Carta al Editor

Insulin resistance as a central pathophysiological state in the original definition of metabolic syndrome

Resistencia a la insulina como estado fisiopatológico central en la definición original del síndrome metabólico

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Dear Director:

The recent article by *Dr. Brito Cando* et al.[1] constitutes an excellent and relevant investigation focused on determining the prevalence of metabolic syndrome in one of the provinces of the Andean population of Ecuador. In addition, it focuses on a multifactorial clinical entity that today constitutes a real non-communicable chronic pandemic the Metabolic Syndrome. Even though the originality and importance of this research, it is striking that throughout the work, insulin resistance has not been mentioned at any time, being it a central pathophysiological state in the original definition of metabolic syndrome.[2]

This Letter to the Editor thus rescues Insulin Resistance as a central concept of Metabolic Syndrome from a brief historical perspective and an updated look.

It was in 1988 that Dr. Gerald M. Reaven (1928-2018), a renowned endocrinologist and scholar at the Department of Medicine at Stanford University, defined, in a *Banting Lecture*, the Syndrome X,[2] later named Insulin Resistance Syndrome and finally termed as Metabolic Syndrome. Reaven characterized this clinical entity as a conjunction of conditions that occur in the individual: Resistance to insulin-stimulated glucose uptake, glucose intolerance, hyperinsulinemia, increased very-low-density lipoprotein triacylglycerols, decreased high-density lipoprotein cholesterol, and hypertension.[2]

As Reaven put it in his classic article, the common feature of the proposed syndrome is insulin resistance, and all other changes are likely secondary to this primary abnormality.[2]

How can we define Insulin Resistance in more detail? Insulin is a critical peptide hormone for energy homeostasis secreted by pancreatic beta cells in response to high glycaemia. It exerts its anabolic effects by inhibiting hepatic lipolysis and gluconeogenesis while increasing glucose uptake in the liver, muscles and adipose tissues.[3] In the last four decades, much research has resulted in a precise understanding of the insulin signaling system, which mediates its physiological activities. Insulin Resistance is a condition defined as a state in which a normal concentration of insulin produces an attenuated biological effect in terms of glucose homeostasis, decreasing the ability of this hormone to exert its biological actions in typical targets such as skeletal muscle, liver or adipose tissue.[4]

A popular theory is that insulin resistance origins from a defect in one or more of its molecular signaling components.[3] With its consequent compensatory hyperinsulinemia, insulin resistance is a risk factor for multiple pathologies, such as type 2 diabetes, hypertension, glucose intolerance, obesity, polycystic ovary syndrome,[5,6] endometrial dysfunction, acanthosis nigricans, fibrinolytic coagulation defects, dyslipidemia, atherosclerosis, and cognitive disorders[4] (fig.).

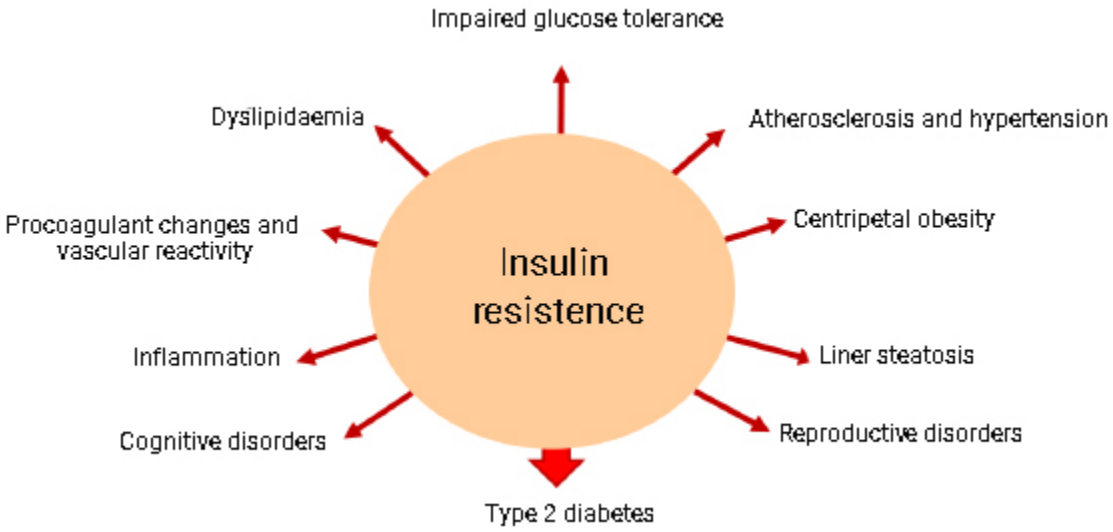

Fig. - Insulin resistance and its comorbidities

The results of several investigations[4,5,6] in the last decades have shown that there is heterogeneity within the population concerning insulin resistance, *i.e.*, that there are subpopulations, subgroups or clusters among people affected with insulin resistance, which has been much more evident in women who suffer from polycystic ovary syndrome and insulin resistance at the same time.[4,5,6] Genetic heterogeneity is likely among the general population regarding susceptibility to insulin resistance. Because of the above, it is surprising to observe that within the five criteria developed over the years for the diagnostic definitions of metabolic syndrome, blood insulin is not currently part of them since measuring this variable for large-scale detection is complicated and cumbersome in clinical practice.[7] Therefore, the diagnosis of insulin resistance includes the measurement of the levels of this hormone, which is not always an examination in routine clinical practice, although this measurement is possible, for example, with the insulin suppression test.[4] Added to the above is the fact that some authors[3] propose that only a tiny fraction of individuals with insulin resistance will develop type 2 diabetes, which is probably due to a propensity for beta cell failure in these individuals.[3] There are no current procedures to identify this susceptible subpopulation.[3] The above would then be why insulin resistance was displaced from the diagnostic criteria of metabolic syndrome.

Notwithstanding the aforementioned facts, insulin resistance, chronic inflammation, and neurohormonal activation seem to continue as essential players among the mechanisms proposed in the progression of metabolic syndrome and its subsequent transition to cardiovascular disease and type 2 diabetes.[7]

Finally, we conclude that insulin resistance was a necessary condition in the historical definition of the current metabolic syndrome and that, over time, it was relegated given the complications of adequately determining the insulin level in clinical practice. Nevertheless, we must not forget to focus on it since years ago was proposed that humankind would suffer from hyperinsulinemia pathologies at a global level,[8] a prediction that two decades later has proven to be entirely accurate.

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Conflict of interest statement

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