Continuing Medical Education

PATHOPHYSIOLOGY OF TYPE 2 DIABETES

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ABSTRACT

Type 2 diabetes mellitus is a heterogeneous syndrome characterized by abnormalities in carbohydrate and fat metabolism. The causes of type 2 diabetes are multifactorial and include both genetic and environmental elements that affect beta-cell function and tissue (muscle, liver, adipose tissue, pancreas) insulin sensitivity. Although there is considerable debate as to the relative contributions of beta-cell dysfunction and reduced insulin sensitivity to the pathogenesis of diabetes, it is generally agreed that both these factors play important roles. However, the mechanisms controlling the interplay of these two impairments are unclear. A number of factors have been suggested as possibly linking insulin resistance and beta-cell dysfunction in the pathogenesis of type 2 diabetes. A majority of individuals suffering from type 2 diabetes are obese, with central visceral adiposity. Therefore, the adipose tissue should play a crucial role in the pathogenesis of type 2 diabetes. Although the predominant paradigm used to explain this link is the portal/visceral hypothesis giving a key role in elevated non-esterified fatty acid concentrations, two new emerging paradigms are the ectopic fat storage syndrome (deposition of triglycerides in muscle, liver and pancreatic cells) and the adipose tissue as endocrine organ hypothesis (secretion of various adipocytokins, i.e. leptin, TNF-α, resistin, adiponectin, implicated in insulin resistance and possibly beta-cell dysfunction). These two paradigms constitute the framework for the study of the interplay between insulin resistance and beta-cell dysfunction in type 2 diabetes as well as between our obesogenic environment and diabetes risk in the next decade.

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Over the last decade, major advances have been made in our understanding of the pathophysiology and molecular biology of type 2 diabetes (1,2). Type 2 diabetes is a bipolar disease characterized by a defect in both insulin secretion and insulin action whose complex interaction leads to a progressive increase of plasma glucose levels (3). It is also well established that the development of type 2 diabetes results from an interaction of a subject's genetic makeup (4) and their environment, and that with the increasing prevalence of obesity, the prevalence of type 2 diabetes is reaching epidemic proportions (5) (Figure 1). Various organs play a crucial role in the pathophysiology of type 2 diabetes. Disruption of the cross-talk between endocrine pancreas, liver, skeletal muscle, adipose tissue and, presumably, gut and central nervous system may lead to alteration of glucose homeostasis and type 2 diabetes (Figure 2) (6,7).

While most patients with type 2 diabetes are overweight or obese (5), the role of fat was initially neglected in the pathophysiology of the disease (6). Its role was highlighted almost a decade ago, especially the interactions of non-esterified fatty acids (NEFA) with glucose metabolism (7). The crucial impact of fat distribution, especially the negative influence of intra-abdominal or visceral fat depot, is now largely recognized (8). More recently, the deleterious role of ectopic triglyceride storage in the development of defective insulin action and insulin secretion has been emphasized leading to

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