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Metabolic syndrome in patients with autoimmune inflammatory rheumatisms.

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Abstract

Background: Systemic inflammation has been associated with obesity, with elevated levels of triglycerides and reduced levels of HDL-cholesterol.
Aim: To determine the frequency of metabolic syndrome (MetS) in patients suffering of rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) and to compare the evolution of MetS parameters during DMARD (Disease-Modifying Anti-rheumatic Drugs) therapy *versus* combination of DMARDs and biologics.
Methods: The study was conducted on 277 RA patients, 115 AS patients and 103 PsA patients. Patients with inflammatory rheumatisms and MetS were randomized into two groups per disease (RA, AS and PsA). Group 1 underwent DMARD therapy. Group 2 followed a combination of DMARDs and biologics. Patients were assessed for the inflammatory status (C-reactive protein) and MetS (triglycerides, HDL cholesterol and blood pressure) initially, after 1 y and after 2 y.
Results: 88 RA patients (31.7%), 16 AS patients (14%) and 35 PsA patients (34%) met the criteria for MetS. RA, AS and PsA patients with MetS who followed a combination of DMARDs and biologic therapy had significant improvement of triglycerides and HDL-cholesterol compared to patients who followed only DMARDs both at 1-y and 2-y assessments. There were no differences of the blood pressure in the two groups.
Conclusion: The frequency of MetS was higher in RA and AS patients than in PsA patients. Biologic therapy could influence the evolution of MetS in patients suffering of autoimmune inflammatory rheumatisms.

Keywords: Metabolic syndrome, Rheumatoid arthritis, Ankylosing spondylitis, Psoriatic arthritis, Biologic therapy.

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Introduction

Metabolic syndrome (MetS) is a common clinical condition characterized by the clustering of cardiovascular risk factors related to insulin resistance, including central obesity, impaired glucose tolerance, hypertension and dyslipidaemia [1,2]. MetS and its components have been consistently associated with the presence of "low-grade" systemic inflammation [3,4]. Various studies have shown that the pathogenesis of MetS involves an inflammatory process. Pro-inflammatory cytokines, such as tumour necrosis factor alpha (TNF-alpha), reduce the activity of insulin, promoting thus insulin resistance [5]. Inflammation has also been associated with obesity, with elevated levels of triglycerides and reduced levels of High-Density Lipoprotein (HDL) cholesterol [6].

Patients with rheumatoid arthritis (RA) are at increased risk for cardiovascular disease independently of traditional vascular risk factors [7,8]. Cohort studies have demonstrated increased prevalence of metabolic syndrome in patients with RA, correlating with disease activity and markers of atherosclerosis [9-11]. Observational studies suggest that anti-TNF therapy improves disease activity and may reduce cardiovascular events in RA patients [12,13]. This effect is thought to be mediated by reduction in insulin resistance and metabolic syndrome components demonstrated in patients treated with TNF blockade [14-18].

Duration and severity of ankylosing spondylitis (AS) and its typical cardiovascular (CV) complications such as aortic insufficiency, conduction disturbances, mitral valve disease, cardiomyopathy, and pericarditis have been implicated as risk factors in AS patients [19,20]. In the last years, a clear relationship between CV risk factors, obesity, and insulin-resistance allowed to propose the existence of MetS that was shown to promote an increase of CV mortality risk [21]. Moreover, some studies have pointed out a relationship among some CV risk factors or MetS and inflammation [22,23].

Patients with psoriasis (Ps) have an increased prevalence of obesity and MetS compared to that of matched healthy controls. It seems that Ps precedes the obesity and other

features of MetS in these patients. Although the underlying mechanisms for increased MetS in Ps patients are not well established, a link between inflammation and MetS seems likely [24].

The objectives of our study are to determine the frequency of Mets in patients suffering of inflammatory autoimmune rheumatisms (RA, AS and psoriatic arthritis-PsA) and to compare the evolution of MetS parameters during the DMARD (Diseases-Modifying Anti-rheumatic Drug) therapy *versus* during the combination of DMARDs and biologics.

Materials and Methods

The study was approved by the Ethics Committee of Timisoara University of Medicine and Pharmacy, Romania. Written informed consent was obtained from all the participants.

The study was conducted on 277 RA patients, 115 AS patients and 103 PsA patients. The patients were investigated for the metabolic syndrome (MetS) defined according to the National Cholesterol Education Program [25]. For each rheumatic disease, patients who also had MetS were randomized into two groups. Group 1 underwent DMARD therapy, while group 2 followed a combination of DMARDs and biologic therapy (TNF inhibitors). In addition, some of group 2 patients with RA followed an anti-CD20 biologic therapy.

Data regarding MetS (triglycerides, HDL cholesterol and blood pressure) and inflammatory status (CRP: C-reactive protein) were recorded. The general health was evaluated by the Health Assessment Questionnaire (HAQ). For RA patients DAS28-CRP (Disease Activity Score in 28 Joints) was also calculated. These assessments were performed initially, after 1 y and after 2 y.

Statistical analysis of the obtained results was performed. Data were analysed using SPSS version 16 and STATA 10. Descriptive statistics were calculated (mean and standard deviation). Levene's test was applied to test the homogeneity of variances between groups. Comparisons between the two groups were done by Student's unpaired t-test. A p-value less than 0.05 were considered statistically significant.

Results

The demographic and clinical characteristics of the patients enrolled in the study are included in Table 1. The group patients were homogenous in terms of anthropometrical characteristics (Levene's test-p>0.05).

88 RA patients (31.7%) also had the criteria for MetS, 70 women (79.5%) and 18 men (20.5%). 40 RA patients followed a DMARD therapy, while 48 RA patients followed a combination of DMARD and biologic therapy. The results regarding the MetS items (triglycerides, HDL-C, systolic and diastolic blood pressure), inflammatory parameters (CRP) and disease activity (DAS28-CRP) are presented in detail in Table 2.

Table 1. *Demographic and clinical characteristics of the patients enrolled in the study.*

	RA		AS		PsA	
	n_1 (40)	n_2 (48)	n_1 (8)	n_2 (8)	n_1 (16)	n_2 (19)
Age (y)	51.4 ± 11.3	49.1 ± 12.5	43.4 ± 15.6	44.9 ± 12.3	50.6 ± 15.7	52.1 ± 17.1
BMI (kg/m^2)	27.7 ± 8.8	29.1 ± 10.9	30.3 ± 8.5	29.9 ± 6.9	28.7 ± 8.2	27.6 ± 9.1
Gender						
Male	9 (22.5%)	11 (23%)	6 (75%)	6 (75%)	4 (25%)	5 (26%)
Female	31 (77.5%)	37 (77%)	2 (25%)	2 (25%)	12 (75%)	14 (74%)
Disease duration (y)	10.5 ± 2.2	9.4 ± 2.6	8.3 ± 1.9	8.5 ± 0.7	10.7 ± 1.1	9.1 ± 1.8

n_1: Group 1; n_2: Group 2; BMI: Body Mass Index.

16 AS patients (14%) also had the criteria for MetS, 11 women (69%) and 5 men (31%). 8 AS patients followed a DMARD therapy, while 8 AS patients followed a combination of DMARD and biologic therapy. The results regarding the MetS items (triglycerides, HDL-C, systolic and diastolic blood pressure), inflammatory parameters (CRP) and health status (HAQ) are presented in detail in Table 3.

35 PsA patients (34%) had also the criteria for MetS, 25 women (71%) and 10 men (29%). 16 PsA patients followed a DMARD therapy, while 19 PsA patients followed a combination of DMARD and biologic therapy. The results regarding the MetS items (triglycerides, HDL-C, systolic and diastolic blood pressure), inflammatory parameters (CRP) and health status (HAQ) are presented in Table 4.

Table 2. *MetS items, inflammatory parameters and disease activity in RA patients.*

	Initially	1 y	2 y
	Group 1 (n_1) Group 2 (n_2)	Group 1 (n_1) Group 2 (n_2)	Group 1 (n_1) Group 2 (n_2)
Triglycerides (mg/dl)	217.78 ± 112.7 225.45 ± 100.1	154.66 ± 52.5 133.5 ± 33.79	138.93 ± 45.11 108.13 ± 25.73

	p>0.05	p<0.01	p<0.001
HDL-C men (mg/dl)	34.56 ± 8.13 32.66 ± 3.31	39.45 ± 3.33 44.44 ± 5.48	45.9 ± 6.12 50.22 ± 5.09
	p>0.05	p<0.05	p<0.01
HDL-C women (mg/dl)	43.05 ± 4.23 41.91 ± 5.02	48.34 ± 4.12 52.94 ± 4.76	53.93 ± 6.21 57.77 ± 5.54
	p>0.05	p<0.05	p<0.05
Systolic blood pressure (mmHg)	151.44 ± 31.2 153.5 ± 24	150 ± 21.5 151 ± 19.5	142.3 ± 22 140.5 ± 21.5
	p>0.05	p>0.05	p>0.05
Diastolic blood pressure (mmHg)	85.5 ± 11.3 87.3 ± 9.5	82 ± 12.5 81.5 ± 9.3	78.3 ± 5.5 79.5 ± 8.3
	p>0.05	p>0.05	p>0.05
CRP (mg/dl)	3.42 ± 0.67 3.66 ± 1.07	1.33 ± 0.23 0.91 ± 0.59	0.82 ± 0.38 0.47 ± 0.29
	p>0.05	p<0.001	p<0.01
DAS28-CRP	6.82 ± 1.02 7.06 ± 0.74	3.27 ± 0.41 2.87 ± 0.53	2.71 ± 0.33 2.35 ± 0.36
	p>0.05	p<0.05	p<0.05

n_1=40 patients; n_2=48 patients; DAS28: Disease Activity Score in 28 joints.

Table 3. *MetS items, inflammatory parameters and health status in AS patients.*

	Initially	**1 y**	**2 y**
	Group 1 (n_1) **Group 2 (n_2)**	**Group 1 (n_1)** **Group 2 (n_2)**	**Group 1 (n_1)** **Group 2 (n_2)**
Triglycerides (mg/dl)	219.2 ± 103.6 224.6 ± 101.7	157.2 ± 55.8 138.1 ± 34.8	139.1 ± 48.7 112.13 ± 26.1
	p>0.05	p<0.01	p<0.01
HDL-C men (mg/dl)	33.51 ± 8.13 34.66 ± 4.21	39.44 ± 3.22 44.33 ± 5.48	47.9 ± 6.18 51.22 ± 6.11
	p>0.05	p<0.05	p<0.05
HDL-C women (mg/dl)	44.15 ± 4.93 42.91 ± 6.02	47.34 ± 4.02 53.01 ± 4.01	54.23 ± 6.6 58.22 ± 5.03
	p>0.05	p<0.05	p<0.01
Systolic blood pressure (mmHg)	152.5 ± 30.5 154.5 ± 21	150 ± 21.5 151 ± 19.5	142.3 ± 22 140.5 ± 21.5
	p>0.05	p>0.05	p>0.05
Diastolic blood pressure (mmHg)	86.5 ± 12.3 88.3 ± 10.5	82 ± 12.3 81.5 ± 9.5	78.3 ± 6 79 ± 9
	p>0.05	p>0.05	p>0.05
CRP (mg/dl)	2.42 ± 0.8 2.46 ± 1.27	1.62 ± 0.43 1.1 ± 0.29	0.78 ± 0.28 0.45 ± 0.21
	p>0.05	p<0.01	p<0.01
HAQ	1.22 ± 0.52 1.24 ± 0.61	0.97 ± 0.22 0.96 ± 0.38	0.43 ± 0.06 0.31 ± 0.11
	p>0.05	p<0.05	p<0.001

n_1=8 patients; n_2=8 patients; HAQ: Health Assessment Questionnaire.

Table 4. *MetS items, inflammatory parameters and health status in PsA patients.*

	Initially	**1 y**	**2 y**
	Group 1 (n_1) **Group 2 (n_2)**	**Group 1 (n_1)** **Group 2 (n_2)**	**Group 1 (n_1)** **Group 2 (n_2)**
Triglycerides (mg/dl)	222.77 ± 112.8 224.43 ± 101.9	159.66 ± 51.5 138.5 ± 34.02	137.93 ± 45.04 107.13 ± 25.13
	p>0.05	p<0.01	p<0.001
HDL-C men (mg/dl)	35.26 ± 9.13 32.77 ± 6.39	38.45 ± 2.33 41.44 ± 6.48	44.9 ± 7.12 50.08 ± 5.29
	p>0.05	p<0.05	p<0.01
HDL-C women (mg/dl)	42.25 ± 4.13 42.91 ± 5.02	47.34 ± 6.12 51.94 ± 4.76	53.93 ± 6.21 56.99 ± 5.54
	p>0.05	p<0.05	p<0.01
Systolic blood pressure (mmHg)	152.5 ± 31.5 154.5 ± 24	149.5 ± 21.3 150.5 ± 19	144.5 ± 22 142.5 ± 22.5
	p>0.05	p>0.05	p>0.05
Diastolic blood pressure (mmHg)	86.5 ± 13.3 86.3 ± 10	82.5 ± 12 82.5 ± 9.3	79.3 ± 5 79.5 ± 8.3
	p>0.05	p>0.05	p>0.05
CRP (mg/dl)	3.44 ± 1.1 3.56 ± 1.17	1.2 ± 0.41 1.01 ± 0.7	0.52 ± 0.22 0.41 ± 0.33
	p>0.05	p<0.01	p<0.01
HAQ	1.32 ± 0.82 1.34 ± 0.91	1.07 ± 0.92 0.95 ± 0.66	0.41 ± 0.09 0.41 ± 0.61
	p>0.05	p<0.05	p<0.01

n_1=16 patients; n_2=19 patients; HAQ: Health Assessment Questionnaire.

Discussion

The study of Medina et al. reviewed the recent evidences of the interaction between MetS and autoimmune rheumatic diseases [26].

Our study showed that RA, AS and PsA patients with MetS who followed a combination of DMARDs and biologic therapy presented a significant improvement of triglycerides and HDL-cholesterol in comparison to patients who followed only DMARD therapy both at 1-y and 2-y assessments. There were no differences of the blood pressure in the 2 groups.

The frequency of MetS was higher in RA and AS patients than in PsA patients. Biologic therapy could influence the evolution

of MetS in patients suffering of autoimmune inflammatory rheumatisms.

Conflict of Interest

None.

References

1. Adams KF, Schatzkin A, Harris TB, Kipnis V, Mouw T, Ballard-Barbash R. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. New Engl J Med 2006; 355: 763-778.
2. Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1998; 37: 1595-1607.
3. Strandberg T, Tilvis RS. C-reactive protein, cardiovascular risk factors, and mortality in a prospective study in the elderly. Arterioscler Thromb Vasc Biol 2000; 20: 1057-1060.
4. Grundy SM, Brewer Jr. HB, Cleeman JI, Smith Jr. SC, Lenfant C. Definition of metabolic syndrome: report of the national heart, lung, and blood institute/American heart association conference on scientific issues related to definition. Circulation 2004; 109: 433-438.
5. Nilsson J, Jovinge S, Niemann A, Reneland R, Lithell H. Relation between plasma tumor necrosis factor-alpha and insulin sensitivity in elderly men with non-insulin-dependent diabetes mellitus. Arterioscler Thromb Vasc Biol 1998; 18: 1199-1202.
6. Piché ME, Lemieux S, Weisnagel SJ, Corneau L, Nadeau A, Bergeron J. Relation of high-sensitivity C-reactive protein, interleukin-6, tumor necrosis factor-alpha, and fibrinogen to abdominal adipose tissue, blood pressure, and cholesterol and triglyceride levels in healthy postmenopausal women. Am J Cardiol 2005; 96: 92-97.
7. del Rincon ID, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. Arthritis Rheum 2001; 44: 2737-2745.
8. Karvounaris SA, Sidiropoulos PI, Papadakis JA, Spanakis EK, Bertsias GK, Kritikos HD. Metabolic syndrome is common among middle-to-older aged Mediterranean patients with rheumatoid arthritis and correlates with disease activity: a retrospective, cross-sectional, controlled, study. Ann Rheum Dis 2007; 66: 28-33.
9. Chung CP, Oeser A, Solus JF, Avalos I, Gebretsadik T, Shintani A. Prevalence of the metabolic syndrome is increased in rheumatoid arthritis and is associated with coronary atherosclerosis. Atherosclerosis 2008; 196: 756-763.
10. Boers M, Dijkmans B, Gabriel S, Maradit-Kremers H, O'Dell J, Pincus T. Making an impact on mortality in rheumatoid arthritis: targeting cardiovascular comorbidity. Arthritis Rheum 2004; 50: 1734-1739.
11. Dessein PH, Joffe BI. Insulin resistance and impaired beta cell function in rheumatoid arthritis. Arthritis Rheum 2006; 54: 2765-2775.
12. Jacobsson LT, Turesson C, Gulfe A, Kapetanovic MC, Petersson IF, Saxne T, Geborek P. Treatment with tumor necrosis factor blockers is associated with a lower incidence of first cardiovascular events in patients with rheumatoid arthritis. J Rheumatol 2005; 32: 1213-1218.
13. Dixon WG, Watson KD, Lunt M, Hyrich KL, Silman AJ, Symmons DP. Reduction in the incidence of myocardial infarction in patients with rheumatoid arthritis who respond to anti-tumor necrosis factor alpha therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 2007; 56: 2905-2912.
14. Gonzalez-Gay MA, De Matias JM, Gonzalez-Juanatey C, Garcia-Porrua C, Sanchez-Andrade A, Martin J, Llorca J. Anti-tumor necrosis factor-alpha blockade improves insulin resistance in patients with rheumatoid arthritis. Clin Exp Rheumatol 2006; 24: 83-86.
15. Gonzalez-Gay MA, Gonzalez-Juanatey C, Vazquez-Rodriguez TR, Miranda-Filloy JA, Llorca J. Insulin resistance in rheumatoid arthritis: the impact of the anti-TNF-alpha therapy. Ann N Y Acad Sci 2010; 1193: 153-159.
16. Kiortsis DN, Mavridis AK, Vasakos S, Nikas SN, Drosos AA. Effects of infliximab treatment on insulin resistance in patients with rheumatoid arthritis and ankylosing spondylitis. Ann Rheum Dis 2005; 64: 765-766.
17. Seriolo B, Paolino S, Ferrone C, Cutolo M. Impact of long-term anti-TNF-alpha treatment on insulin resistance in patients with rheumatoid arthritis. Clin Exp Rheumatol 2008; 26: 159-160.
18. Tam LS, Tomlinson B, Chu TT, Li TK, Li EK. Impact of TNF inhibition on insulin resistance and lipids levels in patients with rheumatoid arthritis. Clin Rheumatol 2007; 26: 1495-1498.
19. O'Neill TW, Bresnihan B. The heart in ankylosing spondylitis. Ann Rheum Dis 1992; 51: 705-706.
20. O'Neill TW, King G, Graham IM, Molony J, Bresnihan B. Echocardiographic abnormalities in ankylosing spondylitis. Ann Rheum Dis 1992; 51: 652-654.
21. Kahn R, Buse J, Ferrannini E, Stern M. The metabolic syndrome: time for a critical appraisal. Diabetes Care 2005; 28: 2289-2304.
22. Rutter MK, Meigs JB, Sullivan LM, D'Agostino RB Sr, Wilson PW. C-reactive protein, the metabolic syndrome and prediction of cardiovascular events in the Framingham Offspring's Study. Circulation 2005; 110: 380-385.
23. Ridker MK, Wilson PW, Grundy SM. Should C-reactive protein be added to metabolic syndrome and to assessment of global cardiovascular risk? Circulation. 2004; 109: 2818-2825.
24. Mallbris L, Ritchlin C, Stahle M. Metabolic disorders in patients with psoriasis and psoriatic arthritis. Curr Rheum Reports 2006; 8: 355-363.

25. Grundy SM, Cleeman JI, Merz CNB, Brewer HB. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation 2004; 110: 227-239.
26. Medina G, Vera-Lastra O, Peralta-Amaro AL, Jiménez-Arellano MP, Saavedra MA, Cruz-Domínguez MP, Jara LJ. Metabolic syndrome, autoimmunity and rheumatic diseases. Pharmacol Res 2018.

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