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EDITORIAL

A Paradigm Shift and New Therapeutic Options for the Metabolic Syndrome

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ABSTRACT

The metabolic syndrome, characterized by obesity, dyslipidemia, insulin resistance and hypertension, increases the risk of cardiovascular morbidity and mortality. In recent years, the convergence of evidence from several studies has resulted in a major shift both in the understanding of the pathophysiology and the treatment options for this disease. Shunning away from the glucocentric hypothesis, this is now based on a unified 'lipotoxicity' hypothesis, according to which metabolic syndrome and type 2 diabetes mellitus can be caused by the ectopic accumulation of triglycerides and long-chain fatty acids in liver, muscle and pancreatic islets. This lipocentric approach is integrated with the analysis of inflammatory reactions associated with end-organ damage, including the vascular wall. Transcription factors and coactivators, including peroxisome proliferator-activated receptor coactivator-1 are crucial in mediating insulin resistance and accelerating vascular wall inflammation, and represent promising therapeutic targets. This new integrated view of the metabolic syndrome also takes into account the genetic differences among individuals and consequent variant response to therapy.

KEY WORDS: *metabolic syndrome; obesity; insulin resistance; diabetes; hypertriglyceridemia; hypertension*

INTRODUCTION

The metabolic syndrome, characterized by obesity, dyslipidemia, insulin resistance and hypertension, contributes to early atherosclerosis and increases the risk of cardiovascular morbidity and mortality.[1,2] Unfortunately its prevalence starts early in life; in the period between 1999 and 2002, the prevalence rate of metabolic syndrome in US adolescents varied overall from just >9% to as low as 2%.[3] Most current views on the pathogenesis of the metabolic syndrome and its existing treatments have been dominated by a glucocentric approach: the glycemic response to insulin is suboptimal, with dire metabolic consequences.[4-6] Such consequences are compensatory hyperinsulinemia, β cell glucotoxicity and lipotoxicity and the deposition of amyloid in pancreatic islets, with concomitant inflammation, endothelial dysfunction, a procoagulant state and dyslipidemia. In addition, these views have been applied on the premise that effector molecules involved in disease pathogenesis or response to therapy are invariant across the population. However, most current therapies have limited efficacy and limited tolerability.

List of Abbreviations:
IL-6 = interleukin 6
MMPs = metaloproteinases
PPARγ = peroxisome proliferator-activated receptor γ
TNF-α = tumor necrosis factor α

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"LIPOTOXICITY" HYPOTHESIS AND PRO-INFLAMMATORY MARKERS

In recent years, the convergence of evidence from several studies has resulted in a major shift both in the understanding of the pathophysiology and the treatment options for this disease. This is based on a unified 'lipotoxicity' hypothesis, according to which metabolic syndrome and type 2 diabetes mellitus can be caused by the ectopic accumulation of triglycerides and long-chain fatty acids in liver, muscle and pancreatic islets. Similar lipid changes in selective hypothalamic neurons regulate insulin action and glucose homeostasis, in addition to food intake and body weight. This lipocentric approach is integrated with the analysis of inflammatory reactions associated with end-organ damage, including that in the vascular wall.[5-14] The integration of inflammatory and metabolic mechanisms in obesity is based on the functional overlap of macrophages and adipocytes. The latter reflects the plasticity of macrophage and pre-adipocyte. Adipocytes produce inflammatory "macrophage" proteins such as tumor necrosis factor α (TNF-α), interleukin 6 (IL-6) and metaloproteinases (MMPs).[8,9] In addition adipokines, such as adiponectin, resistin and visfatin have immunological activity along with metabolic functions. Moreover, lipids themselves exert inflammatory and metabolic actions through lipid-targeted pathways via nuclear receptors. Meanwhile macrophages express peroxisome proliferator-activated receptor γ (PPARγ).[10-13]

Transcription factors and coactivators, including PPARγ coactivator-1, are crucial in mediating insulin resistance and accelerating vascular wall inflammation, and represent promising therapeutic targets. New pharmacological strategies include dual PPARα/γ agonists, drugs with pleiotropic effects or combination therapies.[11-16]

GENOMICS

Finally, the application of genomic and proteomic methodologies in animal models of diabetes, and in serum and tissues from normal individuals and patients with type 2 diabetes mellitus, has identified clusters of genes and proteins that might contribute to cardinal aspects of this disease such as insulin resistance, β cell dysfunction and vascular wall damage.[16-18] The new integrated view of the metabolic syndrome takes into account the genetic differences among individuals when the clinical heterogeneity of the clinical phenotypes or variation of the response to therapy is considered.

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