

HOSPITAL PHYSICIAN®

ENDOCRINOLOGY BOARD REVIEW MANUAL

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The *Hospital Physician Endocrinology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in endocrinology. Each manual reviews a topic essential to the current practice of endocrinology.

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Insulin Secretory and Insulin Resistance Defects in Type 2 Diabetes Mellitus

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Insulin Secretory and Insulin Resistance Defects in Type 2 Diabetes Mellitus

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INTRODUCTION

Type 2 diabetes mellitus (DM) accounts for at least 85% to 90% of all cases of diabetes in the United States.¹ In recent decades, the number of people in the United States and throughout the developed world affected by type 2 DM has steadily climbed to the point of an epidemic, placing a staggering clinical and economic burden on modern society. The estimated worldwide prevalence of type 2 DM in 2001 was 150 million, and it has been estimated that this number may double by 2025.² Fueling the diabetes epidemic is the rising incidence of obesity, food intake hypercaloric with regard to metabolic need, and sedentary lifestyle. These environmental factors play a contributory role in the development of type 2 DM, influencing expression of disease in genetically predisposed individuals.

Type 2 DM is a disease of complex pathogenesis, with a typically subtle onset and an inexorably slow progression. The study of the natural history of type 2 DM is complicated by the disease's insidious, often asymptomatic onset and the fact that the most common inheritance pattern is polygenic. Nevertheless, the natural history has been mapped on a population basis and in susceptible families to the extent that we can define both subtle early defects and phenotypes at risk for type 2 DM. This allows identification of high-risk individuals who should be targeted for therapy early after the onset of disease—or even prior to disease onset, so as to delay or prevent the emergence of type 2 DM. Fortunately, an increasing array of pharmacotherapy options targeting specific pathophysiologic defects are available to help combat type 2 DM.

Despite the typically multifactorial inheritance, all forms of type 2 DM are defined by fasting and/or postprandial hyperglycemia caused by 2 definable defects: subnormal responsiveness to insulin (insulin resistance) in key sites of glucose homeostasis (including skeletal muscle, adipose tissue, and the liver) and an insulin secretory defect preventing otherwise compensatory insulin hypersecretion. Which of these defects comes first

has been a topic of debate for several decades. Most of the available evidence favors the view that the ultimate triggering event is impaired insulin secretion, which, when superimposed on a background of impaired insulin action (insulin resistance), leads to overt type 2 DM. Neshet et al³ demonstrated that insulin resistance is neither necessary nor sufficient for the development of type 2 DM but, rather, that defective insulin secretion is the primary defect responsible for unmasking overt diabetes. Specifically, the study showed that while most patients with type 2 DM had some degree of insulin resistance, there were patients with a confirmed diagnosis of diabetes who had no evidence of insulin resistance. These individuals remained normoglycemic by compensating for the reduction in insulin sensitivity with increased insulin secretion.³ Therefore, insulin resistance alone is insufficient to cause type 2 DM. The development of overt type 2 DM must involve a defect in insulin secretion at the level of the beta cell that prevents compensatory insulin hypersecretion.

This manual is the first of a 2-part review of well-defined as well as newly identified pathogenetic mechanisms in type 2 DM. This half of the review examines in further depth the roles played by the dual defects of impaired insulin secretion (beta cell dysfunction) and subnormal insulin action (insulin resistance) and highlights the clinical implications of these defects. The discussion continues in the next manual with a review of the evolving knowledge of how gut-derived peptides (incretins) and adipocyte-derived cytokines (adipokines) influence insulin secretion and action in type 2 DM.

NORMAL GLUCOSE HOMEOSTASIS

GLUCOSE SOURCES AND PRODUCTION

The serum glucose concentration represents the net sum of glucose entering the circulation from endogenous or exogenous sources minus glucose removed from the circulation for storage or utilization (**Figure 1**). Exogenous glucose is derived solely from dietary food