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Editorial

Subclinical Atherosclerosis Associated with Metabolic Syndrome: Identification of Early Inflammatory Markers and Oxidative Stress

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Editorial

The continuous study and review of risk factors play an important role in preventive strategies for cardiovascular diseases. In this context, subclinical atherosclerosis confers relevance, causing vascular bed involvement for years without the patients clinically showing a cardiovascular event. The addition of factors such as arterial Hypertension (HT), obesity, dyslipidemia and Diabetes Mellitus (DM) in the same individual converge in an entity recognized worldwide as Metabolic Syndrome (MS). In its pathophysiology, glycolipid metabolic dysregulation, proinflammatory and prothrombotic processes converge and they associate the state of MS with an increase in the prevalence and incidence of coronary heart disease, and as a predictive factor for the development of DM. Consequently, we understood the clinical importance of identifying early markers that can help to find strategies to prevent or delay the development of DM, since glucose intolerance is a pro-inflammatory, pro-atherogenic, prothrombotic and facilitating condition of DM. During 15 years of research carried out in experimental models of rats, for atherosclerosis generated by hyperfibrinogenemia as well as for metabolic syndrome induced by the administration of fructose in the drinking water of rats, we analyzed the relationship between inflammatory biomarkers and oxidative stress to determine its participation in atherogenesis and explain the probable pathophysiological mechanisms involved. The atherogenic model developed allowed us to corroborate the modifications of plasma inflammatory markers such as high concentrations of fibrinogen and oxidative stress markers among them, low bioavailability of Nitric Oxide (NO) and inactivation of the antioxidant enzyme Superoxide Dismutase (SOD) by substrate saturation (excess of free radicals as superoxide anion) showing a systemic involvement. In addition, the analysis of aortic tissue allowed us to investigate endothelial dysfunction in depth, noticing denudation of the endothelium, thickening of the intimal layer and alterations of the mitochondria at the level of the vascular smooth muscle, confirmed by analysis both at a morphological and functional level. Also, we study the complexes of the mitochondrial respiratory chain, concluding that the atherogenic process generates alterations in hemostasis and lesions in the vascular wall that are accentuated in direct relation to the increase in reactive

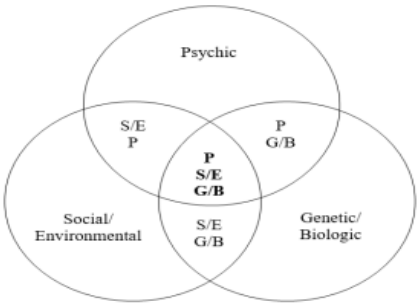

Figure 1: Etiologic factors in alcoholism. Each circle represents one group of factors. In the overlapping areas, the group names are abbreviated to the initials.

Table 1: Average age, alcoholism pattern, literacy, average income and religion of men under the three skin color groups.

	White	Black	Brown	p
	n=149	n=32	n=25	
Age (years)	39.0±10.5	38.6±12.1	41.7±11.7	NS
Consumption (g/day)	203±129	195±164	186±121	NS
Duration of consumption (years)	22.0±10.8	22.7±10.7	21.6±10.1	NS
School attendance	n%	n%	n%	
None	8*5.4	618.8	520.0	S
First degree (Fundamental 8 years)	11979.9	2165.6	1456.0	NS
Second degree (Medium, plus three years)	64.0	13.1	0-	NS
Third degree (University)	42.7	0-	0-	NS
Not informed	128.0	412.5	624.0	NS
Family income (minimum wage)	n%	n%	n%	
<1	2516.8	618.8	520.0	NS
2-Jan	3523.5	515.6	832.0	NS
2-3	2315.4	412.5	416.0	NS
3-5	2214.8	412.5	416.0	NS
5-10	1711.4	721.9	0-	NS
Not informed	2718.1	618.8	416.0	NS
Religion	n%	n%	n%	
Catholic	13590.0	2887.5	2080.0	NS
Spiritualist (Kardecist)	149.0	39.3	416.0	NS
Evangelic (various)	21.0	13.2	14.0	NS

*School attendance incomplete; S: Significant; NS: Not Significant; p≤0.05

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Table 2: Average age, alcoholism pattern, literacy, average income and religion of women under the three skin color groups.

	White	Black	Brown	p
	n=50	n=31	n=13	
Age (years)	43.1±10.9	41.8±9.8	42.5±14.9	NS
Consumption (g/day)	218 ±157	230 ±163	228 ±163	NS
Duration of consumption (years)	18.0±11.6	21.7±10.4	15.8±9.8	NS
School attendance	n%	n%	n %	
None	1428.0	1238.7	538.5	NS
First degree (Fundamental 8 years)	1734.0	929.0	13.2	NS
Second degree (Medium, plus three years)	1632.0	1032.3	753.8	NS
Third degree (University)	36.0	0-	0-	NS
Family income (minimum wage)	n%	n%	n%	
<1	0-	13.2	120.0	NS
2-Jan	2754.0	1754.8	932.0	NS
2-3	24.0	13.2	0-	NS
3-5	0-	0-	0-	NS
5-10	0-	0-	0-	NS
Not informed	2167.0	1651.6	323.0	NS
Religion	n%	n%	n%	
Catholic	4693.0	2994.0	1184.0	NS
Spiritualist (Kardecist)	36.0	26.0	18.0	NS
Evangelic (various)	12.0	0-	1*8.0	NS

NS: Not Significant.

oxygen species. This described situation concludes in mitochondrial dysfunction, modifying the enzymatic activity of the complexes and generating a vicious cycle of cellular oxidative stress, which further emphasizes vascular lesions.

On the other hand, the MS model allowed to validate that the chronic administration of fructose in the diet of rats produces an effective replica of the pathology observed in humans, objectifying an increase in fasting blood glucose, a state of dyslipidemia verified by hypertriglyceridemia, elevated levels of LDL-C, decrease in the concentration of HDL-C and increase in circulating levels of total cholesterol along with hyperinsulinemia. These biochemical alterations observed at carbohydrate and lipid metabolism are promoters of the systemic inflammatory state that is present in MS. This model showed an increase in plasma fibrinogen, demonstrating that excess fructose can simultaneously trigger inflammatory responses that disrupt metabolic function. In addition, the decrease in the bioavailability of nitric oxide confirms the existence of a pro-oxidative state, allowing us to quantify the production of reactive oxygen species, mainly superoxide anion. In this oxidative context, an increased SOD activity demonstrates an oxidative stress environment generated by chronic excess of nutrients, such as lipids and glucose that simultaneously trigger inflammatory responses disrupting metabolic function and produce lesions in different organs. We were able to verify lesions in the aortic wall such as endothelial dysfunction, proliferation of vascular smooth muscle and thickening of the vascular intima, in addition we observed morphofunctional alterations at the mitochondrial level coinciding with the atherogenic process. Also in this MS model, liver tissue samples were analyzed, verifying alterations consistent with cholestasis, sinusoidal congestion, binucleation and periportal inflammatory infiltrate, compatible with the first changes in Non-Alcoholic Hepatic Steatosis, which corroborates the liver lesions characteristic of MS. We continued our research on this multisyndromic pathology by analyzing the mitochondria of hepatocytes, and the results showed altered morphology and dysfunction of the mitochondrial complexes. Therefore, oxidative stress would be the unifying mechanism in both experimental models.

The hypothesis of an inflammatory etiology is confirmed for MS as well as for atherosclerosis. The reduction of NO, a key regulator of endothelial homeostasis, and the increase in reactive oxygen species that shows an increase in SOD result in endothelial dysfunction and a pro-atherogenic vascular bed.

The determination of inflammatory biomarkers and oxidative stress should be taken into account when evaluating the cardiovascular risk presented by patients with MS, since it cannot be explained only by traditional risk factors.

A confirmation was made with clinical models of MS, where, regardless of the age of the patients studied, plasma fibrinogen modified its concentrations independently of other risk factors already established such as hypertension, DM, and smoking. It was

Table 3: Relationships between average age, alcoholism pattern and male/female ratio according to the skin color groups.

	White		p	Black		p	Brown		p
	Men	Women		Men	Women		Men	Women	
	n=149	n=50		n=32	n=31		n=25	n=13	
Age (years)	39.0±10.5	43.1±10.9	0.02	38.6±12.1	41.8±9.8	NS	41.7±11.7	42.5±14.9	NS
Consumption	203±129	218±157	NS	195±164	230±163	NS	186±121	228±163	NS
Duration of usage	22.0±10.8	18.0±11.6	0.03	22.7±10.7	21.7±10.4	NS	21.6±10.1	15.8±9.8	NS
Male/female ratio	2.98			1.03			1.92		S
Non-alcoholics population	n=193	n=197		n=28	n =14		n=60	n=50	
	-49.50%	-50.50%		-66.70%	-33.30%		-54.50%	-45.50%	
Male/female ratio	0.98			2.00			1.20		S
General population (Marília 2006)	n=65.898 (47.9%)	n=71.661 (52.1%)		n=4.048 (51.3%)	n= 3.839 (48.7%)		n=23.402 (51.5%)	n=22.013 -48.50%	
Male/Female ratio	0.92			1.05			1.06		NS

S: Significant; NS: Not Significant; p≤0.05.

verified in patients with MS, regardless of the diagnosed components that presented, an increase in oxidative stress with modifications of pro-inflammatory, pro-oxidative and antioxidant biomarkers reflecting the increase in the total atherogenic load.

Therefore, early identification of biomarkers in patients with MS would allow intervention in preclinical and reversible phases, preventing or delaying the development of cardiovascular complications, and the pathological association cannot be denied.

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