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EDITORIAL

Inflammation and the Metabolic Syndrome

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The prevalence of the metabolic syndrome is increasing in developed and developing Countries. Metabolic syndrome is constellation of disturbances including glucose intolerance, central obesity, hypertension and dyslipidemia (hypertriglyceridemia, elevated non-esterified fatty acids and decreased high density lipoprotein cholesterol) present in several forms, depending upon the combination of the different components of the syndrome. It is well accepted that the metabolic syndrome increases the risk for the development of cardiovascular disease, type 2 diabetes, stroke and cancer [1]. However, it is a matter of debate about the causes for the onset of the metabolic disturbances that constitute the syndrome and there have been several attempts to define it with special attention to one or another component. The American Association of Endocrinology does not consider obesity as a component and highlights the importance of insulin resistance to the syndrome [2]. The initial definition of the World Health Organization also considered insulin resistance as an important feature of the metabolic syndrome [3], while National Cholesterol Education Program: Adult Treatment Panel III [4] definition gives equal weight to any of the components of the syndrome: fasting blood glucose, glucose intolerance, obesity (measured as waist circumference), hypertension and dyslipidemia. More recently the International Diabetic Federation (IDF) provided worldwide definition for use in clinical practice, considers central obesity and insulin resistance as important causative factors [5]. The IDF consensus group has further highlighted a number of other parameters including pro-inflammatory state that appear to be related to the metabolic syndrome, with the aim to determine the predictive power of these extra criteria for CVD and/or diabetes.

Thus several explanations have been proposed to explain the origin of the metabolic syndrome. Some consider an initial insulin resistant state progressing to the other components, while others are of view that obesity is the main initiator of the syndrome [6]. More recently, the chronic low-grade inflammatory condition that often accompanies the metabolic syndrome has been implicated as a major factor both in the installation of the metabolic syndrome and its associated pathophysiological consequences [7]. However, the inflammatory state that accompanies the metabolic syndrome does not completely fit into the classical definition of acute or chronic inflammation, as it is not accompanied by infection; there is no massive tissue injury and the dimension of the inflammatory activation is also not large. So it is often called 'low grade' chronic inflammation or 'meta-inflammation', meaning metabolically-triggered inflammation [8] or even 'para-inflammation' an intermediate state between basal and inflammatory states [9]. Whatever the term used, the inflammatory process that characterizes the metabolic syndrome has its own unique features but its causes are far from being fully understood.

Several studies support to the concept that a proinflammatory state is a component of the metabolic syndrome because of the strong association of elevated C-reactive protein (CRP) with metabolic syndrome risk factors and high CRP levels impart risk for major coronary events beyond that imparted by the other metabolic risk factors. High-sensitivity CRP (hs-CRP) has been developed and used as a marker to predict coronary vascular diseases in metabolic syndrome and it was recently used as a predictor for non-alcoholic fatty liver disease in correlation with

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serum markers that indicated lipid and glucose metabolism. However the reasons for a link between inflammation and metabolic syndrome are not fully understood. One explanation may be that adipose tissue in obese persons with the metabolic syndrome releases increased amounts of cytokines into the circulation which in turn accounts for a greater production of CRP by the liver. Another possibility is that insulin resistance per se is responsible for a higher production of cytokines. Regardless of mechanism, the finding that patients with metabolic syndrome exhibit characteristics of a proinflammatory state provides a new and exciting connection between inflammation and metabolic processes. This connection promises to yield new insights into pathways whereby the metabolic syndrome leads to atherosclerosis and acute coronary syndromes [10].

Further tissue malfunction or homeostatic imbalance of one or several physiological systems seems to be associated with inflammatory process, but it is sometimes difficult to understand how this would bring out a host defense mechanism. Instead of being beneficial, it seems to progress to a deregulated state and is implicated in the worsening of the condition. It has even been questioned whether there is any physiological counterpart for this inflammatory response. It is possible that the initial response provides short-term benefits and later on in a chronic phase it becomes maladaptive. In fact, inducible adaptive changes generally occur at the expenses of many other physiological processes and, therefore, cannot be sustained without adverse side effects caused by the decline in the affected functions [9].

It is difficult to pin point a single cause for the activation of inflammation, as it is a sequential events related to the deterioration of metabolic homeostasis. Apparently, metabolic overload evokes several stress reactions including oxidative, inflammatory, organelle and cell hypertrophy stresses, generating vicious cycles that amplify each other leading to dysfunction [11]. The difficulty in the management of the syndrome is linked to its multifactorial nature where environmental, genetic and psychosocial factors may play a vital role. Undoubtedly, the connections between inflammation and metabolism are complex and present a challenge for new research. The awareness of the importance of inflammation in the metabolic syndrome may help to develop new strategies for the prevention and treatment of metabolic syndrome related disorders.

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