ABSTRACT

Type 2 diabetes is an epidemic disorder. Although its complications can be treated, prevented, or ameliorated through tight glycemic control, it is difficult and expensive to do so. As with many epidemics, prevention is essential. In the mid 1990s, the Diabetes Prevention Program (DPP) was implemented to identify potentially safe and effective therapies that may prevent type 2 diabetes. The patient population consisted of persons at high risk for diabetes; the goal was to prevent or slow the development of type 2 diabetes in overweight persons with impaired glucose tolerance. Compared with placebo, metformin and the intensive lifestyle regimen reduced the development of diabetes by 31% and 58%, respectively. In patients older than 60 years, the lifestyle regimen resulted in a 71% reduction in the development of diabetes.

The DPP offered a novel approach to treating this epidemic. It has demonstrated that there are alternatives to this epidemic and that diabetes and its complications are not inevitable. We can stop diabetes before it develops. The question remains how to apply resources most effectively to accomplish this monumental task.

Diabetes imparts an enormous cost in human lives and in dollars. Data from 1992 attributed more than $100 billion in medical costs annually to diabetes. In other words, 15% of total healthcare expenditures were being accrued by 5% of the population. Bagust estimated the increase in diabetes over the course of the next 50 years with the general population and the working population (ages 20 through 59 years) growing at relatively slow rates. The growth in the type 2 diabetes population is predicted to far outstrip the growth of the rest of the population, increasing at a rate of more than 115%. We are facing an epidemic of a chronic degenerative disease associated with profound health problems that increase over a lifetime, and a population that will not grow at a rate sufficient to pay the costs to care for the disease and its complications.

Much of the cost of diabetes is associated with the care of both microvascular and macrovascular complications. We know from the Diabetes Control and Complications Trial (DCCT) and the Stockholm Diabetes Intervention study that intensive therapy is clearly merited for type 1 diabetes. Therapy directed at controlling glucose levels in the near-normal range profoundly reduces the development of diabetes-specific complications.

Until the completion of the United Kingdom Prospective Diabetes Study (UKPDS), it was not known whether intensive therapy to normalize glucose levels in type 2 diabetes would reduce macrovascular or microvascular complications. The UKPDS, which began approximately 25 years ago, sought to determine whether an active policy of therapy with hypoglycemic medications, aimed at normalizing glycemia, was superior to the conventional dietary policy. The second major question addressed by this study was to determine whether any medications or treatment strategies had particular advantages over others. Type 2 diabetes patients were assigned to diet, sulfonylurea, or insulin, and if they were obese, to metformin. If therapy failed, other agents were added.

The UKPDS successfully answered the first question. The hemoglobin A1c (HbA1c) levels of patients receiving intensive therapy (insulin, sulfonylurea, or metformin) were lower than those receiving conventional treatment (Figure 1). The UKPDS was able to improve the aggregate outcomes in type 2 diabetes. Intensive therapy reduced diabetes-related aggregate outcomes by 12% (P = .029); laser therapy outcomes by 29% (P = .003); and cataract extraction outcomes by 24% (P = .046). Overall, the UKPDS demonstrated the important long-term benefits of intensive therapy and established a similar association between glycemic levels and the risk for complications as in the DCCT. Managing type 2 diabetes, however, appeared to be more challenging than managing type 1 diabetes. In the UKPDS, glycemic levels rose progressively over time in the intensive treatment group, suggesting that type 2 diabetes is a progressive metabolic disorder.

The UKPDS and the Kumamoto study that preceded it corroborated the findings of the DCCT that intensive therapy reduced the development and progression of
most, if not all, diabetic complications. These studies established a metabolic goal for therapy and showed that lowering the HbA1c level provided significant long-term benefits. The lower the glycemia, the lower the risk of complications.

**Hypoglycemic Agents**

Several tools are available to assist us in lowering glycemia in type 2 diabetes, including diet, exercise, insulin, and hypoglycemic agents. In the UKPDS, it was possible to lower HbA1c levels in patients with new-onset type 2 diabetes; however, levels rose progressively over time. Maintaining lower levels proved a constant battle.

Do the new oral hypoglycemic agents contribute substantially to this battle? The glitazones, the alpha glucosidase inhibitors, and the thiazolidinediones may help to maintain lower HbA1c levels; however, lacking long-term data, we cannot be sure whether they will prevent the worsening metabolic control seen in the UKPDS.

In a study conducted by Horton et al, approximately 700 patients were randomly assigned to nateglinide, metformin, or a combination of the drugs. From a baseline HbA1c of 8.4%, nateglinide used as monotherapy lowered the HbA1c merely 0.5%. Metformin proved somewhat more effective as monotherapy. Using nateglinide plus metformin, however, lowered the HbA1c to 7%.

Aronoff et al examined the efficacy of pioglitazone as monotherapy. After maximal therapy (45 mg), the HbA1c was lowered only to 9.4% from 10.3% at baseline. The thiazolidinediones may not be as effective as the older sulfonylureas or metformin when used as monotherapy; however, when used in combination (eg, combining rosiglitazone with metformin), the HbA1c may decrease from 9% to 8% (Figure 2). Although the newer agents are useful, they may not provide the long-term answer to the worsening glycemia in type 2 diabetes.

Insulin remains an important treatment and has been used in numerous studies. Aggressive insulin therapy in all of these studies successfully lowered HbA1c levels to near 7%. Insulin clearly works. Unfortunately, physicians and patients are reluctant to use it at all or to use it in adequate doses. Insulin is often suggested to patients only after they have had diabetes for 10 or 15 years. At that time, glycemia has often been out of control for many years, and patients already have established complications.

Data from the UKPDS suggest we are at risk to lose this metabolic battle. The long-term complications of type 2 diabetes appear to be unrelenting. Macrovacular disease accounts for the majority of complications in persons with type 2 diabetes. More than 75% of people with type 2 diabetes die from cardiovascular disease.

**Prevention**

Type 2 diabetes is an epidemic disorder. Although its complications can be treated, prevented, or ameliorated through tight glycemic control, it is quite difficult and expensive to do so. As with many epidemics, prevention is essential. The rationale for a prevention trial can be summarized in 3 points:

- The prevalence of type 2 diabetes is increasing in epidemic proportions, not only in the United States, but also throughout the world.
- When type 2 diabetes develops, it is difficult to treat; it is therefore difficult to prevent resulting complications.

**Figure 2. Combination Therapy With Rosiglitazone Compared With Metformin**

![Graph showing the effect of combination therapy with rosiglitazone and metformin on HbA1c levels.](image-url)
• Prevention of type 2 diabetes would significantly reduce mortality and associated healthcare expenditures.

In the mid 1990s, the Diabetes Prevention Program (DPP) was implemented to identify potentially safe and effective therapies that may prevent type 2 diabetes.16,17 The patient population comprised persons at high risk for diabetes. Because most people who develop type 2 diabetes pass through an intermediate state of impaired glucose tolerance, such individuals were chosen as the research population. The goal of the DPP was to prevent or slow the development of type 2 diabetes in persons with impaired glucose tolerance. Eligibility was determined by having impaired glucose tolerance and being overweight.

Eligible participants were randomized to 1 of 4 regimens: intensive lifestyle therapy (n = 1079), metformin (n = 1073), placebo (n = 1082), and troglitazone (n = 585), which was discontinued in June 1998 because of safety concerns. The lifestyle intervention regimen required following an intensive program with the following goals: weight loss of 7% or more, maintenance of weight loss, and 150 minutes or more per week of physical activity. A large number of racial and ethnic groups that are affected disproportionately by type 2 diabetes were purposely included in the study population (n = 3234). We included Caucasians (55%), African Americans (20%), Hispanic Americans (16%), Asian Americans and Pacific Islanders (4%), and Native Americans (5%).

Long-term weight loss in this population had not been demonstrated in previous studies. In the DPP, however, subjects randomized to the intensive lifestyle regimen achieved their weight-loss goal (7 kg), representing more than a 7% loss of body mass. Over time, some weight was regained, resulting in an overall weight loss of 5% in 4 years. Subjects actually exercised more than recommended (30 minutes, 5 nights per week); they maintained 210 minutes of activity per week (30 minutes, 7 nights per week). Eleven percent of subjects randomized to placebo developed diabetes. Only 7.8% of subjects randomized to metformin and 4.8% of subjects randomized to the intensive lifestyle regimen developed diabetes. Compared with placebo, metformin and the intensive lifestyle regimen reduced the development of diabetes by 31% and 58%, respectively.

The DPP interventions were successfully introduced in a variety of communities, and they were effective in all of them. Metformin did not work as well in the older population, but lifestyle worked surprisingly well, resulting in a 71% reduction in the development of diabetes in persons older than 60 years. This is particularly important because 20% of the population older than 60 years develops diabetes. In the younger population, metformin and lifestyle were similarly effective in reducing diabetes.

The DPP offered a novel approach to treating this epidemic. It has demonstrated that there are alternatives to this epidemic and that diabetes and its complications are not inevitable. We can stop diabetes before it develops. The question remains how to apply resources most effectively to accomplish this monumental task.

REFERENCES

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