

Diabetes Care and Patient-Oriented Outcomes

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A MAJOR PROBLEM IN CONTEMPORARY diabetes mellitus care is the poor translation of knowledge derived from clinical research into routine clinical practice.¹ To improve standards and outcomes of diabetes care, efforts in the following areas appear crucial: diagnostic procedures and therapeutic management must be evidence-based; patients need to become more actively involved in their disease management; and every center/geographic area needs to perform quality assessment based on patient-oriented outcomes.

Patient-Oriented Treatment Goals and Evidence-Based Diabetes Care

Only recently has appropriate evidence according to the criteria of evidence-based medicine² become available to guide the routine management of diabetes to achieve specific patient-oriented outcomes.

Type 1 Diabetes Mellitus. Patient-oriented outcome goals of type 1 diabetes therapy include maintenance of a quality of life as little affected by the disease as possible, prevention of acute complications (ketoacidosis, iatrogenic hypoglycemia), and prevention of microangiopathic late complications and subsequent macrovascular disease. During the early 1990s, the Diabetes Control and Complications Trial³ and other studies⁴ demonstrated the causal relationship between the degree of glycemic control and the incidence and progression of diabetic microangiopathy in type 1 diabetes mellitus. In the Diabetes Control and Complications Trial, intensified insulin therapy (multiple daily insulin injections or continuous subcutaneous insulin infusion with insulin dosages adjusted according to blood glu-

cose self-monitoring) achieved improvement in glycemic control with a decrease in median glycosylated hemoglobin (HbA_{1c}) level of approximately 2% compared with conventional therapy, but it was associated with a 3-fold increase in the risk of severe hypoglycemia. This finding has raised concern about the safety of intensified insulin therapy in usual practice. However, when integrated into a specific treatment program that emphasizes patient self-therapy, intensification of insulin therapy has been shown to decrease HbA_{1c} levels without an increased risk of severe hypoglycemia even when used as routine treatment.⁵⁻⁹ In patients who have already developed microangiopathic organ damage, laser photocoagulation for diabetic retinopathy,¹⁰ normalization of elevated blood pressure,¹¹ and special foot care¹² have been shown to be effective treatments that decrease the incidence of visual loss, renal failure, and amputations, respectively.

On the other hand, the alleged benefits of prescribing dietary meal planning and physical exercise for patients with type 1 diabetes have not been supported by appropriate evidence, even though they have been carried forward as cornerstones of diabetes treatment well into the 1990s.¹ The prescription of regular physical exercise has only recently been abandoned,¹³ whereas nutrition prescription in the format of meal planning, including eating at consistent times, is still being recommended.¹⁴

Therapeutic practices under investigation include fast-acting insulin analogs, such as insulin lispro. Although the pharmacokinetic properties and bioavailability of insulin lispro following subcutaneous injection appear favorable because of a more rapid action-time profile, documentation of its potential advantages over regular human insulin in clinical practice is pending. In

a meta-analysis of 8 large randomized clinical trials comparing insulin lispro with regular human insulin, there was no improvement in HbA_{1c} levels and the reduction in risk of severe hypoglycemia from 18.2 to 14.2 events per 100 patient-years among patients treated with insulin lispro was of only marginal clinical significance.¹⁵ Results of studies that suggested improvements in quality of life associated with insulin lispro¹⁶ are hardly interpretable because none of the studies was appropriately blinded. Long-acting insulin analogs with improved action profiles for the substitution of basal insulin requirements are also in development, but whether these efforts will translate into improvements in intensified insulin therapy remains to be seen. Because none of these insulin analogs occur in nature, they possess potential biological risks¹⁷ that need to be balanced against any benefit they may have, a decision process that requires active participation of the informed patient.

Type 2 Diabetes Mellitus. The main therapeutic objective of the treatment of type 2 diabetes is to prevent the excess cardiovascular morbidity and mortality associated with this condition. Similar in design to the only other previous study on the effects of antidiabetic therapies on vascular complications,¹⁸ the recently published United Kingdom Prospective Diabetes Study (UKPDS) compared the effects of intensive blood glu-

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cose control with conventional treatment over 10 years in approximately 4000 relatively young (mean [SD] age, 53 [9] years) patients with newly diagnosed type 2 diabetes.¹⁹ Following 3 months of dietary therapy (mean weight loss of 3.7 kg) and after stratification by ideal body weight, patients were randomly assigned to intensive therapy with dietary treatment and various oral medications and/or insulin or to conventional dietary treatment with oral medication or insulin added as deemed necessary. The treatment goal for the intensive therapy group was a fasting plasma glucose level of less than 6 mmol/L (108 mg/dL) and for the conventional therapy group, less than 15 mmol/L (270 mg/dL) without hyperglycemic symptoms. During the 10-year follow-up, patients allocated to intensive treatment had lower median HbA_{1c} levels than patients in the conventional treatment group (7.0% vs 7.9%; $P < .001$).

None of the antidiabetic treatment approaches in either the University Group Diabetes Programme or UKPDS^{18,19} effectively reduced macroangiopathic complications. In fact, in the UKPDS, there was no risk reduction in macrovascular end points in patients treated with intensive therapy compared with patients who received conventional treatment.¹⁹ Only intensive plasma glucose control with metformin monotherapy in obese patients with type 2 diabetes decreased all-cause mortality compared with conventional therapy.²⁰ The validity of this finding has been questioned on biometrical grounds,²¹ especially since, in the same study, metformin treatment in combination with a sulfonylurea drug was associated with increased diabetes-related mortality.

Earlier concerns about the possible cardiotoxic effects of sulfonylureas in the treatment of patients with type 2 diabetes and coronary artery disease,¹⁸ supported by recent pathophysiological data,²² remain because patients with clinically significant coronary artery disease were excluded from the UKPDS.¹⁹ In a prospective randomized trial, treatment with insulin-glucose infusion for at least 24 hours followed by multidose

insulin treatment of patients with type 2 diabetes after acute myocardial infarction resulted in a major improvement in mortality risk: the 3.5-year actuarial mortality fell from 44% in the standard treatment group to 33% in the intervention group (relative risk, 0.72; 95% confidence interval [CI], 0.55-0.92; absolute risk reduction, 11%; number needed to treat [NNT]_{3.5 years} = 9).²³ The reason for this finding is not entirely clear, but discontinuation of sulfonylurea treatment in the intervention group may have contributed to the improved prognosis of patients with diabetes following a myocardial infarction.

The UKPDS did demonstrate the benefit of intensive blood glucose control for the prevention of microangiopathic organ damage. The improvement in median HbA_{1c} level of 0.9% in the intensive treatment group compared with conventional treatment was associated with statistically significant absolute risk reductions of 5.1% (NNT_{10 years} = 20; 95% CI, 10-500) for the aggregate outcome of any diabetes-related end point and of 2.8% (NNT_{10 years} = 36; CI, not reported) for microangiopathic complications.¹⁹ Another study question was whether any of the medications had advantages or disadvantages. Intensive first-line therapy with insulin or glyburide (glibenclamide), but not with chlorpropamide, resulted in better microvascular outcomes than conventional therapy. Chlorpropamide was associated with an increase in blood pressure.¹⁹ These findings underscore the need to establish efficacy and safety for each oral antidiabetic agent separately. Based on the UKPDS, glyburide (glibenclamide) is an evidence-based alternative to insulin as the first-line pharmacological treatment of younger patients with newly manifest type 2 diabetes who are free of coronary heart disease.

With regard to acarbose and troglitazone, no data exist to support their role in the prevention of vascular diseases in patients with type 2 diabetes, and there is concern about hepatotoxic effects and other aspects of their safety.

In addition, the UKPDS²⁴ has reemphasized the benefit of tight control of

arterial hypertension in patients with type 2 diabetes. First-line treatment with the cardioselective β -blocker atenolol or the angiotensin converting enzyme inhibitor captopril aiming at blood pressure values less than 150/85 mm Hg was found to improve not only diabetes-related mortality (absolute risk reduction, 6.6%; NNT_{10 years} = 15; 95% CI, 12-18), but also microvascular complications (absolute risk reduction, 7.2%; NNT_{10 years} = 14; CI, not reported), which is an effect size apparently superior to that found with intensive blood glucose control alone. Lipid lowering by simvastatin²⁵ and aspirin²⁶ treatments are also considered evidence-based therapeutic measures in patients with type 2 diabetes. The recent controversy following reports suggesting increased cardiovascular event rates among patients with diabetes treated with calcium-channel blockers should represent a further warning against the use of nonevidence-based treatments.²⁷⁻²⁹

Patient Education and Self-management

Patient self-management, including metabolic monitoring and adjustment of drug dosages, has been successful in improving treatment outcomes in type 1³⁰ and type 2³¹ diabetes. When intensified insulin therapy is integrated into a structured educational program using a formal curriculum for small groups of patients,^{30,32} HbA_{1c} levels and the risk of severe hypoglycemia have been shown to decrease simultaneously and it is feasible to liberalize stringent rules for diet and lifestyle.^{5-9,33} In a recent study of 1103 patients with type 1 diabetes, participation in such a program was associated with a decrease in HbA_{1c} level of approximately 1.2% and a reduction in the risk of severe hypoglycemia from 0.35 to 0.16 cases per patient-year.⁹ Such programs of therapeutic education are likely to overcome the notorious problem of patient noncompliance with prescribed therapies because the informed patient defines his/her treatment goals and chooses therapeutic strategies that

he/she will carry out in the long run.⁸ This new approach goes far beyond traditional diabetes education strategies because it aims at enabling patients to define individual HbA_{1c} target levels depending on the risk they are prepared to take and the efforts they are prepared to make.

Quality of Care

Finally, as therapeutic and preventive strategies for the care of patients with diabetes become supported by evidence from rigorous clinical investigation, the question arises as to what extent these advances are actually being implemented in day-to-day practice. Six years after the publication of the Diabetes Control and Complications Trial, it is estimated that only 10% of patients with type 1 diabetes in the United

States compared with 80% in Germany³⁴ are using a version of intensified insulin therapy that aims to reach near-normal HbA_{1c} levels. The center-to-center differences in the incidence of severe hypoglycemia in patients with type 1 diabetes appear unacceptable.^{8,32,35} In Europe, the St Vincent Declaration³⁶ has encouraged continuous quality improvement procedures by motivating a growing number of centers to document and submit process and outcome data related to the quality of diabetes care. If made public in regular intervals and discussed in peer review groups, this type of information could help improve outcomes and standards of care in type 1 diabetes.⁹

Other initiatives to assess quality of care have been based on the documentation of outcomes in a population,

such as performed by a perinatal or an amputation registry. In the United States, a Patient Outcome Research Team conducted a cohort study that combined longitudinal data from clinical information systems, administrative data, and patient reports to examine the effectiveness and outcomes of care in clinical practice settings for people with type 2 diabetes.³⁷ Data gathered by these approaches can reveal differences in patient-oriented outcomes such as mortality and incidence of terminal renal failure in patients with type 1 diabetes and nephropathy.³⁸ Variation in patient outcomes and processes of care should be made public and available to patient organizations and health care providers and policymakers as the basis for clinical and policy decisions.

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