

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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Use of Insulin in Type 2 Diabetes: When Maximal Oral Therapy Fails

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Use of Insulin in Type 2 Diabetes: When Maximal Oral Therapy Fails

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INTRODUCTION

Evidence suggests that type 2 diabetes is diagnosed 4 to 7 years after the onset of glycemic changes capable of causing microvascular complications.¹ Unfortunately, most patients do not achieve or maintain recommended target levels of glycemia on usual care. Furthermore, the traditional management approach is to wait until one treatment regimen is failing before adding another agent or intensifying therapy. This holds true for the use of insulin, which is often seen as the treatment of last resort.

Among the many lessons revealed by the United Kingdom Prospective Diabetes Study (UKPDS) is a dark aspect of the natural history of type 2 diabetes: gradual failure of therapy over time correlating with a decline in insulin secretion and an increase in plasma glucose concentration.^{2,3} UKPDS participants required progressively more intensive therapy, including insulin in many cases, to attain or approximate the treatment goal. After 6 years of antihyperglycemic monotherapy, approximately 55% of patients were able to attain glycosylated hemoglobin (HbA_{1c}) levels below 7%, but by 9 years only 24% were able to do so.⁴ Most practitioners with sufficient longitudinal experience treating patients with type 2 diabetes can relate to this problem of progressively treatment-resistant hyperglycemia and can be comforted that their experience is affirmed by the UKPDS.

PATHOGENETIC MECHANISMS IN TYPE 2 DIABETES

A brief review of the pathogenetic mechanisms of type 2 diabetes may shed light on why progressive therapeutic failure is so often encountered. The pathogenesis of type 2 diabetes is characterized by variable expression of 2 major defects: impaired insulin secretion and impaired response to the action of insulin (insulin resistance).⁵ Complex genetic factors involving the function of muscle, adipose, and islet cells dictate susceptibility to type 2 diabetes, but lifestyle and other factors that promote obesity appear to influence disease expression. Clearly, all obese individuals are not destined to become diabetic; however, obesity is associated with insulin resis-

tance, and the presence of obesity appears to increase the degree of expression of diabetogenic genetic factors.⁶ Studies in lean children of patients with type 2 diabetes have identified abnormalities in muscle mitochondrial function, excessive myocyte fatty acid accumulation, and reduced glucose phosphorylation, underscoring the genetic aspect of insulin resistance.⁷

One distinction between the insulin resistance of simple obesity and that of obesity associated with type 2 diabetes is that in simple obesity, hypersecretion of insulin provides full metabolic compensation for insulin resistance. In type 2 diabetes, insulin hypersecretion gradually falters, and in the continued presence of impaired insulin action the net result is hyperglycemia. In longitudinal studies of groups at high risk for type 2 diabetes (eg, Pima Indians), sequential oral glucose tolerance tests have demonstrated fasting and postprandial hyperinsulinemia prior to any abnormality in fasting or postprandial glycemia.⁸ In these studies, impaired glucose tolerance was accompanied by a declining response of insulin secretion to feeding, and overt diabetes was heralded by further blunting of meal-induced insulin response and the appearance of fasting hyperglycemia.⁹ When Pima Indians with declining glucose tolerance were compared with weight-matched subjects with normal glucose tolerance, insulin-stimulated glucose disposal declined in both groups over time; however, absolute insulin secretory capacity declined in those who developed diabetes but increased (to compensate for insulin resistance) in the nondiabetic controls.¹⁰

The concepts of *glucotoxicity* and *lipotoxicity* have evolved in recent years as explanations for the progressive decline in insulin secretion and insulin action. Glucotoxicity relative to the pancreatic beta cell may be attributable to impaired proinsulin cleavage into C peptide and bioactive insulin.¹¹ Alternatively, beta cell dysfunction may be reflected by impaired secretion and resultant accumulation of amylin in pancreatic islets.¹² Lipotoxicity may involve a shift in adipocyte gene products from a cytokine that amplifies insulin secretion and insulin responsiveness (adiponectin) to one that impairs insulin secretion (eg, tumor necrosis factor- α).¹³ Also,