Insulin in The Early Management of Diabetic Complications

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Abstract

Improved glycemic control reduces microvascular complications in both type 1 and type 2 diabetes. Macrovascular complications predominate in type 2 diabetes, and the effect of tight control here is less clear. Treatment of other aspects of insulin resistance (BP, lipids) significantly reduces cardiovascular morbidity and mortality in type 2 diabetes. Insulin therapy has favorable effects on endothelial function and lipids, especially compared with sulfonylureas. More information is needed on the effects of diabetes pharmacotherapy on cardiovascular outcomes.

The prevalence of diabetes mellitus has been increasing worldwide in recent decades, and further increases are projected for the foreseeable future. This trend is most evident in South Asia, in the Pacific, and in the Caribbean as high fat diets and sedentary lifestyles encroach on traditional cultures. For example, a recent study suggests that the prevalence of diabetes in India will double over the next 25 years.1

The public health impact of the increase in diabetes is potentially enormous because of the high incidence of complications of diabetes. These complications include retinopathy, nephropathy, neuropathy and macrovascular disease. The consequences of diabetic complications include blindness, renal failure, amputation, myocardial infarction and stroke; these problems are responsible for erosion of quality of life and productivity, as well as significant mortality. In the NHANES study in the USA, for example, a diagnosis of diabetes confers a 30-50% decrease in survival over 10 to 20 years (Fig. 1).2

In patients with type 2 diabetes, who represent the majority (90-95%) of diabetic cases in most countries, atherosclerotic complications are responsible for 50-70% of deaths (Fig. 2).2 These complications include myocardial infarction, stroke and peripheral vascular disease, and are thought to be less specific for hyperglycemia than microvascular complications because they occur at increased frequency in individuals with insulin resistance who do not have diabetes, and are also associated with hypertension and dyslipidemia - elements of the insulin resistance syndrome that are often present in diabetic individuals. The risk of myocardial infarction and cardiovascular death is increased two- to four-fold in diabetic patients.3

Some studies suggest that microvascular complications such as retinopathy and nephropathy are less prevalent in type 2 diabetes than in type 1 diabetes. The cumulative incidence of both retinopathy and nephropathy may be as much as 50% lower in type 2 diabetic individuals.4,5 Nonetheless, the public health impact of these microvascular complications should not be underestimated considering that individuals with type 2 diabetes are so much more numerous than those with type 1 diabetes.

Although the complications of diabetes have been recognised for over a century, for many years there was controversy regarding the relationship between hyperglycemia and those complications. Early studies suggested that diabetic complications had a genetic basis and were therefore not amenable to treatment. Because of this controversy, two major studies were initiated between 1975 and 1985 to investigate the effect of treatment on outcomes. These studies were made possible by improvements in treatment, including improved pharmacological agents and the availability of self-monitoring of blood glucose and glycated hemoglobin measurements. The Diabetes Control and Complications Trial (DCCT) was conducted in the USA and Canada and demonstrated that intensive treatment of type 1 diabetes significantly reduced the incidence and progression of retinopathy, nephropathy and clinical neuropathy compared to conventional treatment.6 This was not achieved without cost; there was a two- to three-fold increase in severe hypoglycemia in the intensively treated patients. On the other side of the Atlantic, the United Kingdom Prospective Diabetes Study, which was reported 5 years after the DCCT,
reported similar findings in type 2 diabetic patients treated intensively with insulin or sulphonylureas. These two landmark studies together have firmly established a rationale for aggressive glycemic control in patients with diabetes mellitus. (Fig. 3)

Although enormous progress has been made in the development of new oral agents for type 2 diabetes, insulin remains a mainstay of treatment. It has been estimated that 40% or more of type 2 diabetic individuals in North America require insulin. (Fig. 4) Either as monotherapy or in combination with oral agents such as metformin or thiazolidinediones. (Fig. 5) There has also been improvement in the insulins available for use. Human insulin became available almost 20 years ago, and since that time, its formulations have improved. More recently, synthetic insulin analogues have appeared, including short acting agents such as aspart and lispro insulins, and long acting analogues such as insulin glargine. (Fig. 6) These agents have made it possible to more closely simulate normal insulin secretory physiology in patients with type 1 diabetes. The standard of care in the management of type 1 diabetes in many countries is a “basal-bolus” regimen consisting of a preprandial bolus of soluble insulin and basal insulin delivered either as a single injection or via continuous subcutaneous insulin infusion. The role of the new “designer” insulins in the management of type 2 diabetes is still unclear, although reports have appeared suggesting that their use is associated with less hypoglycemia than traditional preparations.

Much remains to be learned about the use of insulin in type 2 diabetes. A review of the history of insulin use is enlightening; it indicates that in almost every respect, the regimens that are used, especially in type 2 diabetes, have not been subjected to rigorous scientific evaluation. In the era prior to the availability of depot insulins, Regular (soluble) insulin was injected four times a day, and a bedtime snack was not recommended. Subsequently, Hagedorn reported the synthesis of protamine zinc and NPH insulins, and by the early 1950s, authorities were recommending a daily morning injection of PZI with three insulin injections are probably necessary, at least in patients achieving truly satisfactory glycemic control, twice daily insulin injections are probably necessary, at least in patients with sulfonylurea failure.

It is noteworthy that Lawrence proposed an insulin regimen consisting of one injection of PZI with three preprandial injections of regular insulin in an attempt to simulate physiological insulin secretion within one year of the introduction of PZI insulin by Hagedorn. Lawrence proposed further that a diet plan should be formulated first, and then insulin should be given to cover it. However, his recommendation was not widely adopted; instead, non-physiological insulin regimens were implemented, then meal plans which included snacks were devised to cover the insulin. Additional studies of more physiological insulin regimens are needed in type 2 diabetic patients.

The effect of intensive insulin treatment on cardiovascular outcomes in type 2 diabetes has been disappointing. In the UKPDS, there was a 15% reduction in myocardial infarction in the intensively treated group that did not reach statistical significance. Considering that the incidence of myocardial infarction is increased ~200% in this group of patients, this result suggests that mere restoration of euglycemia will not adequately address the problem, possibly because of input from other aspects of the insulin resistance syndrome, such as hypertension and dyslipidemia. It has been clearly established that insulin and sulfonylureas, even with excellent glycemic control, do not normalise diabetic dyslipidemia or improve hypertension. In fact, sulfonylureas have vasoconstrictive properties and have been shown to interfere with ischemic preconditioning in the myocardium. (Fig. 7) On the other hand, insulin therapy has been shown to improve endothelial function in the forearm, (Figs. 8, 9) and insulin
treatment is associated with improvements in LDL cholesterol and triacylglycerol levels. Moreover, insulin given acutely in the coronary care unit was shown in the DIGAMI study to reduce mortality by 30-50%. (Fig. 10) The disappointing results of the UKPDS may indeed relate to a multifactorial pathogenesis of atherosclerotic risk. Certainly, both antihypertensive and lipid lowering agents have been shown to reduce cardiovascular events in diabetic subjects. However, it may also in part be a result of inadequate insulin treatment. Most studies of insulin therapy in type 2 diabetes have shown that 0.75-1.0 unit/kg is required to optimize glycemic control, but the intensively treated subjects in UKPDS received <0.5 U/kg.

In summary, insulin remains an effective treatment for patients with type 2 diabetes. Much remains to be learned
about the optimal use of insulin in this group of individuals, but it seems likely that future therapy will include judicious use of insulin and oral agents, often in combinations designed to produce euglycemia and improvement in other cardiovascular risk factors such as hypertension and dyslipidemia.

REFERENCES


