Challenges Associated with Insulin Therapy in Type 2 Diabetes Mellitus

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ABSTRACT

Despite advances in treatment for type 2 diabetes in recent decades, many patients are failing to achieve adequate glycemic control. Poor glycemic control has been shown to have a detrimental effect on patients’ health and well-being, and to have significant negative financial implications for both patients and healthcare systems. Insulin therapy has been proven to significantly reduce glycated hemoglobin levels; however, both patients and physicians can be reluctant to initiate insulin therapy. Research shows that both patient and provider factors contribute to a delay in initiation of insulin therapy. This review discusses the most common barriers contributing to this delay with potential solutions to overcome them.

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Diabetes has become a national and global epidemic. In the United States, an estimated 8.3% of the population (25.8 million people) are currently living with diabetes, with 1.9 million adults (aged >20 years) newly diagnosed in 2010 and an estimated 35% of US adults (50% of those aged ≥65 years) with pre-diabetes.1 Type 2 diabetes accounts for approximately 95% of diabetes cases in adult patients in the United States.

Treating diabetes is costly, with each person with diabetes requiring double to triple the healthcare resources of people without.2 The direct costs of diabetes (ie, costs of prescription medications and hospital inpatient care) are a major financial burden for patients and the healthcare system. In addition, a myriad of indirect costs substantially affects the patients and the economy. For instance, in 2012, diabetes cost the United States an estimated $69 billion in reduced work productivity from absenteeism, unemployment due to chronic disability, premature mortality, and reduced performance at work/home.3

The American Diabetes Association (ADA) recommends that treatment for type 2 diabetes usually begins with diet, exercise, and educational measures. If glycemic targets are not met, this is followed by the initiation of an oral antidiabetic drug, most often metformin. Further oral antidiabetic drugs or injectable treatments often are added in combination to improve glycemic control. Although oral antidiabetic drugs initially can be effective in maintaining glycemic control in patients with type 2 diabetes, eventually, because of the progressive nature of the disease, the majority of people with diabetes will require insulin therapy with or without other oral antidiabetic drugs to achieve adequate glycated hemoglobin (HbA1c) levels.4,5 On oral antidiabetic drug monotherapy, patients can be expected to achieve a maximum of a 2.0% decrease in HbA1c. This increases to approximately 3.0% in patients on maximum doses of oral antidiabetic drugs in triple-combination therapy. Therefore, patients with HbA1c levels >10.0% at diagnosis cannot be expected to achieve HbA1c target levels <7.0% on oral antidiabetic drug therapy alone.6

Current American Association of Clinical Endocrinologists/American College of Endocrinology guidelines recommend that insulin (with or without other agents) is...
initiated in patients failing to achieve HbA1c ≤6.5% with dual or triple therapy (oral agents or a glucagon-like peptide-1 receptor agonist) or in treatment-naïve patients with an HbA1c >9%.5

Despite the need to minimize hyperglycemia to prevent diabetic complications, a large proportion of patients (43%) are not meeting the recommended glycemic target of HbA1c <7.0%.8 One retrospective study found that people with type 2 diabetes accumulated approximately 5 years of excess glycemic burden, measured as HbA1c >8.0% from diagnosis, before insulin was initiated, increasing to 10 years at HbA1c >7.0%.9 Another study in people with type 2 diabetes found that insulin was initiated on average 11.5 years after initial diagnosis with an average treatment threshold of HbA1c values 9% to 10%.10,11

Both in people with type 1 diabetes and in those with type 2 diabetes, poor glycemic control has been proven to increase the risk of developing a range of complications.12-17 There are a variety of data on potential consequences of prolonged poor glycemic control that suggest any reduction in HbA1c is likely to reduce the risk of hyperglycemic complications occurring. The UK Prospective Diabetes Study (UKPDS) found that for each 1% decrease in HbA1c levels, there is a 21% reduction in the risk of clinical complications associated with hyperglycemia.18 Given the wide ranging metabolic benefits of insulin, early initiation of insulin therapy is recommended as a means of achieving and maintaining HbA1c goals.19 However, physicians can be reluctant to initiate or intensify insulin therapy, even in patients who are consistently failing to meet glycemic targets with other measures.9

There are also significant barriers in the minds of patients, with one study finding that up to one third of patients initially decline insulin or state that they would be unwilling to take it if prescribed.20,21 This article will discuss some of the challenges associated with insulin therapy in people with type 2 diabetes and how these may be addressed in regard to improving patient care and quality of life.

CLINICAL INERTIA
Despite supporting evidence, healthcare professionals often are reluctant to initiate insulin therapy. Physicians tend to favor the use of oral antidiabetic drugs for patients who are not meeting glycemic targets and may consider insulin only as a last resort.22 Only slightly more than half of physicians and nurses agree that insulin therapy can have a positive impact on patient care. This resistance differs by region, with healthcare professionals from the United States and India being the most reluctant to initiate insulin therapy.22

Some physicians have claimed to lack adequate knowledge or experience in the use of insulin therapy and, therefore, do not feel confident in prescribing it to patients. The global Diabetes Attitudes Wishes and Needs study surveyed people with diabetes and those who help them to determine the psychosocial challenges that they face. The study found that nurses and nonspecialist physicians were more likely to delay insulin therapy than physicians specializing in diabetes, which suggests a lack of expertise may account for some of this reluctance.23 A solution may be to improve education for healthcare workers on the range of insulin therapies available and the potential benefits they can provide for patients.

Reasons given by physicians for delaying or not intensifying insulin also relate to concerns regarding the efficacy of insulin treatment, fear of patient anger, concerns over patients’ lack of adherence to treatment, risks of side effects such as hypoglycemia and weight gain, and the impact on a patient’s well-being and quality of life.1,12-20 Following on from the results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes Trial (VADT) studies, more focus is now being placed on individualization of glycemic targets to reduce this risk of microvascular and macrovascular events in susceptible patients. In the most recent ADA and European Society for the Study of Diabetes position statement, there is a renewed focus on patient-centered care, particularly in the case of type 2 diabetes.5 Guidelines for initiating and individualizing insulin treatment are discussed in depth in a separate article in this supplement.27

Physicians also are concerned about the potential risk of hypoglycemia in patients treated with insulin, citing it as a barrier in both initiation and intensification of therapy.25 When queried, more than three quarters of physicians stated that they would treat diabetes more aggressively if not for the risk of hypoglycemia.25 This suggests that insulins with a lower risk of hypoglycemia could be used to treat people with type 2 diabetes more intensively, potentially improving HbA1c levels and reducing the risk of complications associated with poor glycemic control.25

PATIENT BARRIERS: PSYCHOLOGIC INSULIN RESISTANCE AND ADHERENCE TO THERAPY
People with type 2 diabetes often have strongly negative attitudes toward insulin therapy, with a large proportion unwilling to initiate insulin if prescribed.20 This reluctance, often termed “psychologic insulin resistance,” is based on a range of patient concerns, including fear of injections, risk of hypoglycemia and weight gain, difficulty in fitting insulin treatment around normal life, and managing injections. In addition, people with diabetes may think that initiation of insulin denotes a “worsening” of their condition and that they have somehow failed in managing the disease.20,22,28

PSYCHOLOGIC INSULIN RESISTANCE
Many people with diabetes express concerns regarding the implications the illness will have on how they manage their day-to-day life. In a survey of 1267 people with type 2 diabetes, a perceived personal failure was found to be the most profound reason for negative attitudes toward insulin
therapy. Patients may think insulin therapy is being used as a threat by their physician in an attempt to improve adherence to other treatment methods, such as diet and exercise. There is also a concern over the permanence of insulin therapy, that once it has been initiated the patient will remain on insulin for life.

Many patients also fail to see any positive gain from the use of insulin, with one study finding that less than 10% of insulin-naïve patients believed that insulin might help them achieve good glycemic control, improve their energy level, and improve their health. Good communication between healthcare providers and patients may alleviate some patient concerns in this area. Physicians should discuss with patients the natural progression of type 2 diabetes and the benefits of insulin use, and reassure patients that they are not to blame for their need for insulin.

The belief that insulin therapy involves significant pain is still prevalent among insulin-naïve people with type 2 diabetes, with more than one third of patients believing they would not be able to handle the pain every day. This is especially true in the United States, where one study found that only 15% of insulin-treated people with diabetes use a pen device, compared with approximately two thirds of patients in Europe and three quarters of patients in Japan using a pen device. Improvements in the design of insulin injection devices, such as shorter, narrower needles, increased accuracy, and spring-loaded pens that decrease injection force may reduce concerns regarding injection pain in patients undergoing insulin therapy.

These improvements, and the corresponding decrease in injection discomfort, are not necessarily being communicated to patients for whom insulin therapy is indicated. As a result, insulin-naïve patients have a higher fear of needle injection than patients with experience of insulin therapy (47% vs 6%). Again, improved communication between healthcare workers and patients may help. When patients raise their concerns over initiating insulin, physicians should ask patients about their knowledge of insulin therapies and then address any particular concerns or misconceptions.

ADHERENCE TO INSULIN THERAPY: FEAR OF HYPOGLYCEMIA AND WEIGHT GAIN

Once insulin therapy has been initiated, there are additional barriers to treatment that negatively affect patient adherence. In a global survey of physician and patient attitudes to insulin therapy, the authors found that approximately one third (33%) of patients admitted to omitting doses or not adhering to treatment regimens. The primary reasons given by patients for insulin omission or non-adherence in this study were predominantly due to the inflexibility of insulin regimens. Reasons such as “too busy,” “traveling,” and “challenging to take at the same time today” are given, implying that rather than struggling to fit their day-to-day activities around treatment, patients will simply omit insulin doses. In addition, more than two thirds of patients reported that they think their insulin regimen controls their life, and 81.4% stated that they wanted their insulin treatment to fit the changes of their day-to-day life.

Questioning physicians as to their patients’ adherence, investigators in the same study found that although approximately 30% of physicians believed their typical patient to be successful at taking their basal insulin every day, this number decreased to less than 20% for how many believed their patients were successful at taking their basal insulin specifically at the same time every day. It is possible that more flexibility in insulin regimens might allow patients to adhere better to their treatment, allowing therapy to fit in more easily with everyday life.

Hypoglycemia is a major fear for many people with diabetes. Not only does hypoglycemia have immediate dangerous consequences for the patient (eg, coma or death) but also research has found that patients who experience symptoms of hypoglycemia are more likely to have a lower health-related quality of life than those who do not. This was found relevant for several parameters, including decreased mobility and usual activities, and anxiety and depression. Skipping meals and exercise, and mis-calculating insulin doses can lead to hypoglycemic events. Fear of hypoglycemia can result in patients omitting insulin doses, which can have detrimental effects on the patient’s health. One third of people with diabetes report that non-severe hypoglycemic events negatively affect their ability to carry out everyday activities, such as housework, socializing, sports, and sleeping. Patients also may be concerned with how potential hypoglycemic events could affect their employment. It may be useful for physicians to talk to patients about their employment policies and their rights in terms of state and federal laws.

Nocturnal hypoglycemia can be particularly dangerous because symptoms often go undetected during sleep. In one survey, people with diabetes reported that nocturnal hypoglycemic episodes impose significant burdens on their lives, including increased self-management efforts, time required to recover, and impaired sleep and function after the episode.

Past experiences of hypoglycemia also increase the fear of future hypoglycemic events, which may negatively influence adherence to therapy, encouraging patients to skip or decrease doses to lower the risk of future episodes. Patients’ fear of hypoglycemia can be a major barrier to intensifying insulin therapy in patients currently treated with insulin.

Because of the significant consequences of hypoglycemia, ADA guidelines suggest that patients at high risk are treated to less stringent HbA1c goals, for example, 7.5% to 8.0% or even slightly higher HbA1c goals may be appropriate for patients with a history of severe hypoglycemia. Elevated HbA1c levels increase the risk of future complications, and so there is a need for treatments that reduce the risk of hypoglycemia while providing good glucose control. In addition, allowing such patients more control through
broader use of blood-glucose monitors to enable self-monitoring may reduce the risk of hypoglycemia.36

Weight gain from insulin therapy can have negative effects on glycemic control, cardiovascular components, and overall health and well-being.37 Despite the benefits of insulin therapy on glycemic control generally outweighing the risks associated with weight gain, many people with diabetes cite a fear of weight gain as a barrier for initiating or intensifying insulin therapy.37,38 One potential method of overcoming this barrier is to treat patients with oral antidiabetic drugs that have minimal impact on weight in combination with insulin or, if weight gain is of particular concern, to consider treatment with a glucagon-like peptide-1 receptor agonist as per the most recent ADA guidelines.8,19 Healthcare professionals also should encourage a healthy diet and exercise regimen to help reduce the risk of weight gain in insulin-treated patients.

Patients may be unaware of how particular insulin therapies have a lower risk of weight gain compared with other insulins. For example, newer insulin analog products can significantly improve glycemic control without causing significant weight gain.6 The UKPDS Study Group studied early initiation of basal insulin therapy in people with type 2 diabetes with suboptimal glycemic control despite maximal sulfonylurea doses compared with those treated with sulfonylurea alone. They found that the addition of basal insulin did not increase weight gain beyond that of the group treated with only sulfonylurea while significantly improving glycemic control and reducing the frequency of hypoglycemic events.39

Continued educational support alongside self-monitoring is associated with increased flexibility, improved glycemic control, and a better overall clinical outcome42; therefore, it may be beneficial for patients to learn the skills necessary to increase their confidence in adjusting their insulin doses. Self-titrating patients must be provided with adequate education on avoiding hyperglycemia/hypoglycemia and the correct methods for proper injection techniques and timing for self-monitoring.

**COSTS**

Diabetes is associated with a range of costs that can negatively affect both the patient and the healthcare system. In a US study, 75.7% patients reported a perceived financial burden of diabetes, with an average of 36% of patients citing cost as the main reason for nonadherence to diabetes medication. This is often higher for ethnic minorities.43 The cost burden to patients will differ depending on the treatment regimen; however, cost barriers may be overestimated. For instance, one study in the United States attempted to assess whether the perception that insulin delivered via pens was more costly to patients than that provided in vials.44 In this study, the authors found that both basal insulin analogues delivered via pens and neutral protamine Hagedorn insulin in vials were covered by >91% of private and Part D insurance plans and that the majority of copays for both insulin types were in the $10 to $35 range.44 Unfortunately, these costs may still prove a burden to some patients, and physicians should discuss with patients the economic implications of potential treatment regimens.

There can also be a number of indirect costs associated with insulin treatment that may contribute to patient resistance. Many patients have concerns over how hypoglycemia will affect their employment. This can be due to a fear of a direct cost (eg, loss of driving license because of recurrent hypoglycemic episodes) or social perceptions, such as the perceived embarrassment of having a hypoglycemic episode in the workplace, which the patient may fear more than the hypoglycemic episode itself.

Hypoglycemia is a major contributor to absenteeism in insulin-treated patients. For patients without the option of sick leave, this can result in a direct loss of wages. Absenteeism also significantly affects the national workforce and the economy overall, because employers need to cover costs. One study found that 18.3% of people with diabetes have needed to leave work early or miss a full day because of nonsevere hypoglycemic events occurring during business hours, with patients losing an average of 9.9 working hours for each event.34 This increases to an average of 14.7 working hours lost for patients experiencing nocturnal nonsevere hypoglycemic events, with 31.8% of patients reporting that they had missed a meeting or work appointment, or failed to finish a work task as a result of nocturnal hypoglycemia.44

Reducing the risk of hypoglycemia, nocturnal hypoglycemia in particular, may help reduce the financial strain that
employees and employers face from losing working hours because of hypoglycemic episodes. This can be done through better education of patients on how to avoid hypoglycemia, how to recognize the symptoms, and how to improve blood glucose monitoring. Patients with a history of hypoglycemia also may benefit from using an insulin that has a lower risk of hypoglycemia than their current treatment. Insulin degludec, a new basal insulin with an ultra-long duration of action, which is yet to be approved in the United States, along with existing basal insulin analogs detemir and glargine have been shown to have a lower risk of hypoglycemia than other insulin products. Studies have demonstrated that these products can reduce the risk of overall and nocturnal hypoglycemia compared with patients treated with neutral protamine Hagedorn insulin.45-47

This may suggest that individualizing treatment to suit the patients’ needs and concerns may help to alleviate some anxiety about the potential adverse effects of insulin therapy.

CONCLUSIONS

Despite proven efficacy as a treatment option for people with type 2 diabetes, insulin initiation and intensification often are delayed because of a number of factors. Furthermore, once insulin therapy is initiated, adherence to therapy often is poor with many patients omitting or altering their insulin doses.

Adherence to insulin therapy for people with diabetes is vital to reduce the risks of future complications and financial burden for both the healthcare systems and the patients as individuals. Adherence could be improved through a variety of means, in particular, practical approaches based on better communication with patients can be made to improve patient engagement with therapy, ultimately leading to potentially better adherence to their insulin regimens. Involving patients in decision-making in terms of their treatment plans and choosing regimens that are well tolerated and as simple and flexible for the patients as possible are likely to improve adherence to treatment. This may be done through encouraging self-titration and providing the patient the support of a diabetes healthcare professional if necessary.

Patients likely would benefit from their healthcare professionals educating them, and their family members or primary support person(s), in the efficacy of insulin therapy, particularly on improved therapies with decreased risks of issues that they fear, such as hypoglycemia. Healthcare professionals may need to make their patients aware of improvements in insulin therapies and delivery devices, in terms of reducing other adverse effects, including injection pain and weight gain, and increasing dosing flexibility. Working to improve the knowledge of patients with diabetes and healthcare professionals regarding the benefits of insulin therapy may lead to earlier initiation and intensification of insulin regimens. Determining a treatment regimen that fits a patient’s lifestyle and takes his or her concerns regarding insulin therapy into consideration may improve treatment satisfaction and adherence, with the ultimate goal of improving glycemic control.

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References