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Individualizing Insulin Therapy in the Management of Type 2 Diabetes

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ABSTRACT

It is recognized that reducing hyperglycemia early on in disease progression has long-term benefits for patients with diabetes. Insulin therapy has greater potential to reduce hyperglycemia than other therapies; however, there is often a significant delay in insulin initiation and intensification. Insulin replacement therapy in type 2 diabetes should no longer be viewed as the treatment of last resort. With the development of modern insulin analogs, the field has evolved. Large clinical trials have improved our understanding of the potential benefits and risks associated with intensive glycemic control in different patient populations and highlighted the need for individualization of glycemic targets and treatment strategies. Current treatment guidelines recognize the important role of insulin therapy both early on and throughout the progression of type 2 diabetes.

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An estimated 382 million people are living with diabetes, half of whom are undiagnosed.[1] In the United States alone, more than 29 million individuals have diabetes.[2] The most prevalent form, type 2 diabetes, is characterized by insulin resistance and impaired insulin production. Because of the progressive nature of type 2 diabetes, the majority of patients eventually require insulin therapy to maintain adequate glycemic control.[3] There is growing awareness that insulin output, relative to insulin sensitivity, is deficient early in the course of the disease and continues to worsen throughout the disease progression. Therefore, insulin therapy is relevant throughout all stages of type 2 diabetes. This article discusses some of the background studies and trials that shaped the current guidelines and the resulting recommendations regarding insulin use in the management of patients with type 2 diabetes, the evolving role of insulin therapy, and the tailoring of treatment goals to individual patients.

INDIVIDUALIZING THERAPY AND GOALS FOR PATIENTS WITH TYPE 2 DIABETES

Evolution of Insulin Therapy in Type 2 Diabetes: The Lessons Learned from Outcome Studies

The first step in the treatment of patients with type 2 diabetes is setting glycemic targets. The current standard of care involves individualizing these targets on the basis of patient characteristics.[4,5] The individualized targets should take into account not only clinical conditions, such as relevant comorbid conditions, age, duration of diabetes, and history of severe hypoglycemia, but also the patient-specific psycho-socioeconomic context. This includes the psychologic aspects, economic considerations, available support systems, and social functioning of the patient. Ultimately, the goal of any treatment should be to provide the patient with the greatest possible improvement in both short- and long-term quality of life.[5] Large-scale outcome trials

performed over recent decades have demonstrated the merits of this approach and helped to shape current treatment guidelines. Details of some of the pivotal studies follow.

In 1998, the UK Prospective Diabetes Study (UKPDS) demonstrated the link between tight control of glycated hemoglobin (HbA_{1c}) and incidence of microvascular complications in patients with type 2 diabetes.[6] Treatment was insulin/sulfonylurea or metformin for overweight patients (those over 120% of ideal body weight). Intensive glycemic control (median HbA_{1c} 7.0%) over an average 10-year period in newly diagnosed patients led to a 25% reduction in overall microvascular complications compared with conventional glycemic control (median HbA_{1c} 7.9%). Another study, the Diabetes Control and Complications Trial (DCCT), also showed a clear reduction in microvascular complications in intensively treated patients with type 1 diabetes (mean achieved HbA_{1c} ~7.0%) compared with the standard group (mean achieved HbA_{1c} ~9.0%). Over an average of 6.5 years, the development of diabetic retinopathy in those patients with no retinopathy at baseline was reduced by 76%, and its progression was reduced by 54% in those with mild retinopathy at baseline; in this group, the development of proliferative or severe nonproliferative retinopathy was also reduced by 47%. Overall, nephropathy was reduced by 54% and neuropathy by 60%.[7] Thus, the link between tight glycemic control and reduced incidence of microvascular disease associated with diabetes was established. Although these trials clearly demonstrated the benefits of intensive glycemic control on microvascular outcomes, the effects on macrovascular events were inconclusive.

Of note, follow-up studies of the UKPDS cohort suggested a continued benefit in those patients who had been in the intensive treatment arm, years after intensive treatment had ceased—the so-called legacy effect.[8] These findings were similar to those of the DCCT follow-up study (the Epidemiology of Diabetes Interventions and Complications trial), although that study involved patients with type 1 diabetes. Despite a convergence in HbA_{1c} levels between treatment groups at 1 year after the initial study end, patients who were originally randomized to intensive therapy showed a statistically significant risk reduction for any diabetes-related end point and for myocardial infarction and death from any cause at 10 years. Thus, these follow-up studies revealed that when good glycemic control is established early in type 2 diabetes, the prognostic benefits endure.

Although an increased risk of cardiovascular disease associated with type 2 diabetes is well established,[9,10] it remains less clear how intensive glycemic control affects the incidence of cardiovascular events. Both the UKPDS and the DCCT (pre−follow-up studies) showed a trend toward a reduction in cardiovascular events in the intensive treatment arms, but the reductions did not reach statistical significance; however, the follow-up studies did suggest a benefit in the longer term. Three subsequent trials sought to clarify the effect of intensive glycemic control on cardiovascular outcomes in older patients with type 2 diabetes at relatively high risk of cardiovascular disease. Unlike the UKPDS, these trials were performed in older patients (aged 60-66 years) with established diabetes. The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) and the Veteran Affairs Diabetes Trial (VADT) showed that intensive glycemic control (ADVANCE target HbA_{1c} ≤6.5%, VADT target HbA_{1c} <6.0%) yielded no benefit in terms of cardiovascular disease outcome.[11,12] The third trial, Action to Control Cardiovascular Risk in Diabetes (ACCORD), also compared intensive glycemic control (HbA_{1c} <6%) with "standard" glycemic control (HbA_{1c} 7.0%-7.9%), but the study was terminated early because of a statistically significant increase in mortality among those patients in the intensive treatment arm; cardiovascular deaths also were significantly increased.[13] However, all 3 trials did report benefits in various microvascular outcomes in the intensive treatment arms. The cause of the unexpected increase in cardiovascular disease-related deaths in the intensive-treatment arm of the ACCORD study has not been established. Regardless of the cause, the unexpected results of these cardiovascular disease outcome trials demonstrated that aggressive reduction of HbA_{1c} may not be beneficial for all patients and clearly highlighted the merits of adapting treatment targets according to the patient.

Evolution of Insulin Therapy in Type 2 Diabetes: The Lessons Learned from Comparative Clinical Trials

Although outcome studies have highlighted the need for appropriate glycemic control, clinical trials have helped determine the best way to achieve it. The use of insulin in the management of type 2 diabetes has evolved through trials of treatment regimens, facilitated by the introduction and evolution of new insulin analogs. In particular, the long-acting basal insulin analogs, insulin glargine and insulin detemir, have become a cornerstone of insulin therapy in type 2 diabetes. This is partly because there have been a plethora of clinical trials that have ultimately changed paradigms about the way insulin can be used in type 2 diabetes. These analogs introduced the possibility of simple regimens (with a single daily injection) and the prospect of introducing insulin therapy with a low risk of hypoglycemia. Previous intermediate-acting insulins, such as neutral protamine Hagedorn, required at least 2 daily injections. Clinical trials investigating titration protocols aimed to exploit the longer action profile of the new basal insulin analogs, ultimately leading to the simplification of dosing algorithms.

The original "treat-to-target" study by Riddle et al,[14] published in 2003, used a protocol in which the insulin dose was continually titrated toward a predetermined fasting plasma glucose target throughout the study in an attempt to optimize patients' glycemic control.[14] The trial compared a single bedtime injection of insulin glargine or neutral