Inflammatory Markers and Antichlamydial Antibodies in Patients with Metabolic Syndrome

Rosecler Riethmuller Franco[1], Luiz Carlos Bodanese[1], Giuseppe Repetto[1], Jacqueline da Costa Escobar Piccoli[2], Mario Wiehe[1], Cassiane Bonato[1], Marta Maria Medeiros Frescura Duarte[3], Thiago Duarte[2]

Pontifícia Universidade Católica do Rio Grande do Sul[1], Porto Alegre, RS; Universidade Federal Santa Maria[2], Universidade Luterana do Brasil[3], Santa Maria, RS - Brazil

Abstract

Background: The metabolic syndrome is associated with increased risk of cardiovascular events. Inflammatory markers and antichlamydial antibodies have been linked to the development and progression of atherosclerosis and cardiovascular events.

Objective: To evaluate the inflammatory markers interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), as well as anti-*chlamydia pneumoniae* antibodies, in patients with metabolic syndrome (MS), with and without cardiovascular events.

Methods: Cross sectional study consisting of 147 individuals. Out of these, 100 (68%) with MS and without cardiovascular events; and 47 (32%) with MS and with cardiovascular events. Among the individuals who had had cardiovascular events, 13 (6.11%) had acute myocardial infarction (AMI) and ten (4.7%) had cerebrovascular accident (CVA). The diagnosis of MS was determined by the criteria of NCEP-ATPIII.

Results: The mean age of subjects with cardiovascular events was 61.26 ± 8.5 and 59.32 ± 9.9 in subjects without such events (p = 0.279), with a predominance of females. The weight, height, BMI and waist circumference of the group with MS and without event was greater. Among individuals with cardiovascular events (p = 0.001), the inflammatory markers IL-6 and TNF-α and the peripheral vascular disease were significantly greater. There were high levels of IgG antibodies to *C. pneumoniae* in the SM group, without events, and of IgA antibodies in the group with events, when the two groups were compared. With respect to AMI and stroke, the anti-*chlamydia pneumoniae* antibodies showed no statistical significance, compared to the group without cardiovascular events. An association was observed with the use of statins, nonsteroidal anti-inflammatory drugs and injectable, oral hypoglycemic agents, in the group with these events.

Conclusion: The inflammatory markers were significantly elevated in patients with MS, with acute myocardial infarction and stroke. There was no significant difference in anti-chlamydial antibodies in patients with MS, with and without events. (Arq Bras Cardiol 2011; 96(2): 134-139)

Keywords: Biological markers; antibodies; *Chlamydia*; *Chlamydia* infectious; metabolic syndrome.

Introduction

Cardiovascular diseases are the leading causes of death among adults worldwide, particularly in developing countries[1]. Metabolic syndrome (MS) - characterized by central obesity, dyslipidemia, hyperglycemia and hypertension - is considered a worldwide epidemic, which is on the rise in different populations and which results in cardiovascular events and type-2 diabetes[2].

The prevalence of MS increases with age, especially over age of 60, regardless of gender. In the United States, this rate is similar among men and white women in the proportion of 25% after 20 years of age and it may reach 43% in individuals that are over 60 years of age[3]. In Brazil, these rates reach 30% and they may increase to 48% for those over 55 years of age[4].

The presence of MS is significantly associated with the growth of cardiovascular mortality, irrespective of changes in glucose tolerance. However, insulin resistance (IR) is related to endothelial dysfunction, constituting a link between MS and inflammation[5]. Due to this process, there is an increase in the circulation of inflammatory markers, and this leads to a state of subclinical chronic inflammation, followed by increased levels of C-reactive protein[5].

Endothelial dysfunction is the initiating event of many diseases of inflammatory or immune nature, and atherosclerosis results from the build-up of lipids, inflammatory cells and fibrous elements, which are responsible for the formation of fatty streaks or plaques that can cause the rupture of such plaques[6].

Infectious agents, such as *C. pneumoniae*, have been seen as contributors to the pathogenesis in the formation of atherosclerotic plaque[7,8]. Studies have shown that this

Mailing address: Rosecler Riethmuller Franco •
Rua Sete de Setembro, 243 Apto. 301 - Centro - 98700-000 - Ijui, RS - Brazil
E-mail: rosecler.franco@unijui.edu.br
Manuscript received February 23, 2010; revised manuscript received April 16, 2010; accepted June 16, 2010.

microbial pathogen spreads systematically from the lungs through the peripheral blood mononuclear cells. The *C. pneumoniae* is located in the arteries - in which it would infect endothelial cells, smooth muscle cells, monocytes and macrophages - and it may promote the atherogenic inflammatory process[7].

Since the full involvement of this pathogen with heart diseases is not known, studies try to elucidate if the formation of the lesion is due to the severity of the infectious process or, in case there is a plaque, if this agent would favor its development[9].

The aim of this study is to evaluate the serum levels of inflammatory biomarkers, interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), and of anti-*Chlamydia pneumoniae* antibodies in patients with metabolic syndrome, with and without cardiovascular events.

Methods

The cross-sectional study involved patients with metabolic syndrome who were divided into two groups - with and without cardiovascular events. The study population consisted of individuals who regularly received care at and who belonged to the database of the cardiometabolic outpatient clinic of Sao Lucas Hospital's cardiology department, PUC-RS (Pontifical Catholic University, State of Rio Grande do Sul). The participants were selected according to the criteria of NCEP/ATP III for MS, regardless of gender or race, and with informed consent signed by the patient or close relative. Subjects that agreed to participate in the survey answered to questions in an interview structured by socio-demographic, clinical and family history evaluations. The study excluded subjects with the following characteristics: the ones that were below 18 years of age, pregnant women, morbidly obese subjects (BMI ≥ 40 kg/m^2) and all those who were being treated for thyroid disease, chronic inflammatory disease, rheumatic disease, liver disease and neoplastic disease. The study also excluded patients that did not agree to sign the TCLE (*Termo de Consentimento Livre e Esclarecido* = Free and Informed Consent).

Blood samples from patients who agreed to participate in the study were collected after a 12-hour fasting period. These samples were immediately centrifuged to obtain serum and plasma - which were stored in a freezer at -80º C for the subsequent preparation of laboratory dosages. Biochemical analyses to evaluate the lipid profile, IgG and IgA anti-*chlamydia pneumoniae* antibodies and hypersensitive C-reactive protein (hs-CRP) were conducted in the Immunology Laboratory, Sao Lucas Hospital of PUC-RS. *Laboratório de Análises Clínicas Labimed* (Laboratory of Clinical Analyses in the city of Santa Maria, State of Rio Grande do Sul) carried out laboratory tests of inflammatory markers IL-6 and TNF-alpha. The concentration of IL-6 and TNF-alpha was determined by enzyme immunoassay (ELISA), with the use of eBioscience kits of immunological reagents designed for humans - Human IL-6 (Interleukin-6) ELISA - www.ebioscience.com.br. The sensitivity and the established standard curve for IL-6 were, respectively, 2 pg/ml and 2-200 pg/ml, whereas for TNF-alpha, the sensitivity was 4 pg/ml and the standard curve was of 4-500 pg/ml. The hs-CRP was quantitatively determined by using the VITROS Chemistry Products hsCRP reagent with analytical sensitivity of 0.02. Human IgG/IgA *C. pneumoniae* antibodies were detected by enzyme linked immunosorbent assay (ELISA), whose results were obtained by absorbance of the samples, evaluated by spectrophotometry with wavelength of 405 nm. To assess the results, we used a standard curve and table of values, with which the activity of antibodies present could be attributed to each OD value existing in the test preparation. The evaluation table showed the theoretical value of the standard serum, as well as its range of validity. Furthermore, the mean OD value of the standard serum should be within the range of validity stated on the quality control certificate that was specific for the batch, after deducting the substrate blank value.

The body mass index (BMI) was calculated by using the Quetelet index, by dividing the weight (kg) by the height squared (m^2). The following values were considered normal: between 18.5 and 24.9 with low risk of comorbidities; from 25 to 29.9, overweight; 30.0 to 34.9, class I obesity, with moderate risk of comorbidities; 35.0 to 39.9, class II obesity, with a high risk of comorbidities; and greater than or equal to 40 kg/m^2, class III obesity, with very high risk of comorbidities. The abdominal circumference (AC) was measured with the aid of tape measure (cm), in the upright position, at half of the distance between the iliac crest and lower costal margin, with abdomen relaxed.

The data obtained were analyzed by using the SPSS (Statistical Package for Social Sciences) program for *Windows*, version 12.0. The Student's t-test was used to compare the means of the variables between the subjects with MS with and without cardiovascular events. The Mann Whitney test was carried out to compare asymmetric data from independent samples. The association between the categorical variables was calculated by the chi-square (χ^2) test or Fisher's exact test. To verify the independence of variables, a logistic regression analysis by the Backward Conditional method was conducted. The odds ratios (OR) were calculated with confidence interval of 95% (IC95%) to estimate the degree of association between categories of drugs used and events. The associations of variables were shown in tables. All tests were considered statistically significant when $p < 0.05$.

The project was submitted to the Research Ethics Committee of PUC-RS (Pontifical Catholic University of Rio Grande do Sul State), Protocol number 09/04724. Study participants signed a TCLE (Free and Informed Consent) in accordance with Resolution 196/96 of the National Board of Health, which establishes the regulations involving research with humans.

Results

The overall study sample consisted of 147 individuals, 100 of whom (68%) with MS and without cardiovascular events, and 47 (32%) with MS and cardiovascular events, in which 13 (6.11%) had AMI, and ten (4.7%) had stroke. Out of the total participants, 108 (72.8%) were female and 39 (26.5%) were male. The average age of subjects with events was 61.26 ± 8.5 and 59.32 ± 9.92 for individuals without cardiac events, with no statistical difference between the groups ($p = 0.279$).

The means of variables, such as dyslipidemia, glucose intolerance and smoking, were higher in the MS group with

events, than in the MS group without events, with no statistical significance. Peripheral vascular disease was the only variable that showed statistical difference between the groups. The other characteristics are expressed in Table 1.

After adjustments, the logistic regression analysis was conducted to obtain the ORs for the different drug classes in conjunction with MS groups with events and SM groups with no cardiac events. Positive association was observed with the use of statins, injectable and oral hypoglycemic agents and nonsteroidal anti-inflammatory drugs in the group with events (Table 2), demonstrating that these patients of the MS group with events are treated in a more effective way, since they are at a higher risk.

Subsequently, inflammatory markers and anti-*Chlamydia pneumoniae* antibodies were compared to groups of individuals that had MS with and without previous cardiac events. According to Table 3, the levels of markers IL-6 and TNF-alpha were significantly higher in individuals with cardiac events ($p = 0.001$). With respect to the presence of IgG antibodies to *C. pneumoniae*, there were higher levels of positive results in the control group (63%), while IgA was present in the group with cardiovascular events (13%). The serum levels for hs-CRP were similar between groups and no statistical difference was found.

As it was important to compare the groups that had MS, with and without cardiac events, an analysis was conducted between inflammatory markers and positive results for IgG and IgA anti-*Chlamydia pneumoniae* antibodies, and between two cardiovascular events - stroke and AMI -, comparing with individuals with MS without cardiovascular events (Table 4). A total of 13 subjects make up the group of patients with MS and AMI. The average age of these individuals was 56.31 ± 10.4 years, six (46.2%) were female and seven (53.8%) were male. Furthermore, the mean age of subjects with MS and stroke was 64.6 ± 7.6 years, including seven (70.0%) females and three (30.0) males.

The inflammatory levels were significantly higher ($p = 0.001$) in groups with cardiac events compared to control.

Table 1 - General Characteristics of individuals with MS with and without cardiovascular event

Variables	MS with event	MS without event	P
Age (years)	n=47	n=97	
	61.3 ± 8.5	59.3 ± 9.9	0.279
Sex, % number	n=47	n=99	
Female	28 (59.6)	79 (79.8)	0.017
Race, % number	n=38	n=84	
White color	32 (84.2)	65 (77.4)	0.533
Weight, kg	n=44	n=81	
	79.3 ± 14.5	83.2 ± 16.8	0.206
Height, m	n=43	n=78	
	1.58 ± 0.10	1.59 ± 0.08	0.885
BMI, kg/m²	n=43	n=78	
	31.6 ± 5.5	33.1 ± 6.0	0.163
Abd. circ., cm	n=43	n=79	
	104.0 ± 11.2	108.3 ± 15.1	0.106
SH,% number	n=47	n=97	
	43 (91.5)	84 (86.6)	0.564
Dyslipidemia,% number	35 (74.5)	71 (73.2)	1.00
Gluc. intol., % number	20 (42.6)	31 (32.0)	0.289
Current smok., % number	3 (6.4)	3 (3.1)	0.392
Previous smok., % number	n=47	n=96	
	25 (53.2)	32 (33.3)	0.036
PVD, % number	n=47	n=97	
	10 (21.3)	2 (2.1)	< 0.001

MS - metabolic syndrome; n - sample size; BMI - body mass index; Abd. circ. - abdominal circumference; SH - systemic hypertension; Gluc. intol. - glucose intolerance; Smok. - smoking; PVD - peripheral vascular disease.

Table 2 - Odds ratios adjusted for the use of medicines in different groups

Medicines	MS with event n=97	MS no event n=47	OR	IC 95%	P
Diuretics,% number	32 (68.1%)	72 (74.2%)	1.67	0.63-4.46	0.440
Beta-blocker, % number	38 (80.9%)	62 (63.9%)	0.57	0.20-1.52	0.039
ACEI, % number	36 (76.6%)	56 (57.7%)	0.84	0.29-2.41	0.027
CCB, % number	8 (27.6%)	21 (21.6%)	0.88	0.27-2.82	0.516
ARB, % number	3 (6.4%)	9 (9.3%)	2.25	0.37-13.55	0.556
Insulin, % number	15 (31.9%)	6 (6.2%)	0.12	0.04-0.38	<0.001
Glibenclamide, % number	17 (36.2%)	17 (175%)	0.31	0.13-0.76	0.014
Metformin, % number	29 (61.7%)	36 (37.1%)	0.74	0.30-1.87	0.005
ASA, % number	36 (76.6%)	46 (47.4%)	0.68	0.26-1.93	<0.001
Simvastatin, % number	39 (83%)	42 (43.3%)	0.19	0.08-0.48	<0.001

ACE - angiotensin converting enzyme inhibitors; CCB - calcium channel blockers; ARB – AT-1 receptor blockers; ASA - acetylsalicylic acid.

Table 3 - Comparison between inflammatory cytokines and Chlamydia pneumoniae antibodies in patients with MS, with and without previous cardiac events

Variables	MS with event n=46	MS without event n=100	P
IL-6, pg/ml	165.0 ± 16.3	106.6 ± 21.3	< 0.001
TNF-α, pg/ml	216.4 ± 25.3	135.6 ± 12.1	< 0.001
hs-CRP, mg/l	0.31 (0.01-2.00)	0.32 (0.03-20.30)	0.339
C. pneumoniae, % number IgG			<0.001
Positive	22 (47.8)	63 (63)	
Borderline	14 (30.4)	6 (6.0)	
Negative	10 (21.7)	31 (31)	
C. pneumoniae, % number - IgA			0.307
Positive	6 (13.0)	6 (6.0)	
Borderline	1 (2.2)	5 (5.0)	
Negative	39 (84.8)	89 (89.0)	

IL-6 - interleukin 6; TNF-α - tumor necrosis factor-alpha; hs-CRP - hypersensitive C-reactive protein; C. pneumoniae - Chlamydia pneumoniae.

The acute-phase marker (hs-CRP), as well as the presence of anti-*Chlamydia* IgG and IgA antibodies, predominated in patients with AMI and stroke. However, the results were not statistically significant between the groups of individuals.

Discussion

This study evaluated a group of patients that belonged to a cohort of a database from an outpatient cardiometabolic-risk clinic. When we compared individuals with MS, with and without cardiac events, there was a predominance of positive immunoglobulin G in subjects without cardiovascular events. However, when IgG antibodies were linked to AMI and stroke, the proportions of positive results were higher in the group with cardiac events, but without statistical significance. This probably occurred by chance, given the small number of subjects with cardiac events in the sample studied.

According to Maia et al[10], IgG is an immunoglobulin that lives for 20-30 days on average and it is the antibody that best expresses the activity of the infectious process, due to previous reinfections. The presence of the infectious process could be restricted only to the mechanisms of plaque instability, because the group without events could develop an atherosclerotic process in progress[10].

Ustunsoy et al[11] evaluated, in their study, the seroprevalence of IgG antibodies in patients who underwent surgery for peripheral atherosclerosis, compared with healthy patients. We found 60% seroprevalence of IgG to *C. pneumoniae* in the study group and 40% in the control group. Similar results were obtained in our study when we evaluated patients with AMI (61.5%) and with stroke (60%).

This association was also found in a seroprevalence study conducted with patients that were younger than 45 years of age, in southern India, who had acute ischemic stroke. The positive results of IgG antibodies to *C. pneumoniae* and IgA antibodies were 27.5% and 5%, respectively, in the same patients, always compared to the control group[12]. In our research, the values of antibodies for patients with stroke were much higher than for patients with MS without cardiovascular event, with no statistical significance. Our study did not evaluate patients in the acute phase and there was no comparison with a healthy group, which probably made it difficult to detect such antibodies and to observe the statistical power.

However, the consideration of borderline results found in our study as positive would allow observing a higher proportion of IgG in patients with cardiac events. We chose to consider these results statistically because of the small sample size of patients with cardiovascular event, and the laboratory method mentioned was used because it was available in our hospital.

Furthermore, since the 80s, the association between infection and atherosclerosis has been investigated, as *C. pneumoniae* (Cp) is one the most evident pathogens in the

Table 4 - Comparison between inflammatory markers and IgG and IgA antibodies to Chlamydia pneumoniae in patients with metabolic syndrome with AMI, stroke and without cardiovascular events

Variables	MS with AMI n=13	MS no event n=130	P	MS with stroke n=10	MS no event n=133	P
IL-6,p g/ml	164.08 ± 17.5	121.97 ± 32.4	< 0.001	166.80 ± 16.08	122.71 ± 32.53	< 0.001
TNF, pg/ml	208.2 ± 25.8	156.84 ± 40.1	< 0.001	227.10 ± 27.65	156.58 ± 38.34	< 0.001
CRP, mg/l	0.34 (0.01-1.06)	0.31 (0.01-20.30)	0.649	0.29 (0.06-1.19)	0.32 (0.01-20.30)	0.704
C. *pneumoniae*, % number IgG			0.417			0.805
Positive	8 (61.5)	75 (57.7)		6 (60.0)	77 (57.9)	
Borderline	3 (23.1)	17 (13.1)		2 (20.0)	18 (13.5)	
Negative	2 (15.4)	38 (29.2)		2 (20)	38 (28.6)	
C. *pneumoniae*, % number IgA			0.168			0.248
Positive	3 (23.1)	9 (6.9)		2 (20.0)	10 (7.5)	
Borderline	0 (0.0)	6 (4.6)		0 (0.0)	6 (4.5)	
Negative	10 (76.9)	115 (88.5)		8 (80.0)	117 (88.0)	

presence of stable atherosclerotic disease, in AMI and stroke. A meta-analysis study that searched for articles published between January 1966 and October 2002 noted that Cp has a relationship with atherosclerosis, by seroepidemiological and pathological studies, which showed high titres of this agent and evidence of atherosclerotic lesion[13]. However, a study using azithromycin after intracoronary stent implantation showed no attenuation of late angiographic outcomes, but there was attenuation of hs-CRP levels, which may indicate an anti-inflammatory effect[14].

At another moment, Razin et al[15], by means of an autopsy, viewed a large number of cells infected with Cp in atherosclerotic plaques, and they identified the presence of another pathogen called *Mycoplasma pneumoniae* (Mp), which would be characterized as a superantigen that would need cholesterol to survive[15]. Thereafter, there is a chance that the MP would act as a trigger to activate Cp, causing instability of the atherosclerotic plaque[15].

Research shows that heat shock proteins (Hsp) originating from inflammatory agents such as Cp are considered homologous to endothelial Hsp of 60 kilodaltons (kDa). They are directly involved with the atherogenesis by stimulating the migration of smooth muscle cells to the inner layer and activating monocytes. Cross anti-Hsp antibodies could accelerate the autoimmune endothelial damage[16]. The concentrations of inflammatory biomarkers, TNF and IL-6, among patients with MS, with and without cardiac events, were measured once. There was evidence of a statistically significant increase in such levels, especially when we checked their behavior during cardiovascular events, in accordance with the literature. According to Volp et al[17], individuals with heart disease had high levels of IL-6 and there was a relative risk of 2.11 of their death within 24 months. In this context, the levels of this cytokine may be early indications of morbidity in healthy people and mortality in people that have already suffered a cardiac event.

Overweight subjects (> 27 kg/m^2) have higher levels of TNF-alpha compared to people whose weight is normal. However, TNF-alpha and the MS components are correlated, and TNF-alpha may indicate, beforehand, risks of cardiovascular diseases and heart attack, with a relative risk of 3.09 of death within 24 months according to the literature, although it was an independent marker for AMI[18].

In this study, most participants were obese, followed by patients who were overweight, and the inflammatory markers proved to be really high. As for the acute phase marker, the serum levels of hs-CRP remained the same in both groups, with no statistical significance. This result would probably be justified by the fact that these individuals are under strict drug treatment, mainly with statins. The statins act to improve endothelial function, to decrease vascular inflammation, to stabilize atherosclerotic plaque, among other functions[19], and they are a major protective factor of these events. The efficacy of statin therapy is directly related to the decrease in CRP and LDL cholesterol levels. Patients who suffered some type of event are usually treated more effectively with a variety of medications, as seen in this study, in order to control and prevent other events. On the other hand, patients who are at risk are controlled and instructed so as to prevent future cardiac events.

A study conducted by Marcinkowski et al[20], with the assessment of inflammatory markers ten weeks after AMI, noted that patients with recurrent episodes had significant increases in inflammatory markers, including CRP, in the ten weeks following the AMI. However, patients with coronary events between the tenth day and the tenth week showed no increase in such markers, which may show that they are considered independent risk factors for recurrent cardiovascular events.

Peripheral vascular disease and previous smoking also showed significant results when the two groups were compared. *C. pneumoniae* infections are more common in smokers than in nonsmokers. A study conducted in Finland, estimating the relative risk for Cp seropositivity, showed that smokers are 1.5 times more likely to be infected with this pathogen than those who never smoked. Moreover, the presence of positive antibody titers for IgG and IgA is more common in smokers and former smokers than in nonsmokers, regardless of age[21].

Conclusion

There is an association between elevated levels of inflammatory markers - IL-6 and TNF-alpha - and MS in patients with cardiovascular events, compared to those without cardiac events. The hs-CRP proved not to be a marker of risk for such events.

Through the evaluation of patients with MS, with AMI and stroke, we observed that there are no statistically significant differences in the levels of IgG and IgA anti-*Chlamydia pneumoniae* antibodies, compared to the group without cardiovascular events.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of master submitted by Rosecler Riethmuller Franco, from *Pontifícia Universidade Católica do Rio Grande do Sul* - PUCRS.

References

1. James PT, Leach R, Kalamara E, Shayeghi M. The worldwide obesity epidemic. Obes Res. 2001; 9 (4): 228-33.
2. Meigs JB. The metabolic syndrome. BMJ. 2003; 327 (7406): 61-2.
3. Rigo JC, Vieira JL, Dalacorte RR, Reichert CL. Prevalência de síndrome metabólica em idosos de uma comunidade: comparação entre três métodos diagnósticos. Arq Bras Cardiol. 2009; 93 (2): 85-91.
4. Salaroli LB, Barbosa GC, Mill JG, Molina MCB. Prevalência de síndrome metabólica em estudo de base populacional, Vitória, ES – Brasil. Arq Bras Endocrinol Metab. 2007; 51 (7): 1143-52.
5. Bahia L, Aguiar LGK,Villela NR, Bittino D, Bouskela E. O endotélio na síndrome metabólica. Arq Bras Endocrinol Metab. 2006; 50 (2): 291-303.
6. Gottlieb MGV, Bonardi G, Moriguchi EH. Fisiologia e aspectos inflamatórios da aterosclerose. Scientia Medica [periódico online]. 2005; 15 (3): 203-7. [Acesso em 2009 out 21]. Disponível em http://revistaseletronicas.pucrs.br/ojs/index.php/scientiamedica/article/viewFile/1568/1171
7. Sess R, Nicoletti M, Di Pietro M, Schiavoni G, Santino I, Zagaglia C, et al. Chlamydia pneumoniae and atherosclerosis: current atate and future prospectives. Int J Immunopathol Pharmacol. 2009; 22 (1): 9-14.
8. Watson C, Alp NJ. Role of Chlamydia pneumoniae in atherosclerosis. Clin Sci (Lond). 2008; 114 (8): 509-31.
9. Stassen FR, Vainas T, Bruggeman CA. Infection and atherosclerosis: an alternative view on an outdated hypothesis. Pharmacol Rep. 2008; 60 (1): 85-92.
10. Maia IL, Nicolau JC, Machado MN, Maia LN, Takakura IT, Cordeiro JA, et al. Prevalência de Chlamydia pneumonia e Mucoplasma pneumonia em diferentes formas da doença coronariana. Arq Bras Cardiol. 2009; 92 (6): 439-45.
11. Ustunsoy H, Sivrikoz C, Sirmatel F, Bakir K, Murma O, Kazaz H. Is Chlamydia pneumoniae a risk factor for peripheral atherosclerosis. Asian Cardiovasc Thorac Ann. 2007;15 (1): 9-13.
12. Bandaru VC, Boddu DB, Laxmi V, Neeraja M, Kaul S. Seroprevalence of Chlamydia pneumoniae in stroke in young. Can J Neurol Sci. 2009; 36 (6): 725-30.
13. Kalayoglu MV, Libby P, Byrne GI. Chlamydia pneumoniae as an emerging risk factor in cardiovascular disease. JAMA. 2002; 288 (21): 2724-31.
14. Ikeoka DT, Vieira CZ, Lemos PA, Strabelli TV, da Silva EE, Perin MA, et al. Azithromycin does not prevent six-month myointimal proliferation but attenuates the transient systemic inflammation occurring after coronary stenting. Clin Res Cardiol. 2009; 98 (1): 44-51.
15. Razin S, Yogev D, Naot Y. Molecular biology and pathogenicity of mycoplasmas. Microbiol Mol Biol Rev. 1998; 62 (4): 1094-156.
16. Mayr M, Metzler B, Kiechl S, Willet J, Schett G, Xu Q, et al. Endothelial cytotoxicity mediated by serum antibodies to heat shock proteins of Escherichia coli and Chlamydia pneumoniae: immune reactions to heat shock proteins as a possible link between infection and atherosclerosis. Circulation. 1999; 99 (12): 1560-6.
17. Volp ACP, Alfenas RCG, Costa NMB, Minim VP, Stringueta PC, Bressan J. Capacidade dos biomarcadores inflamatórios em predizer a síndrome metabólica. Arq Bras Endocrinol Metab. 2008; 52 (3): 537-49.
18. Barreto-Filho JAS. Síndrome metabólica: um estado pró-trombótico. Rev Soc Cardiol Estado de São Paulo. 2004; 14 (4): 590-5.
19. Rang HP, Dale MM, Ritte JM, Moore PK. Hormônios locais, inflamação e reações imunológicas. In: Rang HP. Farmacologia (tradução). 5ª ed. Rio de Janeiro: Elsevier; 2004. p. 272-3.
20. Marcinkoqski M, Czarnecka D, Jastrzebski M, Fedak D, Kawecka-Jaszcz K. Inflammatory markers 10 weeks after myocardial infarction predict future cardiovascular events. Cardiol J. 2007; 14 (1): 50-8.
21. Maija L. Chlamydia pneumoniae and other risk factors for atherosclerosis. J Infect Dis. 2000; 181 (Suppl 3): 414-6.