

Identifying and meeting the challenges of insulin therapy in type 2 diabetes

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Abstract: Type 2 diabetes mellitus (T2DM) is a chronic illness that requires clinical recognition and treatment of the dual pathophysiologic entities of altered glycemic control and insulin resistance to reduce the risk of long-term micro- and macrovascular complications. Although insulin is one of the most effective and widely used therapeutic options in the management of diabetes, it is used by less than one-half of patients for whom it is recommended. Clinician-, patient-, and health care system-related challenges present numerous obstacles to insulin use in T2DM. Clinicians must remain informed about new insulin products, emerging technologies, and treatment options that have the potential to improve adherence to insulin therapy while optimizing glycemic control and mitigating the risks of therapy. Patient-related challenges may be overcome by actively listening to the patient's fears and concerns regarding insulin therapy and by educating patients about the importance, rationale, and evolving role of insulin in individualized self-treatment regimens. Enlisting the services of Certified Diabetes Educators and office personnel can help in addressing patient-related challenges. Self-management of diabetes requires improved patient awareness regarding the importance of lifestyle modifications, self-monitoring, and/or continuous glucose monitoring, improved methods of insulin delivery (eg, insulin pens), and the enhanced convenience and safety provided by insulin analogs. Health care system-related challenges may be improved through control of the rising cost of insulin therapy while making it available to patients. To increase the success rate of treatment of T2DM, the 2012 position statement from the American Diabetes Association and the European Association for the Study of Diabetes focused on individualized patient care and provided clinicians with general treatment goals, implementation strategies, and tools to evaluate the quality of care.

Keywords: type 2 diabetes, barriers, patient education, individualized therapy, self-management, insulin, insulin analogs, insulin pens, emerging technologies

Introduction

Advances in technology and an increased understanding of the role of insulin in the complexity of both glycemic homeostasis and energy homeostasis have led to insulin preparations that more closely mimic the endogenous pattern of insulin release.¹ Data from the landmark United Kingdom Prospective Diabetes Study 49 on the use of monotherapy, combined with data from United Kingdom Prospective Diabetes Study 28 on combination therapy, led the authors to conclude that after 9 years, a substantial number – possibly the majority – of patients with type 2 diabetes mellitus (T2DM) will require insulin to reach the goal of hemoglobin A_{1c} (HbA_{1c}) <7.0% (<53.0 mmol/mol).^{2,3} To bring and to maintain patients to goal earlier in their disease process, instead of being the treatment of last resort, for many patients, insulin should be instituted much earlier

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in the disease process as part of an individualized preventive treatment strategy. Early intensive insulin therapy in patients with newly diagnosed T2DM significantly improved β -cell function and remission rates from hyperglycemia compared with treatment with oral antidiabetic agents.⁴ The recent introduction of new therapeutic agents for glycemic control offers more treatment options, but it also raises questions among clinicians as to when and how insulin should be initiated in patients with T2DM.

The ultimate goal of glycemic management in diabetes is to safely achieve and maintain glucose and energy homeostasis close to normal levels to slow, and even prevent, the complications of hyperglycemia.⁵ Early use of insulin therapy in T2DM may result in a reduction in chronic glucotoxicity, which increases the rate of β -cell apoptosis and deterioration in β -cell function.^{6–8} Because of the pathogenesis and progressive nature of T2DM, the majority of patients with T2DM will ultimately require insulin therapy.^{2,9} Subset analyses of several studies have demonstrated that intensive glycemic control in patients with a shorter duration of T2DM and no established atherosclerosis may lower the risk of developing cardiovascular complications¹⁰ and positively affect both the macro- and microvascular prognosis.⁵ Although the administration of basal insulin glargine more effectively reduced the incidence of new-onset diabetes in patients with impaired glucose tolerance than standard treatment, it caused an increased incidence of hypoglycemia and a modest increase in weight, and therefore the risk/benefit ratio for early initiation of basal insulin continues to be debated. When the decision is made to intensify, consideration should be given to early initiation of detemir and glargine for their favorable safety and efficacy profiles.^{11–13}

Current American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) treatment guidelines cited the recommendation for more stringent HbA_{1c} targets (6.0%–6.5% [42.1–47.5 mmol/mol]) in selected patients,¹³ although higher goals, such as 8.0% (63.95 mmol/mol), may be more appropriate for patients with severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, long durations of comorbid conditions, and extensive history of inability to meet the goal of greater glycemic control.¹⁴ Such stringent glycemic control usually requires combination therapy that, if initiated early, offers the best chance of modifying the disease process and preserving quality of life. Conversely, less stringent HbA_{1c} targets (7.5%–8.0% [58.5–63.9 mmol/mol] or even slightly higher) are appropriate for patients with a history of severe hypoglycemia, and those for whom the

glycemic target is difficult to attain despite therapy and lifestyle modifications.^{13,15}

A study of 17,306 US patients with diabetes found that only 57% had HbA_{1c} levels that met the 2011 ADA goal of <7.0% (<53.0 mmol/mol).^{13,16,17} The 2012 ADA/EASD position statement also cited the recommendations by the 2011 ADA¹⁷ regarding initiation of metformin therapy and lifestyle modification upon diagnosis of T2DM, unless metformin is contraindicated.¹³ Additionally, starting treatment with a combination of two noninsulin agents or with basal insulin in patients with a baseline HbA_{1c} \geq 9.0% (\geq 74.9 mmol/mol) may be justified because of the low probability of achieving glycemic control on monotherapy.^{13,18} Therefore, if a patient presents with significant hyperglycemic symptoms and/or if the HbA_{1c} level is between 10.0%–12.0% (85.8–107.7 mmol/mol), insulin therapy should be strongly considered from the outset.¹³

Guidelines from the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) recommend initiating insulin therapy in symptomatic patients with HbA_{1c} >9.0% (>74.9 mmol/mol).¹⁹ All of these factors demonstrate the benefits of individualized treatment plans aimed at optimizing glycemic targets.¹³

Despite the efficacy of insulin therapy, it is used in <50% of the patients for whom it is recommended and with poor patient adherence.²⁰ One-third of insulin-naïve patients who are prescribed insulin do not become ongoing users,²¹ and almost 60% of patients miss injections, with 20% missing doses on a regular basis.²² Challenges to insulin therapy may present an even greater hurdle in clinical practice settings that are not specialized in intensive diabetes care or where educational resources are limited.

Challenges associated with insulin use in T2DM treatment are often grouped into three categories: 1) clinician-related challenges; 2) patient-related challenges; 3) and health care system-related challenges. This review will discuss issues encountered by clinicians and patients in the initiation and intensification of insulin therapy; recent advances in insulin therapy and delivery; and practical strategies health care providers (HCPs) can implement to overcome these challenges.

Methods

Articles addressing clinician-, patient-, and health care system-related challenges of insulin therapy in patients with T2DM were identified by a literature search in PubMed covering the period of 1990–2013. The search terms used

included: “insulin therapy”; “type 2 diabetes”; “adults”; “challenges and/or barriers”; “clinicians and/or physicians”; and “healthcare and/or health care”. Selection was limited to English-language, peer-review articles. The search was further refined to include articles addressing clinician-, patient-, and health care system-related challenges of insulin therapy initiation. Internal references were also used if they were applicable to the discussion. In addition, the authors’ clinical experience with T2DM was utilized to analyze the literature to assist HCPs with the assessment and treatment of patients with T2DM. Also, 115 articles were included and reviewed in this paper.

Results

Clinician-related challenges

Understanding and overcoming clinical inertia

Clinicians often are slow to initiate or intensify therapy, a behavior defined as “clinical inertia” that involves recognition of the problem but failure to act.²³ Clinical inertia may be caused by: an overestimation of the care provided; perception by the clinician that glycemic control is improving or that the patient is not compliant to diet and exercise;²⁴ lack of proper clinical training; and the absence of focus on achieving patients’ therapeutic goals.²³

Historically, insulin has been initiated as last resort therapy to help patients with advanced diabetes achieve and maintain their therapeutic goals. Only 18% of patients who were receiving combination therapy with oral antidiabetes agents were switched to insulin before their HbA_{1c} exceeded 8.0% (63.9 mmol/mol).²⁵ Hypothetically, the average patient in this study would have spent 5 years with an HbA_{1c} >8.0% (63.9 mmol/mol) and 10 years with an HbA_{1c} >7.0% (>53.0 mmol/mol) before insulin was initiated.²⁵

A survey of 600 primary care physicians (PCPs) and specialists who treat patients with diabetes indicated that the lack of experience in initiating insulin and time to educate patients present challenges to insulin intensification.²⁶ While 92% of respondents agreed that insulin intensification is an essential component of diabetes management, more than 20% of them never initiated or modified insulin therapy.²⁶ In addition, 49% of the surveyed physicians indicated that not staying current with advances in insulin therapies or delivery methods is one of the main challenges to insulin initiation.²⁶ Because this was a multinational study, it is important to consider the geographical difference in diabetes management. PCPs who treat fewer numbers of patients with T2DM are more reluctant to initiate insulin therapy compared with those who treat a greater number of patients.²⁷

Approximately 40% of PCPs who treat patients with T2DM believed insulin initiation would be unnecessary if patients followed their physician’s recommendations, and that training patients in the proper administration and use of insulin is overly time consuming for the staff.²⁷ Uncertainty about insulin dosing, concerns about individualizing insulin therapy,²⁸ and the lack of consensus among national guidelines and recommendations can also increase clinical inertia on the part of clinicians about appropriate glycemic targets.^{19,29,30} Clinicians should consider these guidelines within the context of the needs, preferences, and tolerances of each patient with a patient-centered approach that uses individualized treatment.¹³

Although T2DM is a progressive disease and the majority of patients will ultimately require insulin therapy,^{2,9} some physicians consider initiation of insulin therapy a personal failure to control their patients’ diabetes with oral antidiabetic agents and feel that they must force their patient to accept insulin therapy. To overcome this challenge, clinicians should actively listen to patients’ concerns and/or fear regarding insulin therapy and explain that type 2 diabetes is a progressive disease and that β -cell failure is common.³¹ For example, if the patient is concerned about insulin-induced hypoglycemia, the clinician can explain that newer long- and short-acting insulin analogs are less likely to cause hypoglycemia compared with older insulin preparations and that severe hypoglycemia is seen mainly in patients with type 1 diabetes mellitus (T1DM).³¹

Hypoglycemia

Hypoglycemia is a primary safety concern for both clinicians and patients; it represents a major challenge to glycemic control. Minor hypoglycemic episodes are significant, as frequent minor events increase the risk for severe hypoglycemia³² via the development of hypoglycemia unawareness. Although few hypoglycemic episodes manifest as “severe” (requiring assistance from another person to remedy),³³ severe episodes may cause significant morbidity, and – sometimes – death.^{34–37}

Anxiety and/or fear in both patients and physicians can interfere with glycemic control.³² Patients who experience hypoglycemia, particularly severe hypoglycemia, may be reluctant to maintain or self-adjust their insulin regimen, resulting in chronic hyperglycemia.³⁸ Additionally, nocturnal hypoglycemia is likely to be underreported because patients may not awaken or recognize the symptoms.³⁹ Because physiologic and symptomatic defenses that combat hypoglycemia are suppressed during sleep, mild or moderate hypoglycemic

episodes may progress to more severe episodes, with more serious consequences.^{39,40}

Risk factors for hypoglycemia associated with insulin therapy include: poorly timed insulin administration; lack of recognition of increased tissue sensitivity to insulin; increased glucose utilization following exercise; and inappropriate use of insulin or insulin secretagogues.³² All of these risk factors can be reduced with timely initiation of therapy using currently available insulin formulations and technologies (insulin pumps and monitoring), and proper patient education, which should empower physicians to overcome their inertia.

Although events of hypoglycemia are more common in individuals with T1DM, they also occur relatively frequently in patients with T2DM using insulin and/or sulfonylurea therapy. Because T2DM is approximately 20 times more prevalent than T1DM, and most of these patients will ultimately require insulin therapy due to a progressive decline of β -cell function, a greater number of hypoglycemic episodes, including severe hypoglycemia, are seen in patients with T2DM.³² Advances in insulin therapy can help address physicians' concerns about hypoglycemia. For example, as discussed below, basal insulin analogs are associated with a reduced risk of hypoglycemia^{41–44} and, importantly, reduced nocturnal hypoglycemia in both T1DM and T2DM.⁴⁵

Strategies to manage weight gain

Weight gain and fluid retention are also common side effects of insulin therapy. Since the majority of patients with T2DM are overweight, clinicians may be reluctant to initiate and intensify insulin therapy in these patients because of the potential for additional weight gain with insulin therapy, which can exacerbate insulin resistance. Compared with neutral protamine Hagedorn (NPH), basal insulin analogs, particularly detemir, have consistently produced less weight gain.^{43,44} Additionally, clinicians can initiate an appropriately titrated basal insulin regimen, coupled with the timely use of mealtime insulin, to reduce weight gain and hypoglycemia. In addition to controlling T2DM, new evidence suggests that the addition of a glucagon-like peptide 1 receptor agonist (GLP-1RA) to insulin glargine abrogates the weight gain associated with insulin and leads to weight loss.⁴⁶

Managing time concerns

In 2007, in the US, PCPs diagnosed approximately 65% of cases of T1DM and T2DM.⁴⁷ In one survey, two-thirds of PCPs indicated that the initiation of insulin and time needed to train patients are two of the most difficult aspects

of managing patients with T2DM.²⁷ Because clinician nurses are often involved in insulin initiation, they will also benefit from protocols for implementing insulin initiation, hands-on training, and local support services.⁴⁸ Access to education is often limited, and without adequate professional training, insulin initiation may be both delayed and suboptimal.^{29,49}

Unfortunately, only 44% of PCPs in the US have access to a Certified Diabetes Educator (CDE),²⁶ the majority of whom are not members of the PCPs' staff. This forces clinicians to send patients to another office to see the CDE; this slows the process, disrupts continuity of care, and may result in miscommunication. These educational resources may be limited or unavailable to some patients.

Although patient education is a time consuming task for physicians,²⁷ clinicians should give patients the time to express their fears and concerns about insulin therapy, thereby identifying preexisting misconceptions and addressing them accordingly.³¹ For example, physicians often overestimate the patient's fear of injection pain, making a preemptive decision to delay or withhold insulin, when – in fact – one study showed that fear of pain ranked fairly low among patients.⁵⁰ The majority of PCPs agree that the potential for insulin to prevent or to delay complications far outweighs the risks of weight gain and hypoglycemia.²⁷ Practical, time-efficient solutions that will help educate patients on the importance of treatment adherence, the proper administration of insulin, and overcome the time concern challenge are presented here.

Patient-related challenges

Balancing complexity of insulin regimen with health-related quality of life potential

Patient perception that insulin therapy is too complicated and time consuming can interfere with its timely initiation.^{51,52} A psychological insulin resistance self-report survey was conducted in a large multicity sample of insulin-naïve patients with T2DM. Almost 50% of insulin-naïve patients believed themselves incapable of managing an insulin regimen, and that such therapy would restrict their lifestyle.⁵¹ Indeed, some tasks, such as determining dosages and handling syringes and vials, can be overwhelming for some patients. Less complex dosing can improve patient adherence, while inflexible complex dosing is often cited as a reason for missing insulin doses.⁵³ A survey of 1,250 physicians who treat patients with T2DM and a telephone survey of 1,530 insulin-treated patients in the US and several other countries revealed that two-thirds of the patients felt that diabetes controlled their

lives and that treatment regimens were too restrictive.⁵⁴ Additionally, 28.2% of patients surveyed reported that they would be unwilling to take insulin if their physician prescribed it.⁵¹

Basal-bolus insulin therapy, which can minimize postprandial glucose (PPG) excursions and maintain glyce- mic control,⁵⁵ can be particularly challenging for patients. However, this regimen likely leads to the highest improve- ments in health-related quality of life.⁵⁵ With proper patient education, patients can match insulin to food choices to main- tain glycemic control and avoid weight gain. Basal-bolus regimens that are simpler to follow may provide an effec- tive strategy. One study compared the stepwise addition of aspart to either the largest meal (titration based on premeal glucose values) or the meal with the largest prandial glucose increment, in 296 individuals with T2DM inadequately con- trolled on basal insulin and oral antidiabetes agents.⁵⁶ The stepwise addition of bolus insulin based on either premeal or postmeal glucose values was equally effective for intensify- ing therapy in patients with T2DM.^{56,57} Another study yielded similar results for the stepwise addition of prandial insulin in patients requiring intensification beyond basal insulin.⁵⁷

Achieving glycemic control with insulin therapy depends to a great extent on educating patients regarding their condi- tion, self-management strategies, and available therapeutic options. Developing less complex treatment plans that meet the glycemic goals may also provide an effective treatment strategy. Given the improved risk–benefit ratios of insulin analogs compared with older formulations, physicians should make informed decisions based on current information on evolving new insulin formulations that highlight the benefits of a preventive, pathophysiologic approach to treatment.

Meeting patient convenience needs

The pharmacokinetic and pharmacodynamic limitations of older insulin therapies can make the use of insulin therapy more challenging. Regular human insulin (RHI) has traditionally been used to replace the endogenous spike in insulin production immediately following meals. Due to its slow absorption rate and onset of action, RHI should opti- mally be administered 30–45 minutes before a meal, which can present logistical difficulties.^{52,58} Injecting RHI too early or too late will result in hypoglycemia or late postprandial hypoglycemia, respectively. Unlike RHI, the rapid-acting insulin analogs lispro, aspart, and glulisine are absorbed more quickly, have an earlier and higher insulin peak con- centration, and a shorter duration of action than RHI.^{58,59} Therefore, rapid-acting insulin analogs can be administered

at meal time, although administration 10–15 minutes before the meal is recommended to optimize control of postprandial glycemic excursions. Compared to RHI, these formulations offer greater convenience, improvement of PPG excursions, and reduction of late postprandial hypoglycemia.^{58–62}

Basal insulin analogs glargine and detemir provide consistent and relatively flat, long-acting insulin levels that mimic the constitutive secretion pattern of endogenous insulin, which provides continuous coverage.^{63–67} Currently available basal insulin analogs are dosed once daily in the majority of patients, but they should be dosed at the same time every day to optimize control. In some patients, basal insulin analogs can be dosed twice daily to provide flatter basal insulin coverage (24-hour coverage).^{66,68,69} Emerging long-acting basal insulins (eg, insulin degludec), which can be administered once daily in all patients and at any time of day without compromising glycemic control, might better address patient convenience and fear of hypoglycemia.^{70–72}

Destigmatizing needles

Recent advances in needle technology have made insulin injections more accurate, less painful, more discreet, and convenient to use than vials and syringes.^{73–75} Use of insulin pens can overcome some of the patient-related challenges (stigma and fear) to initiation of insulin therapy.^{74–76}

Overcoming common misperceptions about insulin

Most patients perceive the initiation of insulin therapy as a reflection on their own failure to manage their disease^{51,52,77,78} and that insulin is not effective or may even cause harm.^{21,78} In a study of patients who accepted insulin therapy, but did not become long-term users, major predictors of insulin nonadherence included the negative impact of insulin on social and work lives, injection phobia, and concerns about side effects.²¹ Nearly one-half of the patients who did not adhere to insulin therapy believed that people who require insulin “have not taken care of themselves in the past”, and 35% believed that insulin causes harm.²¹ Because patients with T2DM tend to be obese, slight weight gain may have an impact on glycemic control.^{52,79} Moreover, fear of hypo- glycemia is a major cause of nonadherence and resistance to insulin initiation in these patients.⁵¹ Interestingly, patients who did not adhere to insulin treatment frequently believed their clinician did not adequately explain the benefits and risks of insulin therapy.²¹ These are legitimate concerns that need to be addressed by the treating clinician. Therefore, the optimal time to educate patients about insulin therapy is soon

after diagnosis, or early in the course of the disease, as this time frame offers clinicians the opportunity to destigmatize insulin use and address patient concerns.

Cost of insulin therapy

The cost of insulin is another patient-related challenge. Although long-acting basal insulin analog therapy is associated with lower rates of hypoglycemia, this therapy is costly compared to conventional insulins.⁸⁰ However, for some patients who are at high risk of hypoglycemia, the use of insulin analogs may prove to be cost-effective compared with the additive cost of treating a single extra hypoglycemic event.^{80–83} Cost-effectiveness of insulin analogs depends on the type of insulin analog, whether the patients have T1DM or T2DM, and the country in which they reside.^{80,84} HCPs are advised to consider the full costs associated with the use of insulin therapy rather than the cost of insulin alone.⁸⁵

Health care system-related challenges

The Medicare Part D program provides prescription drug coverage for Medicare beneficiaries. One unique feature of this program is the coverage gap (or “donut hole”). In 2008, benefits included a deductible and 25% copayment for drug spending between \$275–\$2,510. After the initial coverage period, beneficiaries entered a coverage gap, in which they paid 100% of the drug cost until their true out-of-pocket drug spending reached the catastrophic limit of \$4,050. Under the catastrophic coverage, beneficiaries pay the greater of a 5% or a \$2.25 or \$5.60 copayment for generic or brand-name drugs, respectively.⁸⁶ Gu et al analyzed adherence to antidiabetic agents in a sample of 12,881 Medicare Part D beneficiaries with diabetes who had three different levels of coverage: 1) no coverage; 2) generic drug coverage only; and 3) both generic and brand-name drug coverage.⁸⁶ The study demonstrated that the coverage gap in the Medicare Part D program has a significant negative impact on medication adherence among beneficiaries with diabetes and that the availability of brand-name drug coverage is important to the adherence to diabetes medications. Likewise, in a cohort of patients intensifying their basal insulin therapy with the addition of mealtime insulin, one of the risk factors associated with poor persistence to mealtime insulin therapy was increased average insulin copayment.⁸⁷ Increased levels of copayments were found to be a significant barrier to optimal adherence after conversion to pen therapy from vial and syringe therapy in patients with T2DM treated in a managed care setting.⁸⁸ Another study that compared the cost of thiazolidinedione or insulin therapy for the treatment of patients with uncontrolled T2DM

demonstrated that the cost of therapy with thiazolidinedione was substantially lower than that of insulin therapy in the first year. This is because patients receiving insulin therapy need to use more blood glucose monitoring strips and need to attend an educational session. However, in year 2 and year 3, the costs of the two therapies were comparable.⁸⁹

Evolution of insulin technology

Advances in the understanding of the pathophysiology of T2DM over the last 2 decades and the technological and biochemical advances in insulin analogs have enabled clinicians to more closely mimic the basal and prandial insulin secretory profiles seen in normoglycemia, progress that might help overcome the challenges associated with insulin therapy. All insulins manufactured for therapeutic purposes in the US are the altered basic human insulin molecule with altered absorption profile.⁹⁰

Rapid-acting insulin analogs

Human insulin has a natural propensity to form hexamers in the pancreas during storage in the β -cell,⁹¹ resulting in slow absorption into the circulation. Upon extracellular release, hexamers then dissociate into dimers and monomers, which are the biologically active form of insulin. Rapid-acting insulin analogs have a lowered propensity to form hexamers, and injection of rapid-acting insulin analogs results in quick absorption into the circulation and earlier and higher insulin peak concentration.⁵⁹ Rapid-acting analogs are thus better suited, pharmacologically, to meet the PPG surge. Patients using rapid-acting insulin analogs had lower rates of hypoglycemia compared to older-generation, short-acting insulin formulations (Table 1).^{62,92,93}

Long-acting insulin analogs (basal insulin)

The unique and more predictable pharmacokinetic and pharmacodynamic properties of basal insulin analogs offer significant advantages over NPH. Basal insulin analogs glargine and detemir more effectively mimic the constitutive secretion of endogenous insulin, reduce glycemic variability, and are absorbed more slowly and consistently than NPH. This profile results in a longer duration of action, a flatter pharmacodynamic profile, and better glycemic control.^{41,59,94} Detemir has a lower coefficient of variability than either glargine or NPH⁹⁴ and is the only basal insulin commercially available that does not form microcrystals in the subcutaneous space. Use of detemir in combination with metformin or a GLP-1 receptor agonist may minimize weight gain.⁹⁵ Moreover, basal insulin analogs significantly reduce the rate of hypoglycemia

Table 1 Effects of different insulin formulations on glycemic control and hypoglycemia in patients with type 2 diabetes

Insulin formulation	Background medication	Comparator	Δ HbA _{1c} (%)	Δ FPG (mmol/L)	Δ 2-hr PPG (mmol/L)	Hypoglycemic episodes	Conclusion	Reference
Rapid-acting insulin analogs								
Insulin lispro	Basal insulin	RHI	Equal reduction	NR	48% decrease ^a	Reduced rate ^b	Insulin lispro improves postprandial control in diabetes	Anderson et al 1997 ⁶²
Insulin aspart	Metformin	RHI	Significant change ^{ab}	No significant change with lispro or RHI	Trend toward reduction	No serious events reported for the two groups	Results support use of mealtime insulin aspart plus metformin in patients with T2DM and inadequately controlled postprandial hyperglycemia	Pala et al 2007 ³³
Insulin glulisine	NPH plus prestudy OADs	RHI	Slight reduction ^b	Significant reduction ^b	Significant reduction ^b	Comparable between two groups	Glulisine plus NPH can provide small improvements in glycemic control compared with RHI in patients with T2DM who are relatively well-controlled on insulin alone or insulin plus OADs	Dailey et al 2004 ³²
Long-acting insulin analogs (basal insulin)								
Glargine	Prestudy OADs	NPH	Similar reduction for glargine and NPH; significant reduction from baseline	Significant reduction ^a	Significant reduction ^b	Significant reduction ^a	Insulin glargine is associated with less nocturnal hypoglycemia and lower PPG levels compared with NPH	Yki-Järvinen et al 2000 ⁸⁶
Detemir	Prestudy OADs	NPH	Similar reduction; more patients reached HbA _{1c} \leq 7.0% without hypoglycemia with detemir ^a	Similar reduction	Similar reduction	Significant reduction ^a	Insulin detemir compared with NPH achieves guidelines ^a glycemic control with reduced hypoglycemia and less weight gain	Hermansen et al 2006 ³⁷
LY2605541	Metformin and/or sulfonylurea	Insulin glargine	Similar reduction	Similar reduction	Significant reduction ^b	Similar rates	LY2605541 and insulin glargine had comparable glycemic control and total hypoglycemia rates	Bergental et al 2012 ¹⁴
Insulin premixes								
Biphasic insulin aspart (30/70)	Metformin	NPH, biphasic human insulin (30/70)	Similar reduction	Similar reduction	Similar reduction, with lower values with NPH	Similar rates	Once-daily injections of three formulations in combination with metformin achieve glycemic control	Kilo et al 2003 ¹⁰⁵
Degludec	NR	Human insulin premix (30%)	Similar reduction	Similar reduction	Significant reduction (90 minutes) ³	Similar rates	Biphasic insulin aspart demonstrated significantly better post-prandial blood glucose control	Boehm et al 2002 ¹⁰¹
Future ultra-rapid-acting insulin analogs								
Degludec	Insulin aspart	Insulin glargine	Similar reduction	Similar reduction	Similar reduction	Significant reduction ^b	Optimal glycemic control might be attained with insulin degludec, which is associated with lower risks of hypoglycemia than insulin glargine	Garber et al 2012 ¹⁰⁹

(Continued)

Table 1 (Continued)

Insulin formulation	Background medication	Comparator	Δ HbA _{1c} (%)	Δ FPG (mmol/L)	Δ 2-hr PPG (mmol/L)	Hypoglycemic episodes	Conclusion	Reference
Insulin degludec/insulin aspart (70/30)	Metformin	Biphasic insulin aspart (30%)	Similar reduction	Significant reduction ^a	Twice as many subjects reached PPG control with insulin degludec/aspart	Significant reduction ^a	Insulin degludec/aspart provided comparable overall glycemic control to biphasic insulin aspart, with a significantly lower rate of hypoglycemia	Niskanen et al 2012 ¹⁰
	Metformin	Insulin glargine	Similar reduction	Similar reduction	Lower with insulin degludec/aspart	Similar rates	Once-daily insulin degludec/aspart provided comparable overall glycemic control to insulin glargine and similar low rates of hypoglycemia, but better PPG	Heise et al 2011 ⁹⁸

Notes: ^aSignificant change in favor of drug compared with comparator; ^bsignificant change compared with baseline.

Abbreviations: HbA_{1c}, hemoglobin A_{1c}; FPG, fasting plasma glucose; PPG, postprandial glucose; NPH, neutral protamine Hagedorn; NR, not reported; T2DM, Type 2 diabetes mellitus; OADs, oral antidiabetic drugs; RHI, regular human insulin.

compared with NPH^{96,97} and patients who achieved fasting plasma glucose (FPG) targets experienced less symptomatic hypoglycemia (Table 1).⁹⁶ Therefore, the AACE does not recommend NPH due to its increased risk for hypoglycemia compared to basal insulin analogs.¹⁹

Although currently available basal insulin analogs offer several advantages over NPH, they do not completely reproduce the physiological basal insulin secretion profile, which continues to be an unmet need in the treatment of diabetes.^{98,99} At higher doses, the profile of glargine and detemir show a slight rise and fall in insulin activity,⁹⁹ and when <25 units daily are used in insulin-sensitive individuals, they do not always achieve 24-hour coverage.⁶⁸ Basal insulins also lack postprandial coverage and should be dosed at the same time every day to ensure optimal control. These limitations may, in part, explain why basal insulin treatment for patients with T2DM may fail to reach and maintain HbA_{1c} goals.

Insulin premixes

Insulin premix therapy is a useful option for patients who require prandial insulin coverage but are not able or willing to use multiple daily injections.¹⁰⁰ Biphasic insulin analogs, which consist of part insulin analog and part protaminated version of the same analog, have a more physiological profile compared to human insulin premixes. Premixed insulin analogs can be injected at mealtimes, providing greater patient convenience and dosing flexibility. They may also be associated with a lower risk of major hypoglycemia than human insulin premixes,¹⁰¹ which should be administered 30–40 minutes before meals. Biphasic insulin analogs can be dosed once, twice, or three times daily, depending on patient's needs,^{102–105} and once-daily administration of biphasic insulin analog at dinner time in combination with metformin has been shown to be effective for many patients.¹⁰⁵ Insulin analog premixes are also available in a variety of long- to short-acting dosing ratios: 75/25; 70/30; and 50/50. These formulations are better suited to those who eat regularly and consistently.

Future formulations

Ultra-long-acting insulin degludec

Current basal insulins possess pharmacokinetic and pharmacodynamic properties that are superior physiologically to NPH, but still do not meet the criteria of an ideal basal insulin.¹⁰⁶ These characteristics include: an ultra-long-action profile allowing for once per day dosing in all patients; a flat time-action profile with a very low level of day-to-day variability minimizing both hypoglycemia and hyperglyce-

mia; and the ability to tailor therapy to the individual patient by allowing for flexible dosing schedules.¹⁰⁶ Insulin degludec forms soluble multihexamers upon subcutaneous injection, resulting in an ultra-long-action profile of >42 hours, a long half-life (>24 hours), and a smooth and stable pharmacokinetic profile at steady state.^{107,108} In a 1-year trial in patients with T2DM, insulin degludec given with aspart improved FPG and long-term glycemic control with a significantly lower risk of overall and nocturnal hypoglycemia compared to glargine with aspart (Table 1).¹⁰⁹ Insulin degludec was studied in one trial using extreme dosing in patients with T2DM, to create intervals of 8–40 hours between doses.⁷⁰ Insulin degludec was associated with significantly less nocturnal hypoglycemia ($P=0.0031$)⁷¹ in both the fixed and flexible populations and had the added convenience of flexible daily injections compared to that of conventional basal-bolus therapy. Another study demonstrated that in T1DM, degludec can be administered flexibly at any time of day with similar glycemic control and less nocturnal hypoglycemia compared with glargine given once daily at the same time for 52 weeks.⁷² Insulin degludec significantly reduced variability in insulin action when compared with glargine and lowered the rates of hypoglycemia,¹⁰⁹ as well as significantly reduced hypoglycemic episodes during the maintenance period.¹⁰⁹

Ultra-long-acting insulin degludec/aspart

A combination of degludec and aspart is in development. Because of its unique molecular modification, insulin degludec is the first basal insulin analog that can be combined with a rapid-acting insulin analog while preserving the pharmacokinetic profile and the efficacy of the individual insulins (Table 1).^{98,110}

Ultra-rapid-acting insulin BIOD-095, BIOD-105, and BIOD-107

When a novel combination of excipients is used to modify the insulin hexamer complex, it results in a more rapid dissociation of the hexamers into monomers and dimers following subcutaneous injection.¹¹¹ Ethylenediaminetetraacetic acid, in conjunction with citric acid or sodium citrate to sequester zinc, works to destabilize the insulin hexamer. After injection and dilution in the subcutaneous milieu, BIOD-095 rapidly disassembles into smaller monomeric/dimeric subunits.¹¹² BIOD-105 and BIOD-107 are two new ultra-rapid-acting human insulin formulations with added citrate, ethylenediaminetetraacetic acid, and calcium. BIOD-105 and BIOD-107 showed local injection discomfort comparable to insulin lispro, with more rapid initial absorption and lower

peaks and longer durations of effect compared with insulin lispro.¹¹³

Long-acting PEGylated LY2605541

LY2605541 is a novel once-daily, long-acting basal insulin that is coupled to polyethylene glycol (PEGylated) to delay absorption and clearance. LY2605541 demonstrated comparable glucose control with a more reduced intraday variability, lower rates of nocturnal hypoglycemia, and more weight loss compared with insulin glargine (Table 1).¹¹⁴

Insulin delivery: pen devices

Technological advances in insulin delivery systems include the development of smaller and finer insulin needles, insulin pens, and insulin pumps. Use of either prefilled disposable or reusable pens can overcome some of the patient challenges to initiation of insulin therapy and may improve patient adherence and, possibly, patient outcomes.⁷⁶ A study comparing a modified five-bevel needle pen tip (available globally since 2005) with that of a marketed three-bevel needle pen tip showed that pen geometry affects the penetrating force and, consequently, patient preferences.⁷³ Moreover, compared to vials and syringes, insulin pens are preferred because they are easy to use, convenient, and deliver a precise and controlled amount of insulin.¹¹⁵ Additionally, insulin pens have visual and audible indicators to assist with dose setting and delivery that ensure dosing accuracy and reduce the risk of medication errors.¹¹⁶ Pens are associated with lower rates of hypoglycemia,^{117,118} and patient preference and treatment satisfaction scores,⁷⁴ greater adherence and persistence,^{117,119} and, consequently, greater glycemic control.¹¹⁶

Insulin delivery: pumps

Given the increasing demand for insulin therapy in T2DM and the inability of single-insulin regimens to achieve long-term glycemic control, continuous subcutaneous insulin infusion (CSII) with insulin pumps has become a popular alternative to the use of single or multiple daily injections of insulin.¹²⁰ The CSII provides precise amounts of rapid-acting analog insulin at a continuous basal rate to control glucose when the patient is not eating and as a meal and correction bolus to account for food intake and glucose values that are out of the target range.¹²⁰ The CSII can provide long-term glycemic control while reducing hypoglycemic episodes and glycemic variability, improving lifestyle flexibility for patients and their families.¹²¹ A systematic review of randomized clinical trials comparing the effectiveness of insulin delivery systems and glucose-monitoring modalities in patients with diabetes

receiving intensive insulin therapy was conducted by the Agency for Healthcare Research and Quality. The authors reported that both CSII and multiple daily injections have similar effectiveness on glycemic control and severe hypoglycemia in children and adolescents with T1DM and in adults with T2DM.¹²²

Many technological advances have been made to older-generation pumps to increase the appeal of pump therapy.¹²³ Currently available insulin pumps are discreet, ergonomic, and water resistant. Additionally, the Bolus Wizard® Calculator (Medtronic, Northridge, CA, USA) is a technology specific to insulin pumps that helps patients calculate the bolus insulin dose, based on a blood glucose reading. A tubing-free patch pump that adheres directly to the skin is a new trend in the design of insulin pumps.¹²³ Alternate routes of insulin delivery that are currently in development, such as inhaled, buccal, oral, and transdermal, may also address clinician- and patient-based challenges to insulin acceptance and adherence in the future. Another potential technological advancement could be the use of closed-loop insulin delivery, but unfortunately it has only been studied extensively in patients with T1DM. The only study published that included insulin-naïve patients with T2DM (n=7) concluded that use of closed-loop insulin delivery is both feasible and safe in this patient population.¹²⁴

Meeting challenges of insulin therapy

Roles of patient and clinician in managing insulin therapy

Patient education concerning the critical role of insulin therapy in diabetes management and energy homeostasis is essential to achieving glycemic control. Clinicians should destigmatize patients to insulin early on in the course of the disease as they guide their patients through the decision-making process. As discussed earlier, many obstacles in diabetes management and insulin intensification can be overcome by actively listening to patients to understand their fears and concerns.³¹

Prior to initiating insulin therapy, physicians must outline the goals of the therapy to their patients and explain how these goals will impact their self-management of T2DM and that to achieve treatment goals, diabetes management has to be individualized. For example, if patients are self-titrating their insulin, they must consider when they should inject their mealtime insulin, depending on the formulation they are using. One strategy the clinician can employ is to explain both the physiology and product profile of the insulin

therapy that has been selected in the patient's individualized treatment plan. This discussion can bring attention to the treatment options available to the patient and educate and engage the patient in the treatment plan. Both clinicians and patients may be more accepting of insulin therapy if patients are well-informed about their treatment and do not fear it.

As patient education is a time consuming task for physicians,²⁷ CDEs can be invaluable in educating patients about glucose monitoring, insulin injection techniques, insulin storage, and the recognition and treatment of hypoglycemia. Communication between physicians, CDEs, and patients should be timely and constructive. Physicians can also enlist office personnel (eg, medical assistants) in educating patients about insulin treatment and training patients on the use of insulin pens or syringes, on self-titration, and the administration of first injections. Online educational tools are also available to assist providers in educating themselves and their patients. These resources can focus on: promoting a better understanding of diabetes as a disease state; demonstrating the use of insulin pens; explaining how and when to take medications, monitoring blood glucose and treating hypoglycemia; promoting the importance of adhering to diet and exercise; and engaging the patients in their own treatment process.

Empowering patients to take greater control of their diabetes by living a healthier lifestyle and facilitating self-management may improve glycemic control and reduce the risk of complications.¹²⁵ Enhancing quality of life, particularly through diet, makes patients feel better and has a positive feedback effect on their self-management. Teaching patients the importance of self-monitoring of blood glucose (SMBG) and how to use it as a guide for adjusting therapy can allow patients to be in control of their care. Adherence to SMBG is enhanced when the patient understands why each check is made, knows what specific action to take with that result, and observes first-hand the benefits of self-management as their glucose control improves and they begin to feel better.

Dosing adjustments using self-titration algorithms based on frequent SMBG monitoring have been shown to be effective for improving glycemic control and achieving target HbA_{1c} levels.^{126,127} Treatment with detemir using a simplified, patient-adjusted dosing algorithm (303 Algorithm) achieved comparable glycemic control with patients using standard-of-care physician-driven adjustments with a minimal risk of hypoglycemia and weight gain.¹²⁷ Although there was a higher rate (events/patient/year) of hypoglycemia in the patient-adjusted dosing group compared to the physician-adjusted dosing group, these rates were significantly lower than at

baseline in both groups (9.05 versus 6.44 for the patient-adjusted dosing group [$P=0.0039$] and 9.53 versus 4.95 for the physician-adjusted dosing group [$P<0.0001$]).¹²⁷

Patients must understand that T2DM is a progressive disease that requires prevention and treatment to avoid development of serious complications.¹²⁸ Patients should be brought up-to-date about the advances in technology and the relative ease of use of currently available insulin regimens and delivery systems, such as the small size of the needles in today's pen devices,¹²⁹ which might help dispel the perceived notion of pain and discomfort associated with injection. Importantly, patients must take greater control toward their diabetes management.

Individualizing insulin management: matching insulin to patient

The 2012 ADA/EASD guidelines emphasize the importance of a patient-centered approach in the management of diabetes as the cornerstone of treatment success.¹³ Therefore, it is imperative that clinicians optimize insulin management and overcome the challenges to individualized insulin therapy to meet the patient's lifestyle and specific health care needs.

To appropriately individualize therapy, particularly for insulin-naïve patients, clinicians should consider the patient's glucose profile and residual endogenous insulin level, in addition to such practical considerations as treatment flexibility, convenience, cost, lifestyle, and the patient's cognitive and functional abilities. If the patient can still produce endogenous insulin, a combination of insulin therapy with oral antidiabetes agents or injectable incretins may reduce the required dose of insulin and limit weight gain. FPG levels and the magnitude of PPG excursions are also important factors to consider when titrating therapy. For example, for patients with elevated PPG, rapid-acting or prandial insulins, which have a much quicker onset of action and a shorter duration of action than RHI with less variability in absorption, control PPG and reduce the risk for late hypoglycemia.^{59,76} In addition, understanding that both fasting hyperglycemia and postprandial hyperglycemia contribute to elevated HbA_{1c} levels may help clinicians individualize insulin therapy and make adjustments where required. Measuring PPG levels may help identify when to treat patients who have HbA_{1c} levels that are borderline high due to postprandial hyperglycemia. Accordingly, both the AACE and ACE recommend treating to a 2-hour PPG target of <140 mg/dL (<7.8 mmol/L).¹³⁰ As patients approach target HbA_{1c} levels, PPG levels may contribute more to HbA_{1c} than FPG levels. As hyperglycemia worsens, the contribution of FPG increases.¹³¹

In a study of 1,699 patients with T2DM in whom HbA_{1c} was $>7.0\%$ (>53.0 mmol/mol) despite diet and oral antidiabetes therapy, basal/fasting hyperglycemia (BHG) accounted for the majority of hyperglycemia exposure (76%–80%) across a wide range of HbA_{1c} values.¹³² Intensification of treatment with basal insulin led to lower mean HbA_{1c} levels, and the contribution from BHG was reduced, but it still accounted for approximately one-third of exposure.¹³² These findings indicate that for most patients not achieving HbA_{1c} goals with oral antidiabetes agents, targeting BHG with basal insulin or other treatment methods may be more effective than targeting postprandial hyperglycemia. However, to achieve optimal glycemic control, both BHG and postprandial hyperglycemia will need to be managed properly.¹³²

Identifying candidates for insulin pump therapy

Even though CSII can be a suitable option for patients with T2DM, any given CSII regimen must effectively reduce glucose levels and be simple, unobtrusive, and cost-effective.¹²⁰ CSII may be best suited for technology-savvy patients with T1DM or T2DM who require multiple daily injections and who experience severe hypoglycemia or wide fluctuations in blood glucose levels throughout the day.¹³³ Simple insulin dosing with CSII in patients with T2DM leads to improvements in glucose control, clinical outcomes, quality of life, and treatment satisfaction measures.^{120,134–136} In addition, comprehensive patient education and frequent SMBG or continuous glucose monitoring are necessary components of successful insulin pump therapy.

Discussion

Due to the pathogenesis and progressive nature of T2DM, most noninsulin therapies will not be sufficient in managing diabetes over time,⁹ and the majority of patients will ultimately require insulin therapy. However, despite its efficacy, insulin therapy is underutilized due to easily avoidable, various clinician-, patient-, and health care system-related challenges.

Educating patients early about the critical role of insulin therapy in diabetes management and destigmatizing its use can help to overcome patient-related challenges and promote patient adherence and self-management. As part of a comprehensive educational strategy, clinicians should actively listen to patients and proactively address their concerns that can hinder both the initiation and adherence of insulin therapy. Emphasizing the relative ease associated with today's insulin regimens and delivery systems is an essential element of patient education. Empowering

patients to take greater control of their diabetes management and heeding the ADA/EASD patient-centric approach to care can improve glycemic control and reduce the risk of complications.^{13,28,125,127,137} Physicians should also enlist the services of a CDE or other trained staff member to assist with patient education.

Achieving glycemic control soon after a diagnosis of diabetes is important to avoid complications.⁵ Individualizing insulin therapy to a regimen that is compatible with the patient's glucose profile and residual insulin secretion and that meets the patient's specific health care needs and lifestyle is another strategy clinicians can employ to overcome challenges to achieving glycemic control, keeping in mind that glycemic control can be more or less stringent depending on patient type.¹³ Insulin pen devices can help ease and simplify administration while the use of insulin analogs can help reduce the risk of hypoglycemia. Insulins that are not associated with weight gain (eg, detemir) can be useful in cases where the potential for weight gain could impact adherence or clinical outcomes. Clinicians must strive to remain informed of emerging new insulin analog options that have the potential to simplify and improve adherence to insulin therapy while optimizing glycemic control and mitigating risks. Finally, insulin pumps are often underutilized yet are an appropriate treatment option for both T1DM and T2DM, because they offer the most physiologic and convenient way to manage basal-bolus insulin.

Conclusion

Insulin is the most effective therapy available for managing hyperglycemia; however, hypoglycemia is a common and serious adverse event. Recent evidence suggests that initiating insulin earlier in the course of T2DM may provide important benefits, such as improved glycemic control, which may prevent or delay the development of diabetes-related complications. The physiologic profile of basal insulin analogs, as well as other new insulin formulations, may offer clinicians options to address the hypoglycemia challenge of insulin therapy and to provide patients with multiple options to manage their disease and to fit their lifestyle.

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Author contributions

Each author was involved in literature analysis/interpretation and in drafting and critically revising the manuscript. Both authors reviewed the final manuscript and gave approval for submission.

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CS has received grant research funds from Bristol-Myers Squibb, Eli Lilly, GI Dynamics, and Sanofi-Aventis. CS is also a consultant/advisor to GI Dynamics and a member of the speakers bureau for Amylin, Boehringer Ingelheim, and Novo Nordisk. MKH is a consultant/advisor to Novo Nordisk and a member of the speakers bureau for Novo Nordisk.

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