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Obesity in diabetes mellitus: a great danger to the heart and life

Obesidad en la diabetes mellitus: un gran peligro para el corazón y la vida

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To the Editor,

It is with concern and regrettable foresight that I turn to you, seeing that the comorbidity of obese patients is becoming an epidemic. It is no longer only obesity that is of concern, but also the changes of all kinds that take place in organ structure and function −including the cell− that pose a great danger to the heart and life.

In an article referring to coronary microcirculation and the clinical-epidemiological variables found in 117 diabetic patients with myocardial infarction and normal coronary arteries, a significant prevalence of overweight (19.7%) and obesity (80.3%)[1] was observed. This takes place despite the new drugs available for glycemic control and the maintenance of acceptable, even normal, glycosylated hemoglobin parameters. The sodium-glucose cotransporter-2 (SGLT-2) inhibitors, empagliflozin and canagliflozin and the GLP-1 (glucagon-like peptide-1) receptor agonists, liraglutide and semaglutide; have decreased the risk of cardiovascular death, myocardial infarction and stroke, once they were added to the

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therapeutic protocols for patients with type 2 diabetes mellitus[1-3]. Many of these patients have overweight or obesity, which multiplies their risk of complications and adverse events during their lifetime[4,5].

Obesity is one of the major health burdens of the 21st century, since it contributes to the increasing prevalence of its related comorbidities, including insulin resistance and type 2 diabetes[3-6]. Growing evidence suggests a critical role of over-nutrition in the development of chronic inflammation, which –in adipose tissue– is considered a crucial risk factor for the development of insulin resistance and type 2 diabetes in obese individuals[3-4].

Obesity-induced adipocyte hyperplasia and hypertrophy provide a lot of intrinsic and extrinsic signals capable of triggering an inflammatory response[6,7] and, consequently, dysregulation of fatty acid homeostasis, increased adipose cell enlargement and cell death, as well as local hypoxia, mitochondrial and endoplasmic reticulum (ER) dysfunction and mechanical stress[8-11]. In obese individuals, immune dysregulation in this tissue results in chronic low-grade inflammation, characterized by increased infiltration and activation of innate and adaptive immune cells[3]. Macrophages are the innate immune cells that most abundantly infiltrate and accumulate in the adipose tissue of obese individuals, constituting up to 40% of all adipose tissue cells in these patients. In obesity, adipose tissue macrophages are M_1-polarized (pro-inflammatory) and secrete many pro-inflammatory cytokines (alpha tumor necrosis factor [TNF-α] and interleukin [IL-1β]), capable of altering insulin signaling, thus promoting the progression of insulin resistance. In addition to macrophages, many other immune cells, such as dendritic cells, mast cells, neutrophils, and B and T cells, reside in adipose tissue during obesity. All of them play an important role in the development of inflammation at that level and the insulin resistance. The association of obesity, adipose tissue inflammation and metabolic diseases makes inflammatory pathways an attractive target for the treatment of metabolic complications related to this disease[3-6].

Among the molecular mechanisms responsible for obesity-induced adipose tissue inflammation and progression to associated comorbidities are JAK/STAT (Janus kinases/signal transducers and activators of transcription) signaling in peripheral metabolic organs that modulates a multitude of metabolic processes including adiposity, energy expenditure, glucose tolerance and insulin sensitivity[3-6]. This signaling pathway mediates the action of several hormones that have deep effects on the development and function of adipocytes; which, in turn, also produce hormones that use this pathway. The expression of several STAT is modulated during adipogenesis, and additional functions of JAK/STAT signaling in adipocytes include transcriptional regulation of genes involved in insulin action and lipid and glucose metabolism. Janus kinase 2 (JAK2) proteins are essential for signaling through growth hormone and leptin receptors, and not surprisingly they also play a role in lipid accumulation in obesity, which triggers an inflammatory response with increased secretion of several inflammatory cytokines. Such molecules can also activate JNK (c-Jun N-terminal kinase) and transcription factor NF-κB (nuclear factor enhancer of activated B-cell kappa light chains) signaling pathways in liver and skeletal muscle, thereby inhibiting systemic insulin signaling; important roles in the control of adipose tissue function[7-11].

As discussed above, obesity is associated with the recruitment of M_1-polarized macrophages, which secrete pro-inflammatory cytokines and are associated with the development of insulin resistance. However, this inflammation in response to obesity is not identical to the classic M_1 activation state observed in inflammation associated with acute infection, therefore, it has been named metabolic activation or "Me", rather than M_1[9-11]. All these mechanisms are commonly considered the link between the chronic caloric excess and the inflammation of adipose tissue.

Moreno-Martínez[12] defines obesity as the excess of adipose tissue produced by the progressive accumulation of fat in its reservoirs, due to an imbalance in caloric homeostasis where intake exceeds energy expenditure; but, evidently, its repercussions go much further, since its association –even its causal relationship– with type 2 diabetes mellitus, high blood pressure and dyslipidemia is undeniable, all of which significantly increases the risk of cardiovascular and cerebrovascular disease.

Ortega *et al.*[13] state that the prevalence of this disease has increased worldwide in the last decades. In 2013 it exceeded the 50% of the adult population in some countries in Oceania, North Africa and the Middle East; and although in North America (30%) and Western Europe (20%) this prevalence was lower, it still reached alarmingly high levels. This is why

obesity is considered a health problem that affects the heart and other organs of the body because it triggers metabolic disorders with repercussions beyond the adipocyte and favors the appearance of disabling structural and functional damage, mainly cardiovascular, where the patient passively awaits his or her disability or death if he or she does not prevent or solve this disease that afflicts humanity. For this reason, the lack of awareness of patients and health professionals, both in Cuba and in other countries of the world, is a cause for concern. If action is not taken at all levels of heart care (primary, secondary and tertiary) to prevent or solve this situation from an early age, the patient with obesity will become a heart patient, with diabetes mellitus, dyslipidemia, circulatory and respiratory disorders, and with biopsychosocial problems, which will have disabling effects, and where sudden death is several times more frequent than in a healthy person[14].

CONFLICT OF INTERESTS

None declared.

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