

Adherence to Insulin Therapy

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IN BRIEF Six million people with diabetes use insulin either alone or in combination with an oral medication. Many barriers exist that lead to poor adherence with insulin. However, there is an underwhelming amount of data on interventions to address these barriers and improve insulin adherence. Until pharmacological advancements create easier, more acceptable insulin regimens, it is imperative to involve patients in shared decision-making.

Hyperglycemia characterizes all forms of diabetes. Each individual's diabetes diagnosis is categorized as type 1 diabetes, type 2 diabetes, gestational diabetes mellitus, monogenic diabetes syndromes, a disease of the exocrine pancreas, or drug- or chemical-induced diabetes. Type 1 diabetes results from an absolute deficiency of insulin secretion due to cellular-mediated autoimmune destruction of the pancreatic β -cells. Type 2 diabetes results from insulin resistance and inadequate insulin secretion. Monogenic defects in β -cells result in impaired insulin secretion with minimal or no defects in insulin action (1).

The 2014 National Diabetes Statistics Report estimates that 9.3% of the United States population has diabetes. This equals 21.9 million people in the United States. In 2012, there were 17.1 million cases of newly diagnosed diabetes in people ≥ 20 years of age. The management of diabetes occurs via nonpharmacological interventions, typically in conjunction with either monotherapy or a combination of insulin and oral medications. A 2012 survey examining the number of patients who use diabetes medications found that 2.9 million people with diabetes (14%) use insulin only, 3.1 million (14.7%) use a combination of insulin and oral

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medications, 11.9 million (56.9%) use oral medications only, and 3 million (14.4%) do not use any medications to manage their diabetes (2).

Hyperglycemic crisis was noted as the cause for 175,000 emergency room visits in 2011, with 2,361 deaths resulting from hyperglycemic crisis in 2010 (2). According to 2011 U.S. Census data, 2.9% of deaths (73,831) were attributed to diabetes, making diabetes the seventh leading cause of death in the United States (3). Increased all-cause mortality and hospitalization have been linked to nonadherence to insulin therapy in patients with diabetes (4).

Complications

Diabetic kidney disease, diabetic retinopathy, diabetic peripheral neuropathy, and diabetic autonomic neuropathy make up the microvascular complications associated with diabetes. Complications may greatly affect patients' quality of life. Twenty to forty percent of patients with diabetes develop diabetic kidney disease, the leading cause of end-stage renal disease (5). Diabetic retinopathy may lead to blindness. Hypoglycemia unawareness, resting tachycardia, orthostatic hypotension, gastroparesis, constipation, diarrhea, fecal incontinence, erectile dysfunction, neurogenic bladder, and increased or decreased sweating can result from autonomic neuropathy (5). Furthermore, the leading cause of morbidity and mortality in individuals with diabetes is atherosclerotic cardiovascular disease (6). Achieving glycemic control has been associated with a reduction in microvascular complications in both type 1 and type 2 diabetes and a reduction in all-cause mortality in type 1 diabetes (7).

Treatment Options

To reduce long-term complications, treatment guidelines strongly recommend glycemic control. Although pharmacotherapy may be one part of obtaining glycemic control, diabetes self-management education, medical nutrition therapy, education regard-

ing physical activity, and psychosocial care are also key to managing diabetes (8). Patient preference, cost, antihyperglycemic efficacy, mechanism of action, risk of hypoglycemia, risk of weight gain, tolerability and adverse effects, ease of use, likely adherence, and safety should guide pharmacological treatment (9,10).

Metformin is the preferred initial pharmacological agent for type 2 diabetes. Other noninsulin agents include sulfonylureas, meglitinides, thiazolidinediones, α -glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide receptor agonists, and amylin mimetics. On rare occasions, bile acid sequestrants and dopamine-2 agonists may be used. Although there are many treatment options for patients with type 2 diabetes, insulin is the most effective therapy to reduce glucose levels.

Insulin Therapy

Insulin treatment, first used in 1922, is always indicated in autoimmune type 1 diabetes. Insulin treatment in type 2 diabetes is indicated in the setting of ketoacidosis, acute medical events, major surgery, concomitant disease or chronic steroid treatment, latent autoimmune diabetes, symptoms of hyperglycemia, failure of noninsulin treatments because of contraindications or adverse effects, poor glycemic control with lifestyle modification and noninsulin treatment, and pregnancy (11).

Insulin analogs offer longer or shorter durations of actions to more closely mimic normal secretion either overnight or in response to meals (12). In patients with type 2 diabetes, basal insulin is typically initiated first in a single daily dose and titrated to achieve glucose targets without hypoglycemia (10).

In comparison to NPH insulin, long-acting insulin analogs have a lower incidence of hypoglycemia (13). However, if cost is a concern, NPH insulin is a reasonable choice

for basal insulin (12). Rapid-acting insulin analogs, introduced in the 1990s, have a faster onset and shorter duration of action than human insulin; however, they still only provide an estimate of physiological insulin release (11). In comparison to regular insulin, rapid-acting insulin analogs offer improved control of postprandial glucose levels, decreased frequency of nocturnal hypoglycemia, and increased flexibility (14). Rapid-acting insulin analogs are recommended in multiple-dose insulin injections or insulin pump therapy in patients with type 1 diabetes. Although glycemic control can be achieved in two-thirds of patients taking long-acting insulin and metformin, insulin intensification is necessary for the remaining patients (12).

Insulin intensification in patients with type 2 diabetes should be individualized based on glycemic targets, eating habits, lifestyle, and patient preference. Basal insulin is followed by the addition of mealtime insulin if postprandial glucose remains elevated. Insulin intensification may include one of the following protocols: bolus plus one rapid-acting prandial insulin injection, a basal-bolus regimen, or the use of premixed insulin (11). A single rapid-acting insulin analog injection with the largest meal in addition to basal insulin has been shown to improve glycemic control (15).

Premixed insulin offers the advantage of twice-daily dosing; however, it does not offer the dosing flexibility of basal-bolus regimens (10). The traditional basal-bolus regimen adds a rapid-acting insulin analog with each of the patient's meals to basal insulin. Basal-bolus regimens lead to an improvement in glycemic control over basal insulin alone or premixed insulin (16). Implementation of insulin pump therapy is a costlier basal-bolus alternative (9).

Attempts continue to be made to improve insulin treatment and thus to increase adherence and acceptability. Inhaled human insulin is

available and offers a needle-free delivery system. More concentrated insulin preparations (glargine U-300 and degludec U-200) are available and may allow for better absorption when patients require higher doses of U-100 insulin (9). Insulin pumps enhance adherence and may result in lower insulin doses; however, cost and technology are limitations for use in all patients. New insulin formulations, routes of administration, and treatment strategies are in development to improve the care of patients with diabetes. Table 1 summarizes the available insulin formulations.

Adherence Versus Compliance

An important part of patient care is the relationship that is built with patients. When discussing the use of medications and a care plan with patients, it is important to use terminology that is patient friendly. Patients are often termed “noncompliant” without a second thought. This can make patients feel animosity toward their health care provider, which may not motivate them to take their medications regularly. Perhaps these discussions should occur using the term “adherence.” Among the definitions of “adhere” are 1) to give support or maintain loyalty and 2) to bind oneself to observance (17). This is a more relational term than “comply” (to conform, submit, or adapt as required or requested) (18). Using the term “adherence” implies that there was an agreeable discussion between clinician and patient regarding the treatment regimen. When patients play a role in their health care, they share ownership of the decisions, which has the potential to increase adherence.

Barriers to Insulin Adherence

The American Diabetes Association categorizes barriers to adherence as either patient barriers, medication factors, or system factors. Patient barriers include difficulty remembering to get refills from the clinician or to pick them up from the pharmacy, difficulty remembering to take medications, fear of taking medications,

TABLE 1. Insulin Formulations

Insulin Formulation	Typical Dosing
<i>Basal insulin</i>	
Intermediate-acting NPH insulin	Twice daily
Long-acting insulins	
Detemir	Once or twice daily
Glargine	Once daily
Glargine U-300	Once daily
Degludec	Once daily
Degludec U-200	Once daily
<i>Bolus insulin</i>	
Rapid-acting insulins	
Aspart	Three times daily before meals
Glulisine	Three times daily before meals
Lispro	Three times daily before meals
Inhaled insulin	Three times daily before meals
Short-acting insulins	
Regular human insulin	Three times daily before meals
Regular human insulin U-500	Two to three times daily without basal insulin
<i>Premixed insulin</i>	
NPH/regular	
70/30	Twice daily
50/50	Twice daily
Aspart protamine/aspart	
30/70	Twice daily
50/50	Twice daily
70/30	Twice daily
Lispro protamine/lispro	
50/50	Twice daily
75/25	Twice daily
Degludec/aspart 70/30	Twice daily

depression, or health beliefs regarding medications. Medication regimen complexity, multiple daily dosing of medications, cost, and side effects are all medication factors that may be barriers to adherence. System factors include inadequate follow-up and support (19).

A study published in 2014 examined possible barriers to insulin adherence. Participants included 251 patients with type 1 diabetes and 257 patients with type 2 diabetes. To discover patients’ perceived barriers, medication and patient-related

factors were addressed in a questionnaire completed by each participant. Overall, the most common barriers identified by patients with diabetes (type 1 or type 2) were injection site reactions (90.2%), fear of hypoglycemia (87.4%), injections being time-consuming (63.2%), interference with physical activity (61.6%), and lack of adequate injection instructions (59.6%) (20).

In comparison to patients with type 1 diabetes, patients with type 2 diabetes conveyed more concern about insulin injections interfering

with daily activities ($P = 0.01$), meal planning ($P < 0.01$), and physical activity ($P < 0.01$). Patients with type 2 diabetes report a higher incidence of injection site reaction ($P = 0.03$), weight gain ($P = 0.04$), and forgetfulness ($P < 0.01$). More patients with type 2 diabetes stated that multiple medications ($P < 0.01$) and sick days ($P < 0.01$) interfere with their adherence to insulin therapy compared to patients with type 1 diabetes. Patients with type 1 diabetes described more embarrassment ($P < 0.01$) related to insulin injections. More patients with type 2 diabetes reported that they believe insulin has an overall negative effect on their health ($P < 0.01$) and that they feel worse after taking insulin ($P = 0.02$) (20).

Current Research

In 2014, the Cochrane Collaboration revisited a question regarding the outcomes of high-quality studies examining medication adherence. The update concluded that because of the varied interventions and study characteristics, there is no consistency with regard to methods for improving medication adherence. The authors called for higher-quality research to be conducted to better inform efforts to improve medication adherence (21). More specifically related to type 2 diabetes treatment, a 2009 update to a Cochrane review examining interventions aimed at improving treatment regimen adherence showed only a small effect on outcomes, with no data on morbidity, mortality, or quality of life. Interventions examined included those led by nursing or pharmacy personnel, educational interventions, and alterations in medication dosing and frequency (22).

Studies Specific to Insulin Adherence

A 2015 study by Cani et al. (23) showed a decrease in A1C by 0.57% ($P < 0.001$) in insulin-treated patients with type 2 diabetes. These patients were provided with an individualized pharmacotherapeutic care plan from a clinical pharmacist, as well as a di-

abetes education protocol. The education protocol covered topics such as complications (acute and chronic), lifestyle changes, foot monitoring, and glucose monitoring. This study showed improved adherence as measured by both the Morisky-Green questionnaire ($P < 0.001$) and the Adherence to Medicines Questionnaire ($P = 0.039$).

Farsaei et al. (20) found that patients with type 1 or type 2 diabetes who were classified as having low adherence via the Morisky Medication Adherence scale reported injections being time-consuming, embarrassment, feeling worse after an injection, forgetfulness, hypoglycemia, cost, weight gain, insulin shortage, and difficulties with injection preparation as factors significantly associated with adherence.

Another study published in 2013 by Guo et al. showed a 0.16% greater A1C reduction in patients with type 2 diabetes treated with insulin therapy who were entered into the OPENING education program compared to those with no educational intervention. The OPENING program has seven modules: 1) taking medication, 2) insulin injection technique, 3) blood glucose monitoring, 4) diet, 5) exercise, 6) hypoglycemia prevention, and 7) prevention of complications. Adherence according to the Morisky Medication Adherence Scale improved more in the intervention group ($P < 0.05$) (24).

The 2011 I DO study, with 526 participants, examined the effect of a telephonic intervention to improve insulin adherence. Up to 10 phone calls focusing on medication adherence and lifestyle modification were provided by trained health educators every 4–6 weeks for 1 year. Compared to the control group, the intervention group showed a decrease in A1C of 0.23% ($P = 0.04$). Unfortunately, the change in medication possession ratio, or percentage of time a patient has access to medication, was significant in patients who were not taking insulin ($P = 0.005$),

with no significant change occurring in patients with insulin therapy ($P = 0.28$) (25).

Several studies have examined adherence to therapy when using an insulin pen device compared to insulin vials and syringes. These studies show that, in addition to being preferred by patients, insulin pen devices are associated with improved adherence (26).

A meta-analysis focusing on adherence in pediatric patients with type 1 diabetes concluded that interventions having a greater effect on A1C are those that target several components, such as social and behavioral interventions. The authors did mention that more data on effectiveness are needed, as well as more refined interventions (27).

Conclusion

Delayed introduction of or ineffective insulin therapy contributes to poor glycemic control and places patients at risk of complications (11). Although there is a large amount of information about patient barriers to insulin therapy, there is an underwhelming amount of data on interventions to addressing those barriers or even aimed at improving insulin adherence in general. As stated throughout the available literature, more data are needed to address this concern as we continue to make strides to improve patient care in the area of diabetes management. However, one factor is imperative to encourage adherence and subsequent glycemic control: involving patients in the decision-making process (28). Education and empowerment through shared decision-making allow patients' preferences to be presented and considered and subsequently create the best individualized treatment plan for each patient.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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