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Initiating Basal Insulin Therapy in Type 2 Diabetes: Practical Steps to Optimize Glycemic Control

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ABSTRACT

Primary care practitioners are increasingly responsible for the management of the escalating numbers of patients with type 2 diabetes. The majority of these patients will require insulin replacement therapy as their disease progresses, because glycemic control is often unsustainable using oral antidiabetic drugs. This review explains the practicalities of initiating and optimizing basal insulin in clinical practice, emphasizing the need for regular glycated hemoglobin (A1c) monitoring to allow timely initiation of insulin when the A1c target is not met. The importance of patient education in overcoming barriers to insulin is discussed, as well as the choice of available basal insulins and the necessity to optimize basal insulin dosage by self-titration. The traditional view of insulin therapy as a last resort is challenged with the modern basal insulin analogues (insulin detemir and insulin glargine), which offer simple and effective glycemic control with a reduced risk of hypoglycemia compared with older insulin formulations such as neutral protamine Hagedorn.

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KEYWORDS: Basal insulin; Insulin detemir; Insulin glargine

Diabetes is a global epidemic, with prevalence estimated to reach 439 million by 2030.[1] Type 2 diabetes (T2D) accounts for 90% of all cases of diabetes[2]; however, the vast majority of patients in treatment for T2D have suboptimal glycemic control, with glycated hemoglobin (A1c) levels greater than the 7% target established by the American Diabetes Association (ADA).[3] Studies in the UK and the US have determined that only 30%-50% of patients achieve this glycemic target with a single antidiabetic agent, and that glycemic control tends to worsen over time,[4,5] primarily because treatment is not intensified in a timely manner. In addition, traditional oral antidiabetic drugs (OADs) such as sulfonylureas (SUs), thiazolidinediones (TZDs), and metformin, have limited durability with respect to glycemic control.[6] A 6-year survey determined that 53% of patients allocated to treatment with an SU required insulin therapy for the first time by the end of the study period.[7]

For patients with T2D, the consequences of inadequate glycemic control can be severe, with a significantly increased risk of both microvascular complications (eg, retinopathy, nephropathy) and macrovascular complications (eg, myocardial infarction, amputations). An epidemiological study in the UK determined that a single percentage-point reduction in mean A1c reduced patients' risk of microvascular complications by 37%, their risk of diabetes-related death by 21%, and their risk of myocardial infarction by 14%.[8]

T2D is a progressive disease, characterized by gradual deterioration in pancreatic beta-cell function, decreasing insulin levels, and increasing insulin resistance, ultimately leading to chronic hyperglycemia. At diagnosis, most patients with T2D have already lost 50% of their remaining beta-cell function, which reduces rapidly over a period of just a few years.[9] This rapid beta-cell decline means that insulin replacement quickly becomes necessary in order to achieve and maintain glycemic control, because other available therapies rely on the body's ability to produce insulin.[5,9] As such, insulin replacement is the most effective

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treatment for long-term control of hyperglycemia, and significant improvements in glycemic control can be achieved with this therapy in a short time.[10,11]

There are 3 stages to insulin therapy: initiation, optimization, and intensification. This review focuses on basal insulin initiation and optimization, discussing in particular the role of primary care practitioners (PCPs), who are increasingly responsible for managing the escalating number of patients with T2D. The right time to initiate insulin therapy will be considered, as will suggestions for overcoming patient and physician barriers to initiating insulin therapy. Practical considerations for patients starting insulin therapy will be discussed, including the initial optimization of dose titration to achieve target A1c levels.

As T2D progresses, further insulin intensification usually becomes necessary to maintain patients' glycemic control; this subject is discussed at length in another article in this supplement.[12]

WHEN TO INITIATE INSULIN

When glycemic control cannot be achieved using the maximum-tolerated dose of metformin (or another OAD), insulin initiation must be considered as a next step. The traditional view of insulin as a last resort should not be accepted, because most medical endocrinology societies, including the ADA, the American Association of Clinical Endocrinologists (AACE), and the European Association for the Study of Diabetes (EASD), recommend that insulin therapy be started sooner rather than later. The new ADA/EASD joint position statement recommends the introduction of basal insulin as one of 5 treatment options for dual therapy in combination with metformin, each being equally preferred, although the higher the baseline A1c, the more likely insulin will be required; other options include SUs, TZDs, dipeptidyl peptidase-4 (DPP-4) inhibitors, or glucagon-like peptide-1 receptor agonists (GLP-1RAs).[3] Basal insulin is favored in a triple combination therapy over the other treatment options, as it is likely to be more effective than most other agents, especially when A1c is very high ($\geq$9%).[3]

The main factor affecting the decision to initiate insulin should be the current level of glycemic control, as determined by frequent A1c monitoring; however, in practice, other barriers such as clinical inertia, lack of physician time, and the presence or absence of patient insurance (discussed in more detail in the following section) prevent insulin initiation taking place. The ADA's A1c target $\leq$7% is a reasonable goal for most patients, but should not be considered a universal target.[3,13,14] More stringent goals may be appropriate for patients with a shorter duration of T2D, a longer life expectancy, and lack of cardiovascular problems. A more flexible A1c goal also may be required for patients with long-term T2D, a shorter life expectancy, or those with diabetic complications or severe hypoglycemia. In those patients who experience recurrent or severe episodes of hypoglycemia, identifying and addressing any underlying causes of the hypoglycemia should take precedence over intensification of treatment to lower the A1c.

When deciding whether to initiate insulin, other considerations should include the success of earlier therapies, the patient's physical and cognitive capabilities, and the presence of other medical complications. As always, it is important to individualize therapy to the patient by taking their lifestyle into account. Early insulin initiation as a first-line therapy in combination with metformin is recommended in exceptional circumstances, such as severe hyperglycemia (A1c >10% or plasma glucose >300-350 mg/dL) or the presence of ketonuria, or symptomatic diabetes with polyuria, polydipsia, and weight loss.[3]

Frequent and consistent A1c monitoring is essential for patients who are not meeting their glycemic goals. The ADA recommends that A1c levels be monitored at least every 3 months in patients whose therapy has changed or those not meeting glycemic goals, using point-of-care (POC) testing: this allows timely decisions on therapy changes to be made when an A1c target is not met, in a "treat-to-target" manner.[13] Where glycemic control is stable, the A1c test should be performed at least twice-yearly.[13] The availability of the A1c result at the time that the patient is seen (POC testing) has been reported in some studies to result in increased intensification of therapy and improvement in glycemic control; however, others show no difference.[13] A1c is thought to reflect average glycemia over several months and, as mentioned previously, has strong predictive value for diabetes complications.[8] However, A1c POC testing has its limitations: proficiency testing is not mandated for performing the test, so use of these assays for diagnostic purposes could be problematic.[13] As such, A1c POC testing should be used alongside the other primary technique to assess a patient's glycemic control: self-monitoring of blood glucose (SMBG).[13]

Unfortunately, both patients and clinicians may be reluctant to initiate insulin for various reasons (discussed in more detail in the following section). Such delays, known as "clinical inertia," can worsen diabetic complications, because the greater the A1c upon initiating or changing therapy, the less likely the patient is to achieve glycemic control.[4] Despite this, substantial clinical inertia does exist; a UK study determined that 50% of patients delayed insulin initiation for almost 5 years after failure of glycemic control with multiple OADs, even in the presence of diabetes-related complications.[15] A US study found that more than half of patients treated with SUs and metformin attained, but then failed to maintain, a less stringent A1c goal of <8%. These same patients continued their suboptimal SU/metformin therapy for an average of nearly 3 years, sustaining a glycemic burden equivalent to nearly 32 months of A1c levels of 9%. Another 18% of patients never attained the 8% goal with SU/metformin therapy, yet continued on it for an average of 30 months, reaching mean A1c levels of 10%.[16]

Clinical inertia is a preventable problem that could be tackled in part by increasing awareness among PCPs of the need to keep glucose levels as close to normal as possible in