

## A Paradigm Shift and New Therapeutic Options for the Metabolic Syndrome

Christodoulos Flordellis, MD, Ph.D.

*Professor & Director of Pharmacology,  
Patras University School of Medicine,  
Patras*

The metabolic syndrome, characterized by obesity, dyslipidemia, insulin resistance and hypertension, increases the risk of cardiovascular morbidity and mortality. 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. Such consequences are compensatory hyperinsulinemia,  $\beta$  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.

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. 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  $\alpha$  (TNF- $\alpha$ ), interleukin 6 (IL-6) and metalloproteinases (MMPs). 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  $\gamma$  (PPAR $\gamma$ ).

Transcription factors and coactivators, including PPAR $\gamma$  coactivator-1 are crucial in mediating insulin resistance and accelerating vascular wall inflammation, and represent promising therapeutic targets. New pharmacological strategies include dual PPAR $\alpha/\gamma$  agonists, drugs with pleiotropic effects or combination therapies.

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,  $\beta$  cell dysfunction and vascular wall damage. 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.

*Address for correspondence:*  
Professor Christodoulos Flordellis  
University of Patras  
E-mail: flordell@med.upatras.gr

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