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COMMENTARY

Hypertension and diabetes incidence: confounding factors

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Multimorbidity, defined as the coexistence of two or more chronic diseases, is a common phenomenon. Numerous efforts to establish a standardized instrument to assess the level of multimorbidity have failed until now, and indices are primarily characterized by their high heterogeneity. This problem is ever more relevant, considering the increasing age of the general population and therefore the simultaneous development of more diseases.

Hypertension (HTN) and type 2 diabetes are both common chronic conditions that affect a large proportion of the general adult population. They tend to occur in the same individual, suggesting common predisposing factors, which can be genetic or environmental.[1] This makes it very difficult to correctly evaluate their physiopathological interactions, and in particular, the predictive role of HTN in relation to diabetes incidence, as suggested from some contrasting preclinical and epidemiological evidences.

For instance, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm, in which 19 257 patients were enrolled, systolic blood pressure was one of the main predictors of diabetes.[2] However, in the large Valsartan Antihypertensive Long-term Use Evaluation trial, in which 9995 patients were enrolled with 1298 cases of incident diabetes, HTN was not a significant predictor of diabetes.[3]

The physiopathological link between HTN and diabetes in lean subjects primarily involves the renin–angiotensin–aldosterone system (RAAS). This hypothesis is supported by numerous preclinical tests and by the results of some large clinical trials. Different antihypertensive treatments seems to have different impacts on diabetes incidence, and in particular, the RAAS modulating agents appear to have a protective role against diabetes development.[2–4]

It is also possible that common genetic patterns could influence both HTN and diabetes incidence. The environmental causes of these diseases are actually well known. In fact, obesity and physical activity are the two leading factors that predispose individuals to both diseases. Individuals with abdominal obesity are likely to develop lipid abnormalities and elevations in blood pressure and glucose levels. Overweight, increased blood pressure and dysglycemia are the three main components of the metabolic syndrome, which is well known as a highly prevalent predictor of both HTN and diabetes.

In this context, the study by Lee *et al.*[5] published in the current volume of *Hypertension Research* addresses a very relevant issue. The authors evaluated the influence of different components of the metabolic syndrome on the predictive role of blood pressure with respect to type 2 diabetes. Beyond some limitations of the study (that is, the lack of data about the type of antihypertensive drugs used by the patients and the diabetes diagnosis made on the basis of basal glycemia), the main result is that the predictive role of HTN in the context of diabetes disappears after adjustment for baseline body mass index and fasting glucose levels. This observation is perhaps in agreement with the data published previously on Caucasian subjects.[6]

It is well known that obesity is a primary risk factor for both dysglycemia and diabetes, and relatively obvious that fasting plasma glucose is a risk factor for diabetes. Adipose tissue may have a main role in this context. Despite the historical definition of white adipose tissue as 'a mass primarily responsible for energy storage and isolation', today with increasing knowledge of the physiology and pathophysiology of obesity, it is appreciated as an important endocrine organ producing diverse groups of cytokines and other biologically active molecules. A tentative and simplified classification of the active molecules produced by fat tissue is presented in Figure 1.[7]

Adiponectin is one of the most studied proteins secreted by adipose tissue. Unlike other adipocytokines produced by adipose tissue, adiponectin appears to have anti-inflammatory, anti-diabetic and anti-atherogenic properties. Although secreted solely by adipose tissue, plasma levels of adiponectin are generally negatively related to total adipose mass, with higher plasma adiponectin levels in lean individuals and lower adiponectin levels in obese individuals. Plasma concentrations of adiponectin are lower in patients with insulin resistance compared with insulin-sensitive patients and lower in patients with diabetes compared with non-diabetics. A similar inverse relationship of plasma adiponectin level has been reported with HTN, blood pressure level and albuminuria. Therefore, an imbalance in adiponectin synthesis, strongly related to body mass index, could be a relevant determinant of incident diabetes.[8] Another key player in the adipose tissue regulation system is leptin, which is now recognized as the mandatory afferent signal in the maintenance of weight homeostasis. Leptin insufficiency in the hypothalamus due to the diminished transport of leptin across the blood–brain barrier imposed by environmental causes, such as consumption of energy-enriched diets and diminished energy expenditure, orchestrates unregulated fat accrual and the attendant

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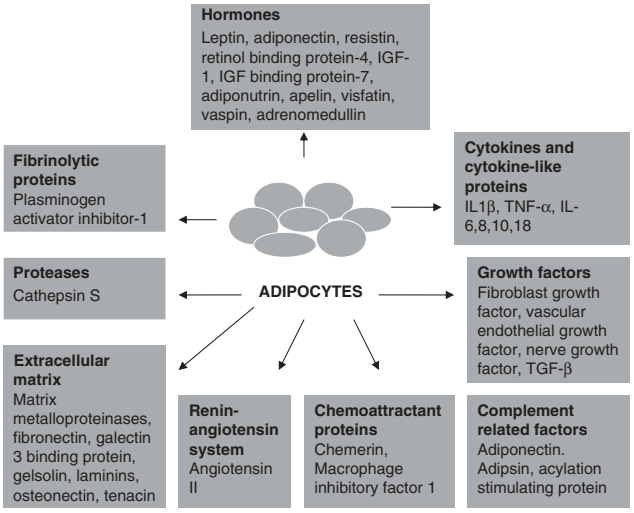

Figure 1 Families of molecules directly or indirectly produced by adipose tissue with known autocrine, paracrine or systemic actions. IGF-1, insulin-like growth factor-1; IL, interleukin; TGF-β, transforming growth factor-β.

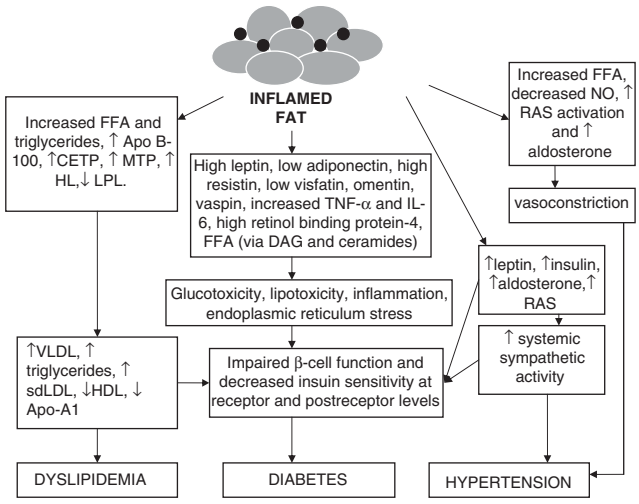

Figure 2 Adipokine involvement in the pathogenesis of diabetes, hyperlipidemia and hypertension in obese subjects. HDL, high-density lipoprotein; IL, interleukin; LDL, low-density lipoprotein; TGF-β, transforming growth factor-β; VLDL, very low-density lipoprotein.

disease cluster of metabolic syndrome and thus of type 2 diabetes.[9] However, the system is much more complex and involves a large number of interconnected molecular pathways. For instance, recent studies also propose a paracrine role for periadventitial adipose tissue in the control of arterial vascular tone. This regulation depends on the anatomical integrity of the vessels and involves adipokines released from either periadventitial adipocytes or perivascular adipose tissue. Although a number of adipokines with vasoactive properties have been identified, a still unidentified adipocyte-derived relaxing factor (ADRF) has a major role in the periadventitial vasoregulation of visceral arteries, such as the aorta and mesenteric arteries. ADRF is released by periadventitial adipocytes and primarily produces endothelium-independent vasorelaxation by opening voltage-dependent (K(v)) K(+) channels in the plasma membranes of smooth muscle cells. At least in part, KCNQ (K(v) 7) channels may represent the subtype of K(v) channels involved. Glibenclamide-sensitive K(ATP) channels either are not involved or have a minor role. Alterations in the paracrine control of arterial tone by periadventitial adipose tissue have been found in animal models of HTN and metabolic disease.[10]

All of these physiopathological data indirectly support the observation of Lee *et al.*[5] with respect to the primary role of obesity and consequently of the dysregulation of adipokine synthesis, as a determinant of insulin resistance and incident type 2 diabetes. In obese subjects, so-called fat inflammation induces a large number of biochemical events that interact at a systemic level in inducing dyslipidemia, HTN and finally diabetes (Figure 2). However, limited data are available to support the role of HTN as a type 2 diabetes predictor in lean and normo-glycemic subjects. In conclusion, the data of Lee *et al.* suggest that the attention of public health experts and national institutes of health must concentrate on preventive campaigns to prevent overweight through organized and well-defined changes in dietary and physical activity habits to prevent type 2 diabetes, among numerous other obesity complications.

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