Preventing Long Term Complications
Implications for Combination Therapy with Acarbose

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Summary
Long term complications continue to be the major source of morbidity and mortality in patients with diabetes. Acarbose could potentially help to reduce diabetic complications if it improved glucose control, reduced lipid levels and hyperinsulinaemia. Acarbose has been shown to effectively reduce postprandial hyperglycaemia and haemoglobin A1c. This effect might be helpful in patients with insulin-dependent diabetes mellitus, as insulin injections do not provide complete control of rises in postprandial glucose levels, and in patients with non-insulin-dependent diabetes mellitus, because it simplifies the treatment programme. If improved control is shown to reduce complications, acarbose may be helpful. Although acarbose does not reduce hyperinsulinaemia, it reduces lipid levels and thus could reduce the risk of atherosclerosis.

Prevention of long term complications continues to be the major challenge in the treatment of patients with diabetes. Unfortunately, available data indicate that standard treatment methods do not significantly reduce the prevalence of complications. However, evidence strongly suggests that the major determinant of the development of long term complications is hyperglycaemia. Biochemical links between elevated blood glucose concentrations and metabolic derangements, which potentially could cause structural changes, and the complications of diabetes are well established. Recent emphasis has been on the polyol pathway (fig. 1) and protein glycosylation (fig. 2; Brownlee et al. 1988; Greene et al. 1987).

Polyol pathway: Aldose reductase is found in a variety of tissues including the retina, peripheral nerves, glomeruli, and the lens of the eye. Each of these tissues has glucose entry which is not modulated by insulin or rate-limiting for glycolysis. Hyperglycaemia leads to increased glucose in these tissues and increased polyol pathway activity. The resulting increase in sorbitol is postulated to lead to the metabolic changes illustrated in figure 1. The change in Na+/K+-ATPase activity may cause functional change such as decreased nerve conduction velocity. Over time the metabolic abnormalities could cause the structural abnormalities found in chronic diabetic complications.

Protein glycosylation: Clinicians know the usefulness of haemoglobin glycosylation to evaluate recent mean blood glucose concentrations. However, glycosylation of many other proteins also occurs as illustrated in figure 2. Most of these proteins do not have the relatively rapid turnover characteristic of haemoglobin, and advanced glycosylation products may persist for a long time. The advanced glycosylation products may modify tissue and cellular function in several ways which could contribute to diabetic complications. Defec-

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Acarbose Therapy and Diabetic Complications

Aldose Sorbitol

Glucose → Aldose reductase → Sorbitol → Sorbitol dehydrogenase → Fructose

- Increased polyol pathway activity
- Decreased nerve conduction
- Decrease in myo-inositol
- Altered phosphoinositide metabolism
- Decrease in Na⁺/K⁺-ATPase activity

Fig. 1. Postulated relationship between the polyol pathway and nerve conduction.

tive basement membrane proteins increase vascular leakage, one of the early markers of complications. Glycosylated cell matrix protein inactivates endothelium-derived relaxing factors which may contribute to hypertension. Glycosylated proteins can interact with specific receptors. For example, glycosylated low-density lipoproteins (LDL) interact with macrophages and may contribute more to atherosclerosis development than nonglycosylated LDL. Glycosylation may also act intracellularly causing direct damage to DNA.

Animal experiments have convincingly demonstrated prevention or reversal of early complications by excellent blood glucose control (Engerman & Kern 1987) and human studies have repeatedly shown a strong association between glucose control and complications (Pirart 1978). Controlled human trials comparing standard and intensive insulin treatment and their influence on diabetic complications have generally been disappointing. The recent follow-up report from the Steno Study demonstrating a reduction in the development of nephropathy is perhaps the most encouraging publication to date (Feldt-Rasmussen et al. 1991). Nonetheless, it must be concluded that the effectiveness of intensive treatment programmes in preventing chronic diabetic complications is not established (Zimmerman 1989). The results of the Diabetes Control and Complications Trial (DCCT Research Group 1987) are awaited with interest.

1. Treatment of Hyperglycaemia

If the DCCT or other studies demonstrate the value of excellent blood glucose control in reducing diabetic complications, application of the findings to all patients with insulin-dependent diabetes mellitus (IDDM) will be extremely difficult. The DCCT utilises a time intensive team approach to achieve the glucose and haemoglobin A₁c (HbA₁c) goals of the study. Each centre usually has physicians, nurses, dietitians and behaviourists, who concentrate on a small group of experimental patients. Even with this effort, results of experimental treatment in some patients are far from the goals, and the most successfully treated patients do not achieve complete normalisation of their blood glucose. In the DCCT and similar studies, excellent blood glucose control is only obtained at the price of an increased incidence of severe hypoglycaemia (Lorenz et al. 1988), the long term cost of which is not established. Clearly, current insulin treatment methods are frequently inadequate in patients with IDDM.

Several methods are being investigated to over-