

Metabolic Syndrome and Inflammation.

A viviparous, oblong, fish?

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“Beauty is placed in the sixteenth category: is a viviparous, oblong fish. These ambiguities, redundancies and deficiencies recall those that Doctor Franz Kuhn attributes to a certain Chinese Encyclopaedia entitled Celestial emporium of benevolent knowledge. In its remote pages it is written that animals are divided in (a) belonging to the Emperor, (b) embalmed, (c) tamed, (d) pigs, (e) sirens, (f) extraordinary, (g) dirty dogs, (h) included in this classification, (i) that are agitated as madmen, (j) innumerable, (k) draw with a very fine camel hair paintbrush, (l) etcetera, (m) that just broke the jar, (n) that from the distance look like flies”.

JORGE LUIS BORGES,

“Other inquisitions. The analytical language of John Wilkins” (1952)

In: Borges JL. Complete Works. Barcelona: Emecé Editors; 1996. p. 84-7.

The metabolic syndrome was described in 1988 by Reaven et al. (1) However, as pointed out by Sarafidis et al, the relation between metabolic alterations and cardiovascular risk was noted in the early decades of last century. (2) At the time of the First World War, Hitzengerber y Richter-Quittner, studied the interdependence between metabolic disorders and hypertension and between the latter and diabetes. In 1921 and 1922, Kylin and Mara  n published two articles on the relation between diabetes and hypertension. It was Kylin who, for the first time defined a syndrome of “hypertension-hyperglucemia-hyperuricemia” On the other hand, in 1936 Himsworth was the first author who divided patients in insulin-sensitive and insulin-resistant. In 1947, Vague differentiated the ginecoid from the android obesity and pointed out the relation of the latter with diabetes, hypertension, gout, and atherosclerosis. In 1966 Albrink and Meighs emphasized the relation between obesity and dyslipidemia and hypertriglyceridemia. As from the ’60 several denominations were proposed for the group of metabolic disorders related to cardiovascular risk. In 1966, Camus noted the “metabolic trisynndrome”, gout, diabetes and hyperlipidemia; in 1967 Avogaro and Crepaldi called “pluri-metabolic syndrome” to the co-existence of hyperlipidemia, obesity and diabetes, occasionally associated with hypertension and coronary disease. In 1968, Mehnert and Kuhlmann defined the “well-being syndrome” that links metabolic abnormalities with nutritional habits and life-style in developed countries. In 1973 Hanefeld stressed the high risk of atherosclerosis in individuals with this group of disorders and, in 1981 described together with Leonhardt the “meta-

bolic syndrome: type II diabetes mellitus, hyperinsulinemia, obesity, hypertension, hyperlipidemia, gout, and thrombophilia, thus enhancing the importance of the genetic substratum and environmental conditions such as over-nutrition and lack of physical exercise. In 1988, Reaven called “X Syndrome” to the presence of glucose intolerance, hyperinsulinemia, high levels of VLDL and triglycerides, low levels of HDL, hypercholesterolemia and hypertension. The etiological common factor of these disorders is insulin resistance, present in patients with type II diabetes mellitus or glucose intolerance, but also in 25% of the individuals with normal glucose tolerance. In 1989 Kaplan added the presence of central obesity thus defining the “death quartet”: central adiposity, glucose intolerance, hypertriglyceridemia and hypertension. DeFronzo and Ferrannini in 1991, and Haffner in 1992 directly referred to “insulin resistance”. (2) This dedicated classification endeavour, that the inspired prologue by Jorge Luis Borges evokes, has not been exhausted until our present time when the definitions of the World Heart Organization (WHO), the European Group for the Study of Insulin Resistance (EGIR), the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) and the International Diabetes Federation (IDF) co-exist to the dismay of clinicians and to challenge their mnemonic capacity.

Recently, a document by the American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) questions the definitions, the physiopathological mechanisms and their value as vascular risk factor. (2)

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Beyond the discussion on definitions, research on the MS, its pathogenesis, its relation with vascular disease, its prevention and treatment is mandatory. In the present edition of the *Revista Argentina de Cardiología* (Argentine Journal of Cardiology), Renna et al analyze a physiopatological aspect of the MS that is very attractive: the vascular expression of pro-inflammatory transcription factors sensitive to redox (3). The concept of inflammation “ruling” atherosclerosis and its complications provides a unicist hypothesis about the relation that exists between risk factors and cellular and molecular disorders underlying the disease, (4). Even though there is evidence supporting that obesity, Type II diabetes mellitus, and vascular disease share an environment characterized by resistance to insulin and low intensity chronic inflammation, the evidences on their relation with oxidative stress are rarer. (5-12). It is acknowledged that physiologically, insulin inhibits the generation of reactive oxygen species [ROS], the nuclear factor kappa B [NF-kappa B] and the expression of p47^{phox}, increases the expression of the inhibitor of NF-kappa

B [I-kappa B] in mononuclear cells and decreases plasma concentration of intercellular adhesion molecule-1 [ICAM1] and of monocyte chemotactic protein-1. Also, insulin suppresses the transcription of pro-inflammatory factors such as the activator protein 1 [AP-1] and of early growth response genes-1, 2 [Egr-1, 2], of matrix 9 metalloproteinase, of tissue factor [TF] and of the plasminogen activator inhibitor-1 [PAI-1]. Hence, insulin has an anti-inflammatory and antioxidant effect (13). Wellen et al, based on the studies by Lin et al and Furukawa et al, reported that glucose metabolism increase can cause an increase in mitochondrial ROS production which induces an activation of the inflammatory mechanisms (Figure 1). (9-11). Furukawa et al argue that fat accumulation is correlated to oxidative stress. In fact, the production of ROS increases the adipose tissue in obese mice, with NADPH oxidase increase and anti oxidative enzymes decrease. In adipocytes culture, the increased levels of fat acids increase oxidative stress by NADPH oxidase activation and cause deregulation in the production of adipocytokines, including adiponectin, PAI-

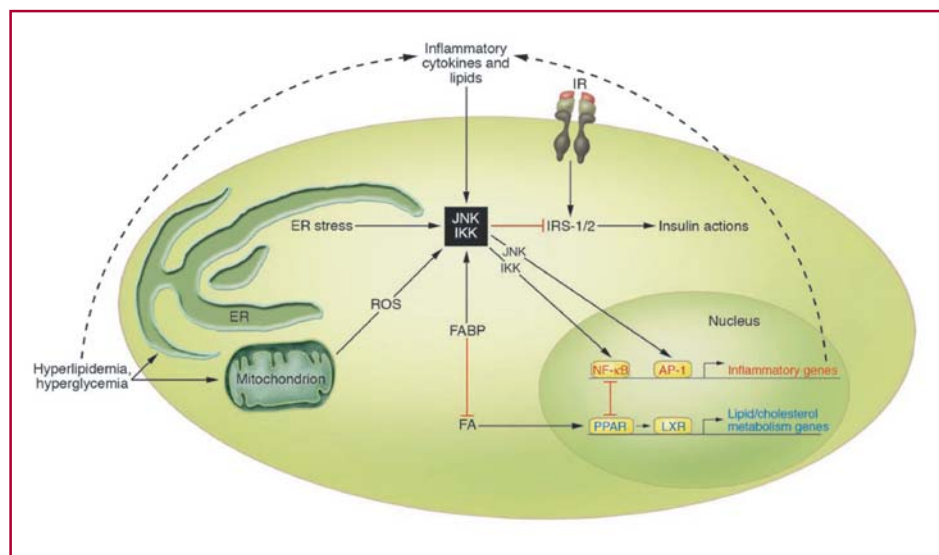


Fig. 1. Model of the juxtaposition of the inflammatory and metabolic paths at the adipocyte or the macrophage. Wellen K, et al. Modified. (9).

The inflammatory paths can be initiated by extracellular mediators such as cytokines and lipids; by intracellular stress such as stress of the *endoplasmic reticulum*, ER; or by excess of reactive oxygen species, ROS production; due to the mitochondria. The signals of these mediators converge with the inflammatory signs included in the c-Jun N-terminal kinase, JNK and the inhibitor of NF-kB kinase, IKK. These paths lead to the production of additional inflammatory mediators through transcription regulation, as well as the direct inhibition of insulin signals. Other paths such as those mediated by proteins suppressor of cytokine signalling, SOCS and by inducible NO synthase, iNOS are also involved in the inhibition of insulin mediated inflammation. In opposition to the inflammatory pathways are the transcription factors of the peroxisome proliferator-activated receptor, PPAR families and those of the liver X receptor, LXR that promote the transportation of nutrients and metabolism, and antagonize the inflammatory activity. A more proximal regulation is performed by fatty acid-binding protein, FABP carriers, which probably sequester ligands of these transcriptional factors and promote a more inflammatory environment. The absence of FABP is anti-inflammatory. The cell should maintain a balance between metabolism and inflammation. This is challenging, particularly under conditions of over-nutrition, due to the fact that the required process to respond to nutrients and to use them, such as mitochondrial oxidative metabolism and ER synthesis increase, could induce an inflammatory response.

AP-1: Protein 1. ER activator: Endoplasmic Reticulum. FA: Fatty Acids. FABP: Fatty Acid Binding Protein. IKK: Inhibitor of KB kinase NF-kB. IRS: Insulin Receptor Substratum. JNK: C-Jun N-terminal Kinase. LXR: Liver X Receptor. NF-kB: Nuclear Factor kappa B. PPAR: Peroxisome Proliferator-Activated Receptor. ROS: Relative Oxygen Species. *ER stress*: Endoplasmic reticulum Stress. *Inflammatory cytokines and lipids*. *Insulin actions*. *Nucleus*. *Hyperlipidemia, hyperglycemia*. *Mitochondrion*. *Inflammatory genes*. *Lipid/cholesterol metabolism genes*.

1, interleukin 6 and monocytes protein chemotactic-1. NADPH oxidase inhibition reduces ROS production at the adipose tissue attenuating the deregulation of adipocytokines and liver steatosis (11). Lavrovsky et al added that the progressive number of oxidative stress due to disorders of redox homeostasis is one of the markers of the aging process. Thus, changes in the genetic expression through ROS transcription factors cause both aging and inflammatory phenotypes. Transcription factors directly influenced by ROS and pro-inflammatory cytokines include the NF-kappa B, the AP-1, the specific protein 1 (Sp1), the peroxisome proliferator-activated receptor (PPAR) and other members of the super family of the nuclear receptor (12). On the other hand, Barbato et al indicated that the vascular damage in the stages of insulin resistance such as MS and type II diabetes mellitus is characterized by an increase in the expression of adhesion molecules and the lecithin-like oxidized low-density lipoprotein receptor-1 [LOX-1], infiltration by inflammatory cells and neointimae formation. Transference of the inducible NO synthase [iNOS] gene inhibits all these events, which would indicate that the increase in the inflammatory response and the oxidative stress in insulin resistance could be reversed by the increase in NO bio-availability. (14)

The outstanding experiment designed by Renna et al corroborates – in an experimental animal model – that oxidative stress and the consequent gene activation that participate in the inflammatory process actively intervene in the development of vascular remodelling (3).

It might be time to forget, even for a few moments, the classification attempts that illustrate Borges' apocryphal Chinese encyclopaedia and revisit MS focused on its intimate physiopathological mechanisms, that have the beauty of a "viviparous, oblong fish" (and probably, as physicians, the wealth of a promising therapeutic future).

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