

Introduction

Diabetes affects ~17 million people in the United States and is projected to double by 2025. This increase is due primarily to the epidemic of obesity with the concomitant metabolic syndrome, which includes insulin resistance, hypertension, and hyperlipidemia. Diabetes translates into increased rates of vascular disease, both microvascular and macrovascular. It is the impact of these complications that affects the lives of our patients and adds tremendously to health care costs. For these reasons, this issue of **Clinical Cornerstone**[®] has been dedicated to a discussion of the major complications of diabetes and their treatment.

In the opening article, Ralph Rabkin, MD, discusses diabetic nephropathy. Diabetes and hypertension are the predominant causes of end-stage renal disease, and the incidence of this complication is increasing. Numerous factors are involved at both the molecular and cellular levels and in the future may contribute to our understanding of the disease process as well as offering potential for new drug targets. A number of fairly straightforward laboratory tests enable the physician to identify early nephropathy, such as measuring levels of microalbuminuria in patients who lack evidence of proteinuria. Once early nephropathy is identified in the diabetic patient, it is probably wise to consult a specialist who will advise on the best form of therapy, including such agents as angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, which have been shown to be useful as antihypertensive agents and in slowing the progression of the nephropathy.

Next, Professor Susan Lightman, FRCP, and Hamish M. A. Towler, MD, discuss diabetic retinopathy. There is undeniable evidence from trials such as the Diabetes Control and Complications Trial (DCCT) that tight glycemic control prevents the progression of retinopathy. Although this is achievable in many type 1 diabetics with multiple

daily insulin injections and in type 2 diabetics with combinations of oral agents and insulin, glycemic control is not always achieved and the progression of retinopathy is still seen in many patients. Since diabetes is the leading cause of blindness in the industrialized countries, it beholds the physician to routinely examine the diabetic patient's eyes or to refer the patient to an ophthalmologist for screening on an annual basis. Once retinopathy has been discovered, the ophthalmologist should continue with follow-up and treatment such as laser therapy, a very powerful modality.

Both the diabetic patient (particularly the type 2 diabetic patient) and the patient with the metabolic syndrome are prone to cardiovascular complications. The etiology of this disorder is multifactorial. As Alan J. Garber, MD, PhD, points out in his article, hyperglycemia, hypertension, and hyperlipidemia are well-known risk and treatable factors. On the other hand, it is becoming increasingly clear from recent studies and clinical testing that other factors affect the macrovascular disorder associated with diabetes. Changes in the endothelial cell and vascular smooth muscle cells, C-reactive protein, and increased type-1 plasminogen activator inhibitor levels, for example, will become more important as we begin to understand their roles and how to treat them individually or collectively. Meanwhile, we can influence macrovascular complications by using the standard forms of prevention.

Aaron I. Vinik, MD, covers a very important and difficult topic, namely the diabetic foot and neuropathy. Today, quite an extensive body of experimental evidence explains the mechanisms involved in the causation of diabetic neuropathy, although there are few effective therapies for the underlying pathology. On the other hand, numerous medications are available that can treat the symptoms. One of the most important procedures that the physician can undertake at very low cost is to

examine the feet of every diabetic patient at every visit! As emphasized by Dr. Vinik, this simple procedure can prevent the progression of foot ulcers, which lead eventually to gangrene.

In the final article, Professor Greet Van den Berghe, MD, PhD, demonstrates the value of using insulin in the critically ill patient. Many patients admitted to intensive care units have hyperglycemia due to the severe stress of their current illness; some are most likely diabetic whereas others may turn out to be nondiabetic. Nevertheless, the presence of hyperglycemia probably has serious consequences on many fundamental processes that can affect the outcome of their present illness. Insulin usage has been shown to reduce morbidity and mortality and to improve glycemic control. While the mechanisms that allow insulin therapy to have this dramatic effect will require intensive ongoing clinical and basic studies, this article highlights a revolutionary idea and suggests to physicians that

they should be aware of this modality for in-patient care with its remarkable outcomes.

Although these articles emphasize the pathogenesis and therapy of diabetic complications that are devastating to patients, it should be emphasized that many of these complications can be prevented or delayed by the judicious use of appropriate medications to control blood glucose, lipids, and blood pressure. Blood glucose control is more easily achievable today with combinations of oral agents, combinations of oral agents and insulin, and with the new insulins that allow flexible regimens. Both fasting and postprandial glucose levels need attention and can be dealt with using the available medications. At the same time, avoidance of hypoglycemia is critical to maintain patient compliance with intensive insulin regimens.

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