < 50mg/dL in women; and (e) waist circumference > 102cm in men and > 88cm in women. The definition also considered treatment with the use of lipid-lowering, glucose-lowering, and antihypertensive drugs [2,3].

Waist circumference was measured with a flexible, inelastic tape measure with the subject in standing position, at the midpoint between the last rib and the iliac crest [37]. Fasting serum glucose, HDL cholesterol, and triglycerides were measured after the recommended 12-hour fast, using an automatic analyzer (Eclipse Vitalab, Merck, Netherlands). Blood pressure was measured with a mercury sphygmomanometer (Tyco's 5097-30, USA) and stethoscope (Littman's Cardiology II, USA). Three measurements were taken at two-minute intervals at least 30 minutes after the last dose of caffeine or cigarettes, and the mean of the last two measurements was used [38].

Potential confounding factors

Potential confounding factors included characteristics that were associated with both the inflammatory markers and metabolic syndrome in previous studies [19,22,25,28,34,39,40]. These factors included: sociodemographic characteristics (sex, age, and schooling), health behaviors (smoking, alcohol intake, and physical activity), health conditions (arthritis, stroke, acute myocardial infarction, depressive symptoms, cognitive impairment, positive serology for *Trypanosoma cruzi*), and use of anti-inflammatory drugs.

Smokers were defined as individuals that reported having smoked at least 100 cigarettes in their lives and continued smoking at the time of the interview. Alcohol consumption was defined as weekly consumption of seven doses or more in the 12 months prior to the interview [41]. To define "doses", participants were shown cards with the amount of liquid corresponding to a dose of beer, wine, or distilled liquor. Physical activity was assessed by the report of 23 activities practiced in the previous 90 days in all the domains, then converted into energy expenditure (metabolic equivalents – MET). Insufficient physical activity was defined as energy expenditure less than 450MET minute/week [42].

History of acute myocardial infarction and arthritis was defined as prior medical diagnosis of these conditions, and the occurrence of stroke was assessed according to a specific protocol (*Plan and Operation of the Third National Health and Nutrition Examination Survey* 1988-1994). Presence of depressive symptoms was defined as a score of five or greater on the *General Health Questionnaire* (GHQ-12), as recommended for this population [43]. Cognitive impairment was assessed by the *Mini-Mental State Examination* (MMSE) and defined as a score below 22, which corresponds to the lower quartile of the elderly population in Bambuí [44]. The study also included the use of anti-inflammatory drugs in the 90 days prior to the interview, assessed by observation of the package label or medical prescription, coded by the *Anatomical Therapeutic Chemical* (ATC) classification system (World Health Organization Collaborating Cnetre for Drugs Statistics Methodology. ATC/DDD index. https://www.whocc.no/atc_ddd_index).

Since Bambuí is an endemic area for Chagas disease, *T. cruzi* infection was considered a potential confounder in the analysis. Infection was investigated with three different serological tests: hemagglutination assay (Biolab Merieux S.A., Brazil) and two immunoenzymatic assays (ELISA) (Abbott Laboratories, Inc., USA; and Wiener Laboratories, Argentina). Infection was defined as positive serology in all three tests, and absence of infection when all three results were negative.

Data analyses

The study population's characteristics were described, as well as the presence or absence of metabolic syndrome, using proportions or means according to the nature of the variables. The groups were compared by Pearson's chi-square test for comparison of proportions or Student's t-test for comparison of means.

Categorization of the biomarkers used the CART method (*Classification and Regression Tree*), an empirical technique based on analysis of the data's recursive partitioning. Since it does not require parametric assumptions, the method readily accommodates the analysis of highly asymmetric variables (as in the case of the cytokines here), in addition to multimodal or categorical variables.

The method involves the sample's segregation via progressive binary divisions in order to obtain the most internally homogeneous subgroups possible, and heterogeneous between each other. The method was used in this study for the definition of cutoff points for each of the inflammatory markers, aimed at comprising homogeneous groups in relation to the presence of metabolic syndrome, and thus discriminating between individuals with and without metabolic syndrome in the population. The method's implementation used (as conditions for interrupting the process of partitioning the dataset) the formation of a maximum of three groups, each consisting of at least 30 participants.

After defining these cutoff points by the method described above, we conducted the frequency distribution for each biomarker in the total population and between the groups with and without metabolic syndrome, comparing these proportions by Pearson's chi-square test. We then estimated the odds ratios (OR) and respective 95% confidence intervals (95%CI), with the biomarkers as the outcome and metabolic syndrome as the principal exposure, without adjusting (crude model) and including progressive adjustment of the variables: model 1, adjusted by the sociodemographic factors and model 2: including sociodemographic factors plus health behaviors, health conditions, and use of anti-inflammatory drugs. These models were estimated by binary or multinomial logistic regression for the biomarkers categorized in two or three levels, respectively. An additional analysis verified the association between metabolic syndrome and the number of biomarkers with positive association and the number of biomarkers with negative association among those with significant association in the previous analysis, using multinomial logistic regression without adjustment and adjusted for all the confounders considered in the study.

The statistical analyses used the Stata package, version 13.0 (http://www.stata.com), except for determination of the cutoff points for the inflammatory markers by the CART method, which used the *rpart* package in the R environment (http://www.-r-project.org). All statistical tests were performed with 5% level of significance.

Results

Of the 1,742 older adults individuals residing in the city of Bambuí and invited to participate in the baseline cohort, 1,606 (92.2%) were interviewed and 1,333 (83%) had all the information used in the current study and were included in this analysis. Of these, 654 (49.1%) presented metabolic syndrome according to the NCEP-ATPIII criteria.

Table 1 shows the distribution of the study population's characteristics and the association between these variables and the presence of metabolic syndrome. Participants' mean age was 68.8 years (SD = 6.9), and the majority were women (61.4%) and had low schooling (63.2%). Current smoking was observed in 17.5% of the elderly, 5.3% consumed seven or more doses of alcoholic beverages per week, and 26.6% were classified as practicing insufficient physical activity. Among the health conditions that were assessed, the most frequent were presence of depressive symptoms (37.4%), positive serology for *T. cruzi* (37.2%), and history of medical diagnosis of arthritis/rheumatism (26.1%). All the variables listed in the table showed a significant association ($p < 0.05$) with metabolic syndrome except for history of medical diagnosis of myocardial infarction and stroke.

Table 2 describes the distribution of inflammatory markers using the cutoff points defined in the study by the CART method, according to diagnosis of metabolic syndrome. This method demonstrated that the best discrimination between individuals with and without metabolic syndrome in the population was with two cutoff points for three markers (IL-6, CXCL9, and CXCL10), generating three groups, and only one cutoff point for the other markers, generating two categories for these variables (IL-10, CXCL8, CCL2, CCL5, and CRP). All the markers showed significant associations ($p < 0.05$) with metabolic syndrome, without adjusting for the confounding factors. In general, elevated levels of IL-6 and CRP and intermediate levels of CXCL10 were more frequent in individuals with metabolic syndrome. On the other hand, the group with metabolic syndrome showed lower levels of IL-10, CXCL8, CCL2, and CCL5, besides intermediate levels of CXCL9.

For IL-1β, IL-12, and TNF, the CART method was not capable of obtaining cutoff points that discriminated between groups with and without metabolic syndrome, indicating lack of significant association between these variables.

Table 1

Characteristics of study population according to diagnosis of metabolic syndrome. Baseline elderly cohort, *Bambuí Health and Aging Study*, Bambuí, Minas Gerais State, Brazil.

Variables	Total (%) * [N = 1,333]	Metabolic syndrome (%) *		p-value **
		No [n = 679]	Yes [n = 654]	
Age in years [mean (SD)]	68.8 (6.9)	69.2 (7.1)	68.3 (6.7)	0.017
Female gender	61.4	46.7	76.6	0.001
Schooling < 4 years	63.2	67.2	59.0	0.002
Current smoker	17.5	22.2	12.5	< 0.001
7 or more doses of alcohol/week	5.3	7.7	2.9	< 0.001
Insufficient physical activity	26.6	22.4	30.9	< 0.001
Positive serology for *T. cruzi*	37.2	39.8	34.6	0.049
History of myocardial infarction	4.7	3.7	5.8	0.067
Stroke	3.2	3.7	2.7	0.337
Medical history of arthritis/rheumatism	26.1	21.3	31.0	< 0.001
Depressive symptoms (GHQ score > 5)	37.4	33.9	41.1	0.006
Cognitive impairment (MMSE score < 22)	17.8	22.2	13.3	< 0.001
Use of non-steroidal anti-inflammatory drugs	16.4	12.2	20.8	< 0.001

GHQ: *General Health Questionnaire*; MEEM: *Mini-Mental State Examination*.

* Except when specified;

** Pearson's chi-square or Student's t-test for differences between proportions or means, respectively.

Table 2

Distribution of inflammatory markers using the cutoff points determined by the study, according to diagnosis of metabolic syndrome. Baseline elderly cohort, *Bambuí Health and Aging Study*, Bambuí, Minas Gerais State, Brazil.

Biomarkers	Total (%)	Metabolic syndrome (%)		p-value *
		No	Yes	
IL-6 (pg/mL)				
≤ 0.035	6.4	9.0	3.7	< 0.001
0.036-0.365	16.0	17.5	14.4	
≥ 0.365	77.6	73.5	82.0	
IL-10 (pg/mL)				
< 0.235	81.9	79.2	84.6	0.012
≥ 0.235	18.1	20.8	15.4	
CXCL8 (pg/mL)				
< 4.99	72.3	68.5	76.3	0.001
≥ 4.99	27.7	31.5	23.7	
CXCL9 (pg/mL)				
< 2.861	59.0	57.4	60.7	0.043
2.861-7.807	29.1	32.0	26.1	
≥ 7.807	11.9	10.6	13.2	
CXCL10 (pg/mL)				
< 2.980	48.8	53.3	44.2	0.001
2.980-5.982	34.7	29.9	39.8	
≥ 5.982	16.4	16.8	16.0	
CCL2 (pg/mL)				
< 25.13	24.5	21.9	27.2	0.025
≥ 25.13	75.5	78.1	72.8	
CCL5 (pg/ml)				
< 1.682	75.6	72.0	79.4	0.002
≥ 1.682	24.4	28.0	20.6	
PCR (mg/L)				
< 2.435	41.6	52.6	30.3	< 0.001
≥ 2.435	58.4	47.4	69.7	

* Pearson's chi-square test.

Table 3 shows the association of metabolic syndrome with the inflammatory markers, using the cutoff points defined in the study, considering the crude model and the model adjusted for potential confounders. After adjustment, metabolic syndrome was significantly and positively associated with intermediate (OR = 2.25; 95%CI: 1.26-4.05) and high IL-6 (OR = 3.15; 95%CI: 1.86-5.35), high CRP (OR = 2.49; 95%CI: 1.95-3.17), and intermediate CXCL10 (OR = 1.53; 95%CI: 1.17-1.98). Meanwhile, presence of metabolic syndrome was significantly and inversely associated with high CXCL8 (OR = 0.71; 95%CI: 0.55-0.93), high CCL5 (OR = 0.69; 95%CI: 0.52-0.91), and intermediate CXCL9 (OR = 0.75; 95%CI: 0.57-0.99).

Table 4 shows the association of metabolic syndrome with the number of altered biomarkers (above the established cutoff points) among those with positive or negative associations with metabolic syndrome in the previous analysis. After adjusting for all the factors included in the study, metabolic syndrome was significantly associated with higher number of altered markers, both in the group with positive associations and that with negative associations. Among the markers with positive associations (IL-6, CXCL10, and CRP), MS increased the odds by more than fourfold (OR = 4.42; 95%CI: 1.25-15.62) of having a marker above the defined cutoff point, more than eightfold (OR = 8.46; 95%CI: 2.42-29.54) of having two altered markers, and by nearly 14 times (OR = 13.84; 95%CI: 3.93-48.74) of having three markers above the defined levels. Meanwhile, for the group of markers with nega-

Table 3

Association of biomarkers with metabolic syndrome in the study population, without and with adjustment for confounders. Baseline elderly cohort, *Bambuí Health and Aging Study*, Bambuí, Minas Gerais State, Brazil.

Biomarkers	Crude model OR (95%CI)	Model 1 OR (95%CI)	Model 2 OR (95%CI)
IL-6 (pg/mL)			
≤ 0.035	1.00	1.00	1.00
0.036-0.365	2.01 (1.16-3.46)	2.07 (1.17-3.67)	2.25 (1.26-4.05)
≥ 0.365	2.73 (1.68-4.45)	2.95 (1.77-4.94)	3.15 (1.86-5.35)
IL-10 (pg/mL)			
< 0.235	1.00	1.00	1.00
≥ 0.235	0.70 (0.53-0.92)	0.74 (0.55-0.99)	0.75 (0.55-1.02)
CXCL8 (pg/mL)			
< 4.99	1.00	1.00	1.00
≥ 4.99	0.67 (0.53-0.86)	0.73 (0.56-0.94)	0.71 (0.55-0.93)
CXCL9 (pg/mL)			
< 2.861	1.00	1.00	1.00
2.861-7.807	0.77 (0.61-0.99)	0.75 (0.57-0.98)	0.75 (0.57-0.99)
≥ 7.807	1.17 (0.83-1.65)	1.24 (0.85-1.81)	1.35 (0.90-2.01)
CXCL10 (pg/mL)			
< 2.980	1.00	1.00	1.00
2.980-5.982	1.60 (1.26-2.04)	1.49 (1.15-1.92)	1.53 (1.17-1.98)
≥ 5.982	1.15 (0.85-1.57)	1.05 (0.75-1.46)	1.08 (0.76-1.53)
CCL2 (pg/mL)			
< 25.13	1.00	1.00	1.00
≥ 25.13	0.75 (0.59-0.97)	0.77 (0.59-1.01)	0.77 (0.59-1.02)
CCL5 (pg/mL)			
< 1.682	1.00	1.00	1.00
≥ 1.682	0.67 (0.52-0.86)	0.74 (0.56-0.96)	0.69 (0.52-0.91)
PCR (mg/L)			
< 2.435	1.00	1.00	1.00
≥ 2.435	2.55 (2.04-3.20)	2.50 (1.97-3.17)	2.49 (1.95-3.17)

95%CI: 95% confidence interval; OR: odds ratios.

Notes: OR (95%CI) estimated by binary logistic regression (IL-10, CCL2, CCL5, CXCL8, and CRP) or multinomial regression (IL-6, CXCL9, and CXCL10), with metabolic syndrome as the exposure variable. Model 1: adjusted for sex, age (continuous), and schooling; model 2: adjusted for variables from previous model plus current smoking, alcohol consumption, physical activity, *T. cruzi* serology, myocardial infarction, stroke, arthritis, depressive symptoms, cognitive impairment, and use of non-steroidal anti-inflammatory drugs.

tive associations (CXCL8, CCL5, and CXCL9), MS significantly reduced the odds of observing two (OR = 0.65; 95%CI: 0.47-0.91) or three (OR = 0.50; 95%CI: 0.29-0.88) inflammatory markers above the defined cutoff points.

Discussion

The study's results show a wide range of inflammatory markers associated with metabolic syndrome in the elderly besides those previously described in the literature, and also allowed identifying the levels at which each of these markers differentiated between individuals in the population with and without the syndrome, independently of other relevant factors considered in the analysis. In general, metabolic syndrome was positively associated with increased levels of IL-6, CXCL10, and CRP and negatively associated with increased levels of CCL5, CXCL8, and CXCL9, besides showing

Table 4

Association of number of biomarkers with metabolic syndrome in the study population, without and with adjustment for confounders. Baseline elderly cohort, *Bambuí Health and Aging Study*, Bambuí, Minas Gerais State, Brazil.

Number of biomarkers	%	Crude model OR (95%CI)	Adjusted model OR (95%CI)
With positive association *			
0	2.1	1.00	1.00
1	23.3	4.31 (1.27-14.6)	4.42 (1.25-15.62)
2	43.9	8.19 (2.45-27.43)	8.46 (2.42-29.54)
3	30.7	13.80 (4.10-46.46)	13.84 (3.93-48.74)
With negative association **			
0	38.0	1.00	1.00
1	36.6	0.84 (0.65-1.08)	0.80 (0.61-1.05)
2	19.9	0.62 (0.46-0.84)	0.65 (0.47-0.91)
3	5.5	0.49 (0.30-0.81)	0.50 (0.29-0.88)

95%CI: 95% confidence interval; OR: odds ratios.

Notes: OR (95%CI) estimated by multinomial logistic regression, with metabolic syndrome as the exposure variable. Adjusted model: includes sex, age (continuous), schooling, current smoking, alcohol consumption, physical activity, *T. cruzi* serology, myocardial infarction, stroke, arthritis, depressive symptoms, cognitive impairment, and use of non-steroidal anti-inflammatory drugs.

* IL-6 (> 0.036pg/mL), CXCL10 (> 2.980pg/mL), and CRP (> 2.435mg/L);

** CCL5 (> 1.682pg/mL), CXCL8 (> 4.99pg/mL), and CXCL9 (> 2.861pg/mL).

a consistent association with the number of altered markers, even after adjusting for the confounders measured in the study.

It is difficult to compare the results from previous studies of the elderly on the association between metabolic syndrome and inflammatory markers, because although the criterion used to define metabolic syndrome was the same as that in the current study (NCEP/ATPIII), the markers are treated differently, especially in the distribution's percentiles [24,25]. Some authors suggest replacing this random categorization of continuous variables with other methods to better test the hypothesis of the association between exposure and outcome [45], which would allow a more detailed study of the distribution of these variables in the different groups for comparison.

The current study thus adds to the existing knowledge by using a categorization method (CART) which allowed identification of the cutoff points for the inflammatory markers that showed the highest discriminatory power in relation to metabolic syndrome. In general, the levels of markers obtained for the elderly in Bambuí were lower than those previously reported in the literature for some metabolic disorders, such as cardiovascular diseases and type 2 diabetes, among others [16,19,46,47]. These results suggest that the metabolic events may be associated with much lower levels of these inflammatory markers, as observed in Bambuí, which should be considered in epidemiological studies on these associations and the potential application of this knowledge to the early detection of metabolic syndrome in clinical practice.

CRP and IL-6 (a pleiotropic inflammatory cytokine), with synthesis in the liver, blood vessels, adipocytes, and muscle, are biomarkers related to acute systemic inflammation and can activate insulin receptors and glucose metabolism and cause resistance and endothelial dysfunction, including atherosclerosis, infection, and systemic tissue injury [48,49,50,51]. Increased plasma concentrations of these markers have been associated with numerous clinical conditions, including phenotypes for metabolic risk, such as obesity, type 2 diabetes, hypertension, and other cardiovascular diseases [19,20,22,48,52,53,54,55,56,57,58,59] and metabolic syndrome itself [20,39,58,60,61]. However, the results described in Bambuí show that this association was already present at lower levels of these markers (above 0.035pg/mL for IL-6 and 2.435mg/L for CRP), contrary to previous reports. Values from 3 to 48.5mg/L for CRP [19,20,22,25,26,39,62] and 1.24 to 36.9pg/mL for IL-6 [19,25,26,28,63] have been described in various populations,

always higher than the cutoff points observed in the current study. One can thus suggest that the use of cutoff points based on the sampling distribution, such as distribution percentiles (the strategy adopted by most of the above-mentioned studies), may not adequately demonstrate the levels of biomarkers based on which metabolic syndrome may be more frequent in the population.

Besides the markers classically described in the literature, the current study showed that metabolic syndrome was associated with lower levels of CCL5, CXCL8, and CXCL9 and higher levels of CXCL10, although the latter two markers were only associated significantly at intermediate levels. Although these associations had not been reported previously in the literature, the results support the hypothesis that metabolic syndrome is accompanied by inflammatory state [40], thus contributing to the understanding of alterations in inflammatory profile in the presence of metabolic syndrome. Aging is accompanied by redistribution of body fat, especially in the abdominal region, which can contribute to changes in inflammatory state, due mainly to production of proinflammatory molecules by adipocytes and macrophages in the adipose tissue, leading to metabolic dysfunction and modification of the unfavorable inflammatory profile [28,60,62], which could lead to an association between metabolic syndrome and these markers.

The role of CCL5, CXCL8, and CXCL9 as markers is similar in relation to the reduction in monocytes/macrophages in the injured vessel, chemotactic regulation of T-lymphocyte extravasation, and recruitment to the adipose tissue, pancreas, muscle, and liver, which are target organs for the initiation and maintenance of characteristic disorders in metabolic syndrome. These results are consistent with the pathogenesis of diabetes, atherosclerosis, and heart failure [30,47,49,62,63,64,65]. The results described in the elderly in Bambuí thus appear to contribute to more in-depth knowledge of the inflammatory changes that are present in metabolic syndrome and are consistent with the biological role of these markers, which had not been described previously in the literature as associated with metabolic syndrome.

Meanwhile, the chemokine CXCL10 has chemoattractant action on Th1 lymphocytes, which in turn secrete interferon gamma (IFN-γ) [66], tending to promote activation and migration of monocytes and macrophages on the endothelial wall, leading to dysfunction and proliferation of smooth muscle cells and greater vascular permeability, resulting in the exacerbation of hypertension or complications such as atherosclerosis, cardiopathic hypertension, and hypertensive nephrosclerosis [67]. Likewise, there is evidence of interaction between CXCL10 and the CXCR3 receptor, a determinant of selective destruction of pancreatic β cells and the development of diabetes [68]. Such evidence thus also suggests the consistency between the association described in this study between metabolic syndrome and increased CXCL10 levels, although it is still necessary to understand the reason why this association is not maintained at very high levels (> 5.982pg/mL).

Beside the previously mentioned markers, other studies have also shown significant associations (although less consistent) between metabolic syndrome or its components, especially insulin resistance and visceral obesity, and IL-10 [18,68] TNF [51,69], and CCL2 levels [70,71]. Still, in some populations, as observed in the elderly in Bambuí, these associations either were not observed or presented conflicting results [22,55,67,68,69,70,71]. Such evidence appears to suggest lack of consistency in the association between metabolic syndrome and these biomarkers as reported in the elderly population in Bambuí.

The current study's main limitation was its cross-sectional design, which did not allow establishing temporal relations between the study variables. However, this was a population-based study with data collected by trained examiners using standardized instruments, thus guaranteeing the data's quality. The analysis also included a wide range of biomarkers and confounding factors, allowing to advance the knowledge already produced on the association of metabolic syndrome with inflammatory profile, besides identifying the cutoff points that best discriminate this association, which had not been described previously in the literature.

Therefore, our results emphasize that although the elderly present important changes in their inflammatory profile, caused by aging itself [36,72], even after adjusting for various confounding factors, the presence of metabolic syndrome was significantly associated with alterations in various biomarkers, suggesting that this syndrome may represent an important component of the inflammatory process in the elderly population. In addition to the markers classically described in the literature, the current study's results point to other biomarkers associated with metabolic syndrome, including at lower levels than those previously reported.

Contributors

C. V. B. Neves, J. V. M. Mambrini and S. V. Peixoto contributed in the study conception, data analysis and interpretation, and elaboration of the article. K. C. L. Torres, A. Teixeira-Carvalho, O. A. Martins-Filho and M. F. Lima-Costa contributed in the data interpretation and critical revision of the manuscript.

Additional informations

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Acknowledgments

The authors wish to thank the Brazilian Ministry of Health (DECIT) and Ministry of Science and Technology (CNPq and FINEP) for supporting the project. A. Teixeira-Carvalho, O. A. Martins-Filho, M. F. Lima-Costa and S. V. Peixoto hold research scholarships from the CNPq.

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Resumo

O objetivo do trabalho foi identificar os pontos de corte dos marcadores inflamatórios que melhor discriminassem a ocorrência da síndrome metabólica entre idosos residentes na comunidade. Foram utilizados os dados da linha de base da coorte de idosos conduzida na cidade de Bambuí, Minas Gerais, Brasil. A exposição de interesse foi a presença da síndrome metabólica, definida pelo critério Adult Treatment Panel III, *e os desfechos incluíram os seguintes marcadores inflamatórios: citocinas (IL-1β, IL-6, IL-10, IL-12 e TNF), quimiocinas (CXCL8, CXCL9, CCL2, CXCL10 e CCL5) e proteína C-reativa (PCR). A definição dos pontos de corte dos marcadores inflamatórios foi baseada no método* Classification and Regression Tree *(CART). As associações entre esses marcadores e a síndrome metabólica foram estimadas por modelos de regressão logística, obtendo-se* odds ratio *e intervalos de 95% de confiança (IC95%), considerando o ajustamento por fatores de confusão. A prevalência da síndrome metabólica foi de 49,1%, e os níveis de IL-1β, IL-12 e TNF não se mostraram associados a essa exposição. Após ajustamento, a presença da síndrome metabólica foi associada a maiores valores de IL-6 e PCR e a menores valores de CXCL8 e CCL5. Associações significativas ainda foram observadas com níveis séricos intermediários de CXCL9 e CXCL10. Além disso, a combinação dos marcadores apresentou associação significativa e consistente com a síndrome metabólica. Além de demonstrar associação entre síndrome metabólica e uma ampla gama de biomarcadores, alguns ainda não descritos na literatura, os resultados ressaltam que essa associação ocorre em níveis muito inferiores aos já demonstrados, sugerindo que a síndrome metabólica desempenha importante papel no perfil inflamatório dos idosos.*

Síndrome Metabólica; Inflamação; Biomarcadores; Saúde do Idoso

Resumen

El objetivo del trabajo fue identificar los puntos de corte de los marcadores inflamatorios que mejor discriminaran la ocurrencia del síndrome metabólico entre ancianos residentes en comunidades. Se utilizaron datos de referencia de una cohorte de ancianos, realizada en la ciudad de Bambuí, Minas Gerais, Brasil. La exposición de interés fue la presencia del síndrome metabólico, definida por el criterio Adult Treatment Panel III, *y los desenlaces incluyeron los siguientes marcadores inflamatorios: citocinas (IL-1β, IL-6, IL-10, IL-12 e TNF), quimiocinas (CXCL8, CXCL9, CCL2, CXCL10 y CCL5) y proteína C-reactiva (PCR). La definición de los puntos de corte de los marcadores inflamatorios se basó en el método* Classification and Regression Tree *(CART). Las asociaciones entre esos marcadores y el síndrome metabólico se estimaron mediante modelos de regresión logística, obteniéndose* odds ratio *e intervalos con 95% de confianza, considerando el ajuste por factores de confusión. La prevalencia del síndrome metabólico fue de 49,1%, y los niveles de IL-1β, IL12 y TNF no se mostraron asociados a esa exposición. Tras el ajuste, la presencia del síndrome metabólico se asoció a mayores valores de IL-6 y PCR y a menores valores de CXCL8 y CCL5. Las asociaciones significativas se observaron incluso con niveles séricos intermedios de CXCL9 y CXCL10. Asimismo, la combinación de los marcadores presentó una asociación significativa y consistente con el síndrome metabólico. Además de demostrar asociación entre el síndrome metabólico y una amplia gama de biomarcadores, algunos todavía no descritos en la literatura, los resultados resaltan que esa asociación ocurre en niveles muy inferiores a los ya demostrados, sugiriendo que el síndrome metabólico desempeña un importante papel en el perfil inflamatorio de los ancianos.*

Síndrome Metabólico; Inflamación; Biomarcadores; Salud del Anciano

Submitted on 01/Jul/2018
Final version resubmitted on 13/Sep/2018
Approved on 27/Sep/2018