Austin Journal of Cardiovascular Disease and Atherosclerosis

Open Access

Austin Publishing Group

Research Article

Metabolic Syndrome, Its Relationship with Disease Activity and Cardiovascular Risk in a Cohort of Patients with Rheumatoid Arthritis

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Received: May 10, 2016; **Accepted:** May 30, 2016; **Published:** June 01, 2016

Abstract

Background: There is a high prevalence of metabolic syndrome in rheumatoid arthritis patients, which also participates in the increase of cardiovascular risk.

Objective: To determine the frequency of metabolic syndrome in a cohort of patients with rheumatoid arthritis and its relationship with disease activity and cardiovascular risk factors.

Methods: We studied 166 patients diagnosed with rheumatoid arthritis according to the ACR/EULAR 2010 criteria. Disease activity was evaluated by means of the DAS-28 CRP work tool, and the presence of metabolic syndrome was established in accordance with the NECP ATP-III criteria.

Results: The 51,8% had metabolic syndrome (53,5% of the women and 22,2% of the men). The main alteracions were abdominal circumference increased (68,1%), hypoalphalipoproteinemia (60,2%) and hypertriglyceridemia (55,4%). It was observed that patients with a greater disease activity were more likely to experience metabolic syndrome. A DAS-28 CRP ≥ 2,3 was associated independently with the development of metabolic syndrome (RR 1,23; IC 1,64-2,35; p 0,028); on the other hand, the use of methotrexate was independently associated with the absence of metabolic syndrome (RR 0,43; IC 0.19-0,96; P 0,04). We found a significant difference between disease activity and systolic blood pressure ≥ 130 mmHg (p 0,018), hypoalphalipoproteinemia (p 0,001) and hypertriglyceridemia (p 0,003).

Conclusion: There is a high frequency of metabolic syndrome in patients with rheumatoid arthritis which can be associated to disease activity; in so much as it may be related to an increased systolic hypertension, hypertriglyceridemia and hypoalphalipoproteinemia.

Keywords: Cardiovascular risk; Metabolic syndrome; Rheumatoid arthritis

Introduction

Metabolic Syndrome (MS) is the term used to refer to a set of cardiovascular risk factors, within its definition includes elevated triglycerides, low levels of High Density Lipoprotein (c-HDL), central obesity, hypertension and insulin resistance [1]. Since its first definition by the World Health Organization in 1999 [2] there were proposed five different diagnostic criteria, using the same variables but with differences in their ranks and their measurement criteria. Being the most used in epidemiological studies the European Group for the Study of Insulin Resistance (EGIR) [3] elaborated in 2001 and modified in the 2005 by the National Cholesterol Education Program Adult Treatment Panel III l (NCEP ATP III) [4]. Rheumatoid Arthritis (RA) is a systemic, inflammatory, autoimmune and chronic disease, characterized by commitment of the synovial with inflammation and hyperplasia, showing destruction of cartilage and bone, as well as affectation mainly extra-articular eye level, cardiovascular and pulmonary [5,6]. Patients with RA have a higher cardiovascular risk than the general population, a risk comparable with that of patients with diabetes mellitus, because chronic inflammation leads to a process of accelerated atherosclerosis [7]. Likewise they have a higher prevalence of hypertension, obesity and MS [8].

Modifying Antirheumatic Drugs Disease (DMARDs) and corticosteroids, in addition to produce disease control and mitigate inflammation, have effects that can decrease or increase the factors of traditional cardiovascular risk such as dyslipidemia, hypertension and resistance insulin and thus favors the development of MS. It has been observed that methotrexate has cardioprotective effects, reducing mortality, decreases the values of c-HDL, triglycerides and the risk of MS [9,10]. Glucocorticoids cause alterations in lipid profile with increased levels of triglycerides and total cholesterol, likewise have been associated with elevation of blood pressure, obesity, hyperglycemia and insulin resistance, which increases the risk of suffer MS [11,12]. Antimalarial drugs have been associated with improved lipid profile, with decreased levels of total cholesterol, Low-Density Lipoprotein (c-LDL) and triglycerides [13]. Leflunomide has been associated with elevation tensional levels and elevated

Citation: Batún JAJ, García OA and Salas M. Metabolic Syndrome, Its Relationship with Disease Activity and Cardiovascular Risk in a Cohort of Patients with Rheumatoid Arthritis. Austin J Cardiovasc Dis Atherosclerosis. 2016; 3(1): 1021.

triglycerides and total cholesterol [10]. Finally it has been observed that azathioprine raises levels of cholesterol LDL, total cholesterol and triglycerides [14]. The aim of this study was to establish the frequency of SM in patients with RA, its relationship with cardiovascular risk factors and disease activity, and its association with the use of DMARDs and glucocorticoids. This is to clarify the relationship of AR, activity and management with the development of SM. We hope to meet one step closer to the establishment of analytical models with which we can determine the best measure cardiovascular risk in this population.

Materials and Methods

A descriptive, transversal and observational study was performed. Patients with RA diagnosis were studied according to the ACR/EULAR criteria 2010 [15] that consecutively came to the outpatient of the service Rheumatology Regional High Specialty Hospital Dr. Gustavo A Rovirosa Pérez, during the period of January- December 2015.The participation in the study was approved by each patient signed an informed consent, with the prior approval of the Bioethics Committee of the Hospital. It was applied a questionnaire to the participants and a review of clinical records was made and recorded as variables the age, gender, tobacco smokings, carriers of hypertension, diabetes mellitus and use of DMARDs (azathioprine, methotrexate, hydroxychloroquine, leflunomide) and glucocorticoids.

For each patient a sample of 10ml of venous blood in the antecubital region was removed in the morning (8:00-9:00 hrs), with a minimum 10-hour fast prior to obtain results of triglycerides, total cholesterol, c-HDL, C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR) and glucose. The levels of c-LDL were obtained indirectly through the Friedewald formula.

The weight of the patients was taken with a scale, previously calibrated, barefoot and in light clothing, expressing the results in kilograms. Height was measured with a standard height board with the patient in standing position, expressing the results in meters. With these results the Body Mass Index (BMI) was calculated using the formula weight / height 2 (Kg/m^2), classifying the results low weight ranges: <18.5 Kg/m^2; normal: 18.5-24.9 Kg/m^2; overweight: 25-29.9 Kg/m^2; Obesity> 30 Kg/m^2.

With the patient in standing position it was measured with a tape measure waist circumference (PA) at umbilical level according to WHO guidelines.

With the patient sitting, after a rest of 20 minutes, blood pressure was taken with a manual mercury sphygmomanometer in the right arm according to the thickness of each patient.

Patients were classified with the presence of SM according to the criteria of the ATP-III 4 requiring the presence of three or more of the following parameters: PA ≥ 88 cm in women and ≥ 102 men, triglycerides ≥ 150 mg / dL, c-HDL ≤ 50 mg / dL in women or ≤ 40 mg / dL in men, fasting glucose ≥ 110 mg / dL, Systolic Blood Pressure (SBP) ≥ 130 mmHg or Diastolic Blood Pressure (DBP) ≥ 85 mmHg or use of a antihypertensive drug.

Factors related to the disease such as the duration of the disease were determined, the disease activity was assessed by DAS-28 CRP classified as remission <2.3, mild ≥ 2.3 to <3.8 activity, moderate activity ≥ 3.8 to <4.9 and serious activity ≥ 4.9. Rheumatoid Factor (RF) positive with values above 15 IU / ml was considered.

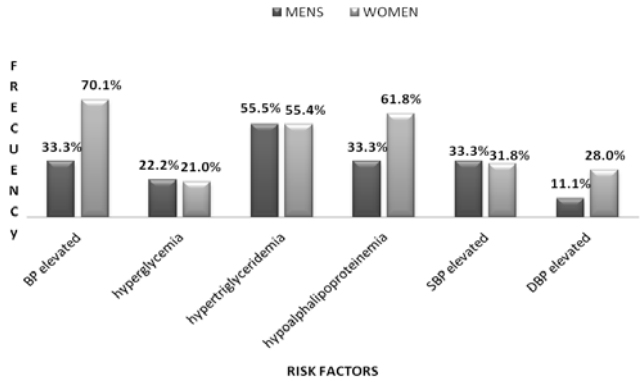

Figure 1: Prevalence of risk factors that constitute the metabolic syndrome according to ATP-III criteria distributed by gender in patients with rheumatoid arthritis.
BP: Blood Pressure,SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure

Statistic analysis

Statistical analysis using the SPSS 22.0 for Windows was made. Considered significant results in a value of P ≤0.05. Compliance of the normal distribution of variables was assessed using the Kolmogorov-Smirnov test.

Categorical variables were presented as frequencies and percentages and were compared with the Chi square test. Continuous variables were presented as median and interquartile range or mean and standard deviation according the normal distribution, and were compared with the nonparametric Mann-Whitney or Student's t-test as the case. Finally, a multivariate logistic regression model was used to determine the association of these variables and the MS.

Results

166 patients with the diagnosis of RA, 51,8% of whom had SM, 5,5% of women and 22.2% of men were evaluated. 68,1% had increased waist circumference, 60,2% hypoalphalipoproteinemia, 55,4% hypertriglyceridemia, 31,9% elevated SBP, 27,1% DBP elevated and 21,1% hyperglycemia.

The mean waist circumference was 94,6 ± 13,3, the one for c-HDL was 47,9 ± 11,1, for the triglycerides 201 ± 140,2, mean SBP was 122,9 ± 15,2 , the DBP 77,7 ± 10,8, the total cholesterol was 201,3 ± 38,8 and c-LDL 116,2 ± 34,5. Frequency components MS by gender is observed in the (Figure 1).

Female gender prevailed with 95,6%. The mean age of the study population was 56,1 ± 11,4 years, mean duration of disease was 7,7 ± 4,6. With respect to the mean BMI was 30,5 kg/m^2, obesity prevailed with 57,2%, followed by 27,7% overweight and 15,1% had normal weight.

With respect to chronic degenerative precedents 33.7% had DM, 21.7% HAS and 8,4% had positive smoking.

According to serology and acute phase reactants 65.7% had positive RF, mean CRP was 3,6 ± 8,9 and 30,6 ± ESR was 14,9.

Table 1: Traditional and non-traditional cardiovascular risk factors in patients with rheumatoid arthritis and metabolic syndrome.

Variable	With MS N (86)	Without MS N (80)	P
Woman (%)	84 (97,7)	73 (91,3)	0,067
Age mean (SD)	56,9 ± 8,7	55,1 ± 13,6	0,297
BMI median (IQR)	31,4 (28,7-34,7)	29,4 (26-32,7)	0,024*
AC median (IQR)	104,3 (89-97)	89 (83,8-99,3)	0,003*
DM (%)	28 (32,6)	28 (35)	0,739
HTA (%)	21 (24,4)	15 (18,8)	0,375
Smoking (%)	3 (3,5)	11 (13,8)	0,017*
FR (%)	52 (60,5)	57 (71,3)	0,143
CRP median (IQR)	1 (0,32-2,5)	0,8 (0,2-2,1)	0,160
ESR (SD)	31,9 ± 14,1	29,1 ± 15,5	0,209
Total Cholesterol Median (IQR)	209,5 (181-229)	187 (170-211,3)	0,004*
c-HDL median (IQR)	49 (39,8-42,4)	47 (42,9-60,4)	< 0,000*
Triglycerides median (IQR)	195 (159-260)	143 (104-195)	< 0,000*
c-LDL median (IQR)	147 (95,7-124,8)	105 (87,7-133,9)	0,019*
Glucosemedian (IQR)	100 (96,3-122,3)	92,5 (84,8-101)	< 0,000
Time evolution median (IQR)	7 (5,3-9)	6,5 (5-10)	0,974
DAS-28 CRP median (IQR)	2,05 (1,72-2,8)	1,7 (1,6-2,4)	0,028*
Diseaseactivity (%)	41 (47,7)	22 (27,5)	0,007*
SBP median (IQR)	130 (115-140)	110 (110-130	< 0,000*
DBP median (IQR)	80 (70-90)	80 (70-80)	0,890

MS: Metabolic Syndrome; SD: Standard Deviation; IQR: Interquartile Range; BMI: Body Mass Index; AC: Abdominal Circumference; DM: diabetes mellitus; HTA: hypertension; FR: rheumatoid factor; CRP: C-reactive protein; ESR: Erythrocyte Sedimentation Rate; c-HDL: High-Density Lipoprotein; c-LDL: Low-Density Lipoprotein; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

(Table 1) summarizes the cardiovascular risk factors present in patients with RA presented by MS or not, determining the association between these and the presence of SM by Chi square test and Mann-Whitney.

According activity index 62% of patients were in remission, 33,2% had mild activity and 4,8% moderate. It was found that 43,6% of patients who were in remission had MS, against 65,1% of the patients with disease activity. In (Figure 2), it can be observed as a

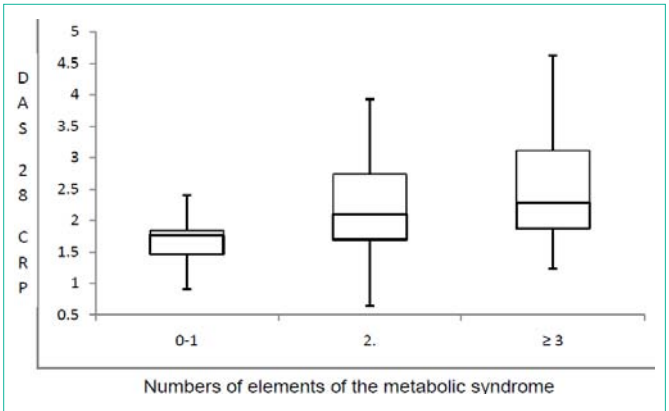

Figure 2: Relation between the number of metabolic syndrome components and index DAS-28 activity by CRP.

Table 2: Relation between treatment used and the development of metabolic syndrome in patients with rheumatoid arthritis.

Drug	Used/ Not used	MS incidence in users	MS incidence in non users	P
HCQ	119/47	46,2%	65,9%	0,021*
Leflunomide	10/156	50%	45,5%	0,906
Sulfasalazine	123/43	52%	51,2%	0,921
MTX	131/35	47,3%	68,6%	0,025*
AZP	82/84	51,2%	52,4%	0,880
GC	95/71	61,1%	38,0%	0,002*

MS: Metabolic Syndrome; HCQ: Hydroxychloroquine; MTX: Methotrexate; AZP: Azathioprine; GC: Glucocorticoids.

Table 3: Multivariate analysis of the studied variables and their association with metabolic syndrome in patients with rheumatoid arthritis.

Multi varíate analysis	RR (IC 95%)	Value of *p*
DAS-28 CRP ≥ 2,3	1,23 (1,64-2,35)	0,028*
Use of MTX	0,43 (0,19-0,96)	0,041*
Use of HCQ	0,36 (0,71-2,61)	0,349
Use of GC	1,01 (0,52-1,91)	0,996

RR: Relative Risk; CRP: C-Reactive Protein; MTX: methotrexate; HCQ: Hydroxychloroquine; GC: Glucocorticoids.

greater number of elements of the SM (PA, triglycerides, c-HDL, SBP, DBP, glucose), the higher the rate of disease activity.

With regard to the use of DMARDs and glucocorticoids and their relationship with the MS, significance was found with the lowest incidence of MS and the use of methotrexate and hydroxychloroquine and higher incidence with the use of glucocorticoids, this is summarized in (Table 2).

A multivariant logistic regression was made using the MS as a dependent variable, and the use of methotrexate, hydroxychloroquine, glucocorticoids, disease activity by DAS-28 CRP, which is summarized in (Table 3). The activity disease was independently associated with the development of MS and the use of methotrexate was independently associated with the absence of MS.

In (Table 4), the association between disease activity and MS components is synthesized according to the NCEP ATP III, finding significance between active disease and triglycerides, c-HDL and the values of blood pressure systolic.

Discussion

In this study we demonstrate the high frequency of MS in patients with RA, even much higher than that reported in other series which oscillate between 17% and 44% [9,10,16-26]. There have been only two studies in our country, which reported an incidence of 17% and 18% [19], this lower frequency with respect to our study may be because in the first despite employing the criteria of NCEP ATP III, the study population had lower BMI, younger age and lower frequency of obesity compared to our population. With respect to the second study also used the criteria for MS NCEP ATP III, however, replaced the abdominal circumference by BMI ≥ 30 kg/m^2, this change may underestimate the frequency of MS, as we observed in our study patients who presented an altered abdominal circumference were more than patients who had a BMI of obesity, just as other studies [17,20,22,25] have shown that although BMI is

Table 4: Association between the activity of the disease by DAS-28 CRP and components of the metabolic syndrome according to NCEP ATP II.

Component MS	Remission of the disease N (103)	Activity of the disease N (63)	*p*
Glucose ≥ 110 mg/dL	18,4%	25,4%	0,286
AC ≥ 88 cm women o ≥ 102 cm mens	67%	69,8%	0,702
SBP ≥ 130 mmHg	25,2%	42,9%	0,018*
DBP ≥ 85 mmHg	17,5%	28,6%	0,092
HDL ≤ 40 mg/dL mens o ≤ 50 mg/dL women	50,5%	76,2%	0,001*
Triglycerides ≥ 150 mg/dL	46,6%	68,8%	0,003*

MS: Metabolic Syndrome; AC: Abdominal Circumference; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HDL: High Density Lipoprotein.

not significant between RA patients and controls, there is a difference between waist circumference, higher in patients with RA. It has been observed that abdominal obesity is a better predictor of cardiovascular risk compared with BMI in patients with RA [27,28]. Similarly, the age of patients in this study was much lower than ours, and there has been a direct association between age and the development of MS. Other causes of this low frequency compared to our study may be the duration of the disease was an average of 5.3 months and a lower average BMI of 25,9 kg/m^2. However, after a follow up to nine years in this population, the authors find a frequency of 34,5% MS, which still much lower than ours. By comparing with other populations, our study still has greater frequency of MS. A study by Bilecik et al. [22] in the Turkish population with RA was found a frequency of 27% MS, these patients were younger, less evidence of inflammation, less abdominal circumference, and much lower concentrations of triglycerides and c-HDL greater than our population. Another study in Turkey Karakoc et al. [25] MS reported a frequency of 42,6%, this population showed lower BMI, age, lower data acute phase reactants, but mostly lower concentrations of triglycerides and c-HDL greater than our population. A study conducted in Vietnamese women with RA [20] reported that 40.9% presented SM, just as previous studies data central obesity, BMI and changes in lipid profile were lower than in our population. Other studies report a frequency of MS in patients with RA of 19% in 16 African population, 36,5% in the Korean population [17], 44% in the Greek population [18], 41.5% in the Swedish population [22] and 19,9% in the Dutch population [24]. In all these studies the same diagnostic criteria for MS was used, so that differences in these results with ours are due to age, gender, race, genetics, disease activity, but especially to differences in waist circumference and lipid profile. It is well known that the Mexican population occupies the first places with respect to obesity and to hypertriglyceridemia and Hypoalphalipoproteinemia [29], which are important components of MS and explain because our population showed a high frequency of it. Our evidence reports that MS is more common in women than in men with RA, being the main difference in waist circumference and concentrations of c-HDL, although the literature reports that the prevalence of MS in men and women with RA is similar [9]. However, our results cannot be generalized because of the low percentage of men included in our study. Different studies have shown that MS components are more frequent in RA patients than in controls groups, however only it found significance in what respects the figures of blood pressure and in some concentrations of c-HDL [17,18,20,21,25].

Our evidence reported that patients with RA and MS had significantly higher concentrations of triglycerides, lower c-HDL, increased waist circumference and higher systolic blood pressure. This major alteration in abdominal fat, and lipid profile, unlike other studies in patients with RA, may be due to the characteristics of the Mexican population bringing about obesity, hypertriglyceridemia and Hypoalphalipoproteinemia [29]. With respect to disease activity was found that the score of disease activity obtained by DAS-28 CRP was associated with the presence of MS, also patients with disease activity compared to patients in remission had higher SM frequency, and this is similar to that reported in other series [19,20,25].This may be partly due to that inflammation is associated directly with an increase factor of traditional cardiovascular risk such as dyslipidemia, hypertension and insulin resistance [30], as has been observed to control inflammation antagonist Tumor Necrosis Factor (TNF) in patients with RA, insulin resistance is decreased and endothelial dysfunction is improved [31]. Furthermore, as there is increased activity, patients have greater limitation of joint movement secondary to pain, which increases physical inactivity and thus cardiovascular risk. Patients with higher disease activity require higher doses of drugs such as glucocorticoids, which have been associated with higher risk of MS. Another cause of this association between disease activity and MS may be because obesity is associated with an increased release of adipokines by adipose tissue among which are leptin and vistatina, which are also high in RA patients, and are associated with increased proinflammatory cytokines such as interleukin-1, interleukin-6, and TNF [32]. We compared the association between disease activity and MS components, finding significance with elevated systolic blood pressure, low levels of c-HDL and elevated triglycerides. These findings coincide with those of Karvounaris et al. [18] who found that disease activity was associated with a decrease in c-HDL and increased systolic blood pressure. This is because the proinflammatory state leads to a decrease in total cholesterol and c-LDL, but also produces a greater decrease in c-HDL values increasing the atherogenic index [33].

In a study by Karakoc et al. [25], found an association between disease activity and increased systolic and diastolic blood pressure. Our study is the first to establish an association between disease activity and increased triglycerides, so the high values of DAS-28 CRP can be associated with increased cardiovascular risk in producing elevation of blood pressure systolic, the concentration of triglycerides and a decrease in c-HDL values. With regard to the use of DMARDs and glucocorticoids with the development of MS, we found that the increased use of hydroxychloroquine and methotrexate were associated with lower frequency of MS, and corticosteroid use was associated with a higher frequency. However, when performing a logistic regression analysis only our results support only the fact that methotrexate has a protective factor for the development of MS. In the literature there are controversial results about the association between the use of methotrexate and development of MS, on the one side it referred to the protector factor as in the study by Toms et al. [9] and performed by Zonana et al [10], in both this DMARDs was associated with lower risk of MS, but other studies report that there is no such protective factor [18,34]. It is well known the effect in reducing cardiovascular risk that has methotrexate, to be associated with a better lipid profile with lower triglyceride levels and higher c-HDL, also has been associated with decreased insulin resistance and

lower glucose concentrations [9,10]. The limitations are that being a cross-sectional study cannot make any cause-effect association; another is the small number of male employed population. Among the advantages is the number of patients which is higher than that reported in other series, plus a detailed description of treatment used is made and none of our patients were using anti-TNF thereby may decrease the actual frequency of MS to be a drug that is associated with lower insulin resistance.

Conclusion

The frequency of MS in patients with RA is high, being associated in the Mexican population particularly to the high levels of triglycerides, and low levels of c-HDL and the values of waist circumference. There is a significant relationship between disease activity and the development of metabolic syndrome, which is important adequate control of the disease to reduce cardiovascular risk, giving priority to the use of methotrexate as much as possible, since it is a protective factor for the development of MS.

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Austin J Cardiovasc Dis Atherosclerosis - Volume 3 Issue 1 - 2016
ISSN: 2472-3568 | www.austinpublishinggroup.com

Citation: Batún JAJ, García OA and Salas M. Metabolic Syndrome, Its Relationship with Disease Activity and Cardiovascular Risk in a Cohort of Patients with Rheumatoid Arthritis. Austin J Cardiovasc Dis Atherosclerosis. 2016; 3(1): 1021.