ABSTRACT

Type 2 diabetes is becoming a modern-day epidemic. It is characterized by hyperglycemia embedded in a wider metabolic disturbance, predisposing to micro and in particular macrovascular complications. Prevention of morbidity and mortality demands multifactorial approaches, where lifestyle measures, like the pursuit of normal body weight and introduction of exercise, are central. In addition, to avoid cardiovascular disease, blood pressure control and statin-introduction are adamant.

Controlling glycemia is an important part of this integrated multifactorial approach and maintaining glycemic levels as close to the non-diabetic range as possible is essential in preventing microvascular complications and is beneficial to the prevention of macrovascular disease.

Achieving and maintaining specific glycemic goals is difficult since the efficacy of available therapies diminishes as disease progresses because of a steady, relentless decline in beta-cell function. New drug classes, like GLP-1 agonists and DPP-4 inhibitors, hold the promise of beta-cell preservation, but in the meantime, insulin will be an integral part in the therapy of many patients as beta-cell function further declines. Focus will be put on how basal insulin analogues will help to safely achieve glycemic targets in more patients.

INTRODUCTION

The incidence and prevalence of diabetes (and especially type 2) are increasing worldwide with 171 million people suffering from diabetes in 2000, expected to increase to more than 350 million by 2030 (1). Due to the initially often silent course of the disease and thus late diagnosis, but also because of gross under-treatment of hyperglycemia and additional cardiovascular risk factors, diabetes is a major cause of morbidity and mortality.

Type 2 diabetes (T2DM) is associated with an increased incidence of various complications including heart disease, stroke, amputations, high blood pressure, blindness, kidney disease and neuropathy. The ultimate goal of diabetes therapy is to prevent micro- and macrovascular complications in order to improve life expectancy and quality of life. The DCCT and UKPDS studies demonstrated that lowering glycemia (measured as HbA1c) leads to less microvascular complications in type 1 as well as in type 2 diabetes (2,3). In both DCCT (EDIC) and UKPDS follow up studies, it was demonstrated that the level of glucose control in the early years of the disease impacts dramatically on the development of later complications (4,5). In both studies, patients with tighter glycemic control during the study developed less micro- and macrovascular complications more than 10 years after discontinuation of the study. These observations emphasize the need to control glycemia as tight as possible as early in the disease process as possible. In macrovascular disease glycemia also plays a role, as again was demonstrated in UKPDS, where in particular metformin therapy in obese patients led to significant improvements in cardiovascular outcomes and overall mortality (6). The relationship is however less pronounced than for microvascular disease, leaving even well controlled diabetic patients at increased cardiovascular risk, due to the contribution of other risk factors to macrovascular disease, such as hypertension, hypercoagulability and dyslipidemia.

DIABETES AS A DUAL DISEASE: INSULIN RESISTANCE AND BETA-CELL DYSFUNCTION

T2DM is a chronic and complex disease that involves multiple pathophysiological defects, including insulin resistance of liver, muscle and fat as well as an impaired islet function. Most individuals who are insulin resistant (caused by obesity or a sedentary lifestyle) will only progress to T2DM when islets fail to adapt to the insulin resistance due to an impaired glucose-potentiated insulin secretion and a decreased alpha-cell sensitivity to the suppressive effects of glucose (7). The relentless decline in pancreatic beta-cell function is illustrated by the worsening glycemic control in UKPDS patients treated with monotherapy (either with diet, sulfonylurea or insulin). The insight that T2DM is a progressive and dual disease, has led to the use of combination therapy with drugs with different mechanisms of action. The combination of oral antidiabetic drugs (OAD) effective on insulin resistance (such as metformin) with OAD stimulating beta-cell function has been shown to be synergistic, leading to a more efficient glycemic control.
Despite major efforts to attract attention to the importance of glycemic control, levels of HbA1c, especially in T2DM patients, remain problematic. Studies in different parts of the world show that HbA1c levels in T2DM patients lay well above the target of 7% (8). A major issue is the fact that additional therapy is often only started when the previous strategy fails to achieve the glycemic goals. Given the inevitable progression of beta-cell dysfunction, along with the relatively limited glucose-lowering capacity of different agents, many patients will eventually require insulin for optimal glycemic control. Patients and physicians however, often fail to initiate insulin early enough for a number of reasons such as fear for injections, weight gain and hypoglycemia.

INSULIN IN THE TREATMENT OF TYPE 2 DIABETIC PATIENTS

Given the (until now) inevitable progression of beta-cell dysfunction, along with the relatively limited glucose-lowering capacity of other agents, many patients will eventually require insulin for optimal glycemic management. Advantages are first the vast clinical experience with insulin since it is the oldest of the currently available medications. It is also the most effective therapy in lowering glycemia. When used in adequate doses it can decrease any level of elevated A1c close to the therapeutic goal. There is no maximum dose of insulin beyond which a therapeutic effect will not occur. The drop in HbA1c that can be achieved by insulin regimens is only limited by the occurrence of hypoglycemia. Relatively large doses of insulin may be necessary to overcome the insulin resistance. Challenges are the risk for hypoglycemia.

The ACCORD study showed an increased mortality rate in the intensive treatment group, possibly related to the higher rate of severe hypoglycemia (9). Another disadvantage of insulin therapy is weight gain. A common feature exists for all insulins: the need for titration and intensification. Installing and intensifying insulin therapy is intricately linked to intensive diabetes education and self-monitoring of blood glucose levels by the patients.

HUMAN INSULIN

Short acting (regular insulin), intermediate acting (NPH) and premix insulins exist. Advantages are the long clinical experience, including treatment during pregnancy and low cost. Moreover human insulins lower HbA1c levels as effectively as insulin analogues. The major advantage of premix insulins is the ease of use, with delivery of short acting and intermediate acting insulin at the same time, thus allowing pre- and postprandial control at the same time. Challenges are the increased incidence of hypoglycemia and the increased risk for unpredictable hypoglycemia with human insulin compared to the insulin analogues. NPH has a highly variable duration of action with a distinct peak of action. Regular insulin has a prolonged action (several hours), not adapted to the meal-induced glucose changes and is characterized by some variability in action.

INSULIN ANALOGUES

Insulin analogues are the modified insulins with changes in either the A or the B chain to alter the pharmacokinetics in order to mimic the normal physiological insulin secretion pattern. In addition to this the aim was to have either similar or better efficacy and safety profile. In the early studies, the molecular safety of these analogues were assessed in terms of mitogenic potential, binding properties to IGF-I and insulin receptors. These studies were important as IGF-I receptor affinity decides the mitogenic potential on long term use (11). Recent retrospective analysis in European countries suggested increased incidence of malignancy, especially breast carcinoma in patients receiving insulin glargine (12). Other analogues like aspart and lispro did not show similar trends. A recent meta-analysis did not show any increase in incidence of cancer with insulin detemir as compared to human insulins (13). The implications for use of glargine remain unclear, but caution is warranted.

Rapid acting analogues include lispro, aspart and glulisine. Advantages are the action profile that is more appropriate to cover meal-related glucose excursions, with better postprandial glucose control and less hypoglycemia before the next meal or in the early nighttime. Challenges include the need for frequent mealtime injections and their cost.

Long acting analogues, glargine and detemir are the most common insulin analogue preparation that is initiated in T2DM patients with insufficient glycemic control under OAD. The advent of insulin glargine and more recently detemir, has revolutionized the concept of basal insulin therapy (16). Both these analogues are long acting which provide relatively peakless basal insulin levels with action profile close to 24 hours permitting once daily dosing (10). Advantages include the lower risk for hypoglycemia (particularly nocturnal hypoglycemia) and less within-subject glycemic variability compared to NPH insulin. Detemir has a lower within-patient variability compared to glargine. This better predictability mainly due the unique albumin binding property of insulin detemir results in more stable nocturnal plasma glucose profile and lower glucose fluctuations leading to lesser number of hypoglycemic events (14, 15).
For detemir, an interesting weight advantage also exists, with less weight gain compared to NPH or glargine. The hassle of injecting insulin, the hypoglycemic risk, the weight-gain and in many T2DM patients the fear for injecting has lead the insulin being initiated too late and not being titrated or intensified properly. Using analogues may allow this intensification with less side effects (hypoglycemia, weight gain) and especially more comfort (17). Challenges are the higher cost and less clinical experience compared to human insulins. At present, data on effects of analogue insulins on long-term diabetes complications are lacking.

Premix analogues are available in different mixtures of short-acting analogues with intermediate insulins (18). Advantages include better shaping of the action profile of the administered insulin to the glycemic excursion profile in each individual patient. Premixes are easy to use and deliver pre-and postprandial control at the same time. Challenges include a decreased flexibility and like for all analogues, a high cost.

**Basal Insulin as First Insulin Regimen After OAD in Type 2 Diabetes**

Current treatment algorithms suggest adding one bedtime dose of long-acting insulin to oral agents (OAD) when HbA1c is not on target (19). Basal insulin added to existing OAD is an easy way to initiate insulin therapy in T2DM patients and achieves HbA1c below 7% in many patients. This concept of basal insulin added on to OAD has been reinforced recently by the 4T study (20,21). This study was conducted in the UK with the aim to discover which insulin regimen was preferable in newly insulin-treated patients: prandial insulin (administered as aspart insulin at three mealtimes), premix insulin (as Novomix® insulin) at the morning and evening meal, and finally basal insulin add on before bedtime (and eventually adding a second basal insulin injection in the morning) (detemir insulin). Results after one year of therapy demonstrated that patients treated with prandial and premix insulin showed a greater reduction in HbA1 levels and postprandial glycemias, but at the price of higher weight gain and more hypoglycemia compared to the detemir-treated patients. After the first year of therapy, patients who were not on target (defined as HbA1c <6.5) stopped their sulfonylurea and added a second type of insulin: detemir bedtime to prandial-treated patients, prandial aspart insulin at lunch in mix-treated patients and prandial aspart (3 times daily) in detemir-treated patients. After 3 years HbA1c levels reached were identical in the three treatment groups, but hypoglycemia risk and weight gain was still lowest in the patients where the first insulin regimen started was the basal regimen using insulin detemir. This is an important lesson for clinicians, where not results after a couple of months are important but where steady results after several years count and where issues like weight and safety, under the form of hypoglycemia are as essential as glycemic control. Indeed, other trials published in recent years (ADVANCE, ACCORD and VAAD) clearly demonstrate that aggressive, strict glycemic control, aiming at low HbA1c targets at the cost of hypoglycemia is undesirable, particularly in already cardiovascularly complicated patients (9,22,23). Thus, initiating a basal insulin, lowering HbA1c to the lowest target possible whilst avoiding hypoglycemia, and in particular severe hypoglycemia, is the way to go after OAD prove to be insufficient as therapy in our type 2 diabetic patients.

**Which Basal Insulin?**

Older studies by Yki-Yrvingen clearly demonstrate that NPH insulin, added to OAD bedtime, is very efficient in suppressing hepatic glucose output during the night, and thus controlling fasting glycemias (24). Fasting glycemias contributes a great deal to overall control, expressed as HbA1c (25) and is easily targeted. Initiating NPH at 0.1U/kg has proven to be an easy and safe way to go and allows to reach HbA1c targets <7%, as suggested by ADA and EASD, in several studies. However, an important hurdle to adding basal insulin to OAD is the occurrence of weight gain and even more importantly (nocturnal) hypoglycemia. The arrival of basal insulin analogues, glargine and detemir, has meant a major breakthrough worldwide of this approach for initiating insulin. The ‘Treat-to-Target’ trial (26) demonstrated that glargine was as efficient as NPH in reaching control in FPG or HbA1c within 6 months, but glargine did so with 21% less hypoglycemia, in particular nocturnal hypoglycemia. Similar results are available for detemir insulin as basal insulin, with not only less overall hypoglycemia and less nocturnal hypoglycemia than NPH, but the additional benefit of causing less weight gain after initiation and intensification of insulin therapy. This weight advantage has been demonstrated in several studies versus NPH, but also versus glargine (27). Also detemir can best be administered once daily in type 2 diabetic patients when initiated after OAD are not able to maintain good glycemic control. Early initiation and swift titration (to FPG <100mg/dl) are key to achieving and maintaining optimal glycemic control with basal insulins, like detemir.

**Conclusion**

T2DM is a chronic disease that has become a modern-day epidemic. Although the last decade new classes of medications have been developed for treatment of hyperglycemia in T2DM, the therapeutic corner stone in T2DM patients should remain patient education on the character of the disease (explaining that type 2 diabetes is a progressive disease from the beginning takes away many misunderstandings on ‘efficacy of treatment regimens’) and motivation on lifestyle adjustments (physical activity and healthy food intake). The insight that lifestyle measures not only affect glucose levels, but are essential for interfering with one of the pathogenic bases for T2DM, insulin resistance, should boost motivation for all healthcare workers to keep on hammering on these interventions. Moreover, their impact on other cardiovascular risk factors, like blood pressure, lipids and weight, is equally important for the life of the patient. Due to the inherent feature of type 2 diabetes that is the progressive failure of the beta-cell, insulin will be a necessary tool in the treatment of most type 2 diabetic patients eventually. As suggested by guidelines and consensuspapers (13), insulin may be the second step after (or together with) metformin when hyperglycemia is excessive.
It is still the necessary step in all patients when combinations of
OAD are not sufficient to control hyperglycemia. The optimal way
to initiate insulin is adding basal insulin to OAD, titrating the dose
of the basal insulin on the basis of FPG. When fasting glycemia is
on target but HbA1c remains suboptimally controlled, the second
step is to add prandial insulin to the regime. Importantly, early and
sustained glucose control is important, but this glucose control
should be embedded in a multifactorial approach, as controlling
glycemia is just one part of type 2 diabetes therapy, where control
of other cardiovascular risk factors, such as lipids and blood
pressure is imperative.

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