

# The Importance of Early Insulin Adoption in Type 2 Diabetes Management

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## Citation

G Grunberger. *The Importance of Early Insulin Adoption in Type 2 Diabetes Management*. The Internet Journal of Family Practice. 2008 Volume 7 Number 2.

## Abstract

Type 2 diabetes mellitus (T2DM) is deadly and costly and there is a need to ensure proper treatment in order to prevent the advance of this chronic progressive disorder and its complications. Comprehensive interventions targeted at glycemic control are essential for the long-term health of patients with T2DM at lower cost. Timely initiation of insulin therapy is an important component of management. However, there is often a lengthy delay from diagnosis until initiation of insulin therapy, which can be further hampered by reluctance to initiate therapy from healthcare providers and patients. This delay means that patients can incur a heavy burden of uncontrolled hyperglycemia over several years. Benefits of early insulin therapy need to be conveyed to both patients and healthcare professionals through targeted education. In the future, combining modern insulins with improvements in patient education should help facilitate early initiation of insulin and make this approach more widely adopted.

## INTRODUCTION

The prevalence of type 2 diabetes mellitus (T2DM) continues to increase dramatically [1] despite primary prevention strategies such as the promotion of physical activity and diet education [2345]. The most recent data from the Centers for Disease Control and Prevention (CDC) report that diabetes now affects nearly 24 million people in the United States, corresponding to nearly 8% of the population, an increase of >3 million in approximately 2 years [1]. Of these, T2DM accounts for about 90-95% of all diagnosed cases of diabetes. Thus, prevention of the advance of this chronic progressive disorder presents an important challenge for healthcare professionals [67].

T2DM is characterized by progressive deterioration of pancreatic  $\beta$ -cell function, impaired insulin secretion, and increasingly severe insulin deficiency. Long-term hyperglycemia (glucotoxicity) and variability in plasma glucose levels can lead to microvascular (diabetic nephropathy, neuropathy, and retinopathy) and macrovascular (coronary artery disease, peripheral arterial disease, and stroke) complications, and consequently, increased morbidity, mortality and cost of treatment [89]. In the United States, diabetes was the seventh leading cause of death listed in 2006, and contributed to a total of 233,619 deaths in 2005 [1]. Treatment of diabetes-related complications also forms a major part of the growing costs

of this disease. In the United States, indirect and direct annual costs due to diabetes were estimated at \$174 billion in 2007, of which \$58 billion was the cost of treatment of diabetes-related chronic complications [10]. Diabetes is therefore a deadly and costly disease and there is a need to ensure its proper treatment.

The importance of aggressive early intervention for T2DM was first indicated by the results of the UK Prospective Diabetes Study (UKPDS) [9111213]; its findings showed that this approach had benefits in reducing microvascular complications. Subsequent long-term randomized trials have demonstrated that maintaining glycemic levels close to the nondiabetic range can prevent or delay the onset and progression of microvascular and some macrovascular complications [1415]. Tight glycemic control has also been shown to result in lower treatment costs in adults with diabetes [16] – with every 1% increase in glycated hemoglobin concentration (A1C) over 6%, healthcare costs rise by 7% over the subsequent 3 years [17]. The key messages from these studies are that comprehensive interventions targeted at glycemic control are essential for the long-term health of patients with T2DM at a lower cost.

This review examines the need and evidence for early initiation of insulin therapy. It also investigates possible barriers that may be preventing a more widespread adoption of this approach and methods to overcome these barriers.

### **GUIDELINE RECOMMENDATIONS FOR GLYCEMIC CONTROL**

The goal of diabetes treatment is to maintain tight A1C control close to normal levels in order to minimize complications. The need for tight glycemic control is specified in the most recent guidelines from the American Diabetes Association (ADA), International Diabetes Federation (IDF) and American College of Endocrinology (ACE)/American Association of Clinical Endocrinologists (AACE) [1819]. Targets for A1C specified in these guidelines are <7.0% (<6% in the absence of hypoglycemia), <6.5%, and ≤6.5%, respectively [1819]. The upper A1C range of the nondiabetic population is 6.1%, and the goal of treatment is to achieve near normalization of A1C levels.

### **INITIAL DIAGNOSIS AND TREATMENT OF PATIENTS WITH TYPE 2 DIABETES**

The first signs and symptoms of T2D may be different in each individual, varying from the classic warning signs of hypoglycemia (trembling, pounding heart, anxiety, hunger or tingling sensations) to neuroglycopenic symptoms (sensations of warmth, fatigue, poor concentration, confusion or even seizures) [20]. In order to help patients achieve glycemic targets, the ADA and European Association for the Study of Diabetes (EASD) have developed a consensus algorithm for initiating therapy in patients with T2D [21], while the ACE and AACE have provided guidelines and an AACE “Treat-to-Target Roadmap” [182223].

The overall objective of the ADA algorithm is to achieve and maintain glycemic control and to change interventions when therapeutic goals are not being met [21]. One of the key highlights of this approach is timely augmentation of therapy with additional agents, including early initiation of insulin therapy, as a means of achieving and maintaining recommended levels of glycemic control. The ADA algorithm recommends metformin plus lifestyle changes as initial therapy at diagnosis. If lifestyle and maximum tolerated dose of metformin fails to achieve targets, addition of a basal insulin or a sulfonylurea is recommended. In selected clinical settings, such as when hypoglycemia is particularly undesirable or when weight loss is important, less well-validated therapies (pioglitazone or a glucagon-like peptide-1 [GLP-1]) may be considered. If these treatments are not effective in achieving target A1C, or are not tolerated, addition of a sulfonylurea may be considered. Alternatively, these interventions should be stopped and basal insulin started. If lifestyle, metformin, and sulfonylurea

or basal insulin do not result in achieving the target A1C, the next step should be to start, or intensify, insulin therapy [21].

The ACE/AACE Roadmap stratifies patients according to the presence or absence of treatment. Within these categories, recommendations are stratified by A1C levels. According to the Roadmap, previously untreated patients presenting with extreme hyperglycemia (A1C >10%) may require insulin as first-line therapy to initially lower glucose levels [22]. For patients with initial A1C levels of 8-10%, insulin should be considered in combination with oral antidiabetic drugs (OADs), while for patients with initial A1C levels of 7-8%, insulin may be considered under special circumstances [22], such as in patients with contraindications for the use of OADs.

In clinical practice, the treatment approach for newly diagnosed patients tends to rely on the experience of the physician in identifying the right combination of lifestyle interventions and medications for each patient and in promoting adherence to long-term therapy [24].

### **NEED FOR EARLY INSULIN THERAPY**

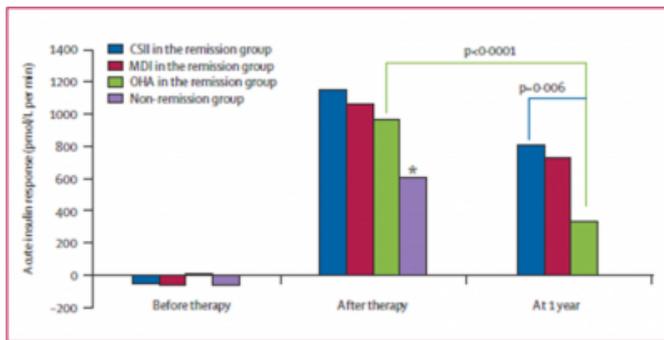
Numerous OADs are available, and recommendations for their use are described in the ADA and ACE/AACE guidelines [2122]. Some of these are recommended as monotherapy, while others are used exclusively as part of combination regimens. As monotherapy, the percentage point reductions in A1C typically achieved by OADs are 1.0-2.0% for sulfonylureas or metformin, 1.0-1.5% for meglitinides, and 0.8-1.0% for thiazolidinediones [25]. Limited high-quality studies are available that provide head-to-head comparisons of the ability of medications to achieve currently recommended glycemic levels, and it should be emphasized that the baseline A1C level needs to be considered before any comparisons are made between trials. However, given the expected decreases in A1C with OAD monotherapy, oral agents may not lower plasma glucose levels sufficiently to reach target A1C levels. In contrast, insulin can lower A1C by ≥2.5%, and therefore this therapy has the potential to decrease any level of elevated A1C to, or close to, the therapeutic goal when used in appropriate doses [24].

Because of the natural progression of T2D, most patients will ultimately require insulin therapy. Timely initiation of insulin therapy is therefore an important component of management. Early adoption of insulin can help lower insulin resistance, reverse glucotoxicity and preserve β-cell

function for longer than is possible with OADs alone [26]. Indeed, increasing evidence suggests that aggressive lowering of glycemia with insulin therapy in newly diagnosed patients can result in sustained remissions, that is, normoglycemia without the need for glucose-lowering medications [27,28,29]. In the most recent and largest of these studies, 382 newly diagnosed type 2 patients achieved target glyemic control in less time following treatment with insulin compared with those patients treated with OADs [29]. After 1 year, remission rates in the insulin groups were significantly higher in the insulin groups than in the OAD group (51.5% vs 26.7%;  $p=0.0012$ ). In addition, the increase in acute insulin response was sustained in the insulin groups but significantly declined in the OAD group at 1 year [29] (Figure 1).

**Figure 1**

Figure 1: Acute insulin response (shown as median) before and after different interventions and at 1 year. \* $p$



The potential advantages of adding a basal insulin analog before patients are unresponsive to oral therapy have been demonstrated in the Canadian Implementing New Strategies with Insulin Glargine for Hyperglycemia Treatment (INSIGHT) study [30]. Patients with type 2 diabetes and receiving 0, 1 or 2 oral agents were randomized to receive evening insulin glargine or conventional oral therapy. Findings of the study showed that patients receiving insulin glargine were 1.68 times more likely to achieve two consecutive A1C levels  $\leq 6.5\%$  with significantly lower mean A1C levels ( $p=0.0007$ ). Individuals receiving insulin glargine also experienced a greater fall in FPG level, total cholesterol, non-high-density lipoprotein (HDL) cholesterol, and triglycerides than those allocated to the control group, as well as a greater improvement in diabetes treatment satisfaction (Table 1).

**Figure 2**

Table 1: Results of the Canadian INSIGHT at 24 weeks (Implementing New Strategies with Insulin Glargine for Hyperglycaemia Treatment) Study [30]

	Insulin glargine	Control group	P value
Reduction in A1C	1.55%	1.25%	0.0005
Reduction in fasting plasma glucose (FPG)	3.89 mmol/L	2.31 mmol/L	0.0001
Reduction in triglycerides	1.08 mmol/L	0.47 mmol/L	0.02
Reduction in cholesterol levels	0.38 mmol/L	0.11 mmol/L	0.015
Reduction in non-HDL cholesterol	0.37 mmol/L	0.13 mmol/L	0.02
Diabetes treatment satisfaction	1.03	0.82	0.045

Despite evidence supporting the early adoption of insulin, in clinical practice treatment tends to follow a stepwise approach, beginning with diet and exercise, followed by the addition of one or more OADs with initiation of insulin therapy as a final step. The ADA/EASD clinical algorithm highlights that interventions need to be changed at as rapid a pace as titration of medication allows until blood glucose targets are met. However, the reality of this approach is often a lengthy delay from diagnosis until initiation of insulin therapy. One study showed that the average period between the transition from OADs to initiation of insulin treatment was  $54.6 \pm 28.6$  months, despite generally poor glycaemic control during this period [31]. Indeed, the failure of nonpharmacologic interventions and OAD therapy, and the delay in initiating insulin therapy, mean that patients can incur a heavy burden of uncontrolled hyperglycemia over a number of years [32]. Brown et al showed that a hypothetical patient progressing from nonpharmacologic interventions to sulfonylurea or metformin monotherapy, then to oral combination therapy, before initiation of insulin could potentially accumulate nearly 5 years of excess A1C glycaemic burden  $>8.0\%$  from diagnosis until starting insulin and about 10 A1C years of burden  $>7.0\%$  [32,33].

Collectively, these data emphasize the importance of early insulin treatment. Healthcare practitioners, in particular, need to ensure that patients have early access to insulin treatment. The two case studies in Table 2 are examples of patients who experienced prolonged periods of

hyperglycemia where earlier treatment with insulin therapy would have been appropriate. Both patients showed improved outcomes following a management approach of education and insulin therapy (Table 2).

Table 2: Case Studies

### Case 1

**Patient presentation:** A 48-year-old woman referred by her primary care physician for assistance with diabetes management. Height, 5ft 4 inches, weight, 266 lbs (BMI 46 kg/m<sup>2</sup>), waist circumference 44 inches. Blood pressure 142/86, pulse 78, regular. Medication: two antihypertensive drugs, a statin, low-dose aspirin and clopidogrel. Taking glyburide (5 mg bid). She is asymptomatic but complains of chronic fatigue and has lower back pain and does not exercise. Monitors glucose levels occasionally, only after overnight fast, reported levels fluctuated between 130 and 160 mg/dL. Her random blood glucose (3 hours after light lunch) was 288 mg/dL. Her point-of-care A1C was 12.8%. Her laboratory values were within reference values, with creatinine 1.3 mg/dL. Microalbuminuria was present.

**History:** Diagnosed 3 years ago following hospitalization for acute myocardial infarction (admission glucose was 336 mg/dL, managed in hospital by intravenous insulin infusion) and placed on glyburide. Administered metformin last year when glucose was still above target levels, but patient did not tolerate this well.

**Management approach:** After a lengthy conversation about the natural history of type 2 diabetes, her location in the disease spectrum, and the current glycemic goals, she agreed to start basal insulin (and stop sulfonylurea) as the first step to achieving fasting glucose targets. She gave herself the first insulin injection (15 units of insulin detemir) before she left the office and agreed to start glucose monitoring 2 hours after meals once a day before her return visit in one week. On return, her fasting glucose over the first week averaged 178 mg/dL and her postprandial readings were in the mid to high 200s. She agreed to keep increasing the dose of insulin detemir every 3 days by 3 units until her fasting glucose level fell to between 80 and 110 mg/dL (303 algorithm) and to return in 1 month. She understood that postprandial hyperglycemia would be tackled once fasting glucose is optimized.

### Case 2

**Patient presentation:** A 59-year-old man weighing 247 lbs

(BMI 33.8 kg/m<sup>2</sup>) and 6 ft tall made an appointment with a specialist following a lack of answers from his primary care physician. His current pharmacological antidiabetic regimen consists of metformin (1000 mg bid), pioglitazone (45 mg qd), and glimepiride (4 mg bid). His A1C on the initial visit was 7.4% and he was entirely asymptomatic. He could not understand why his A1C was still elevated when his fasting glucose levels (which he checked daily) were between 97 and 132 mg/dL (30-day average 118 mg/dL). His random blood glucose level during his initial visit was 239 mg/dL (about 2 hours after his usual breakfast).

**History:** Known history of type 2 diabetes for 7 years. He has tried to adhere to lifestyle modifications, and exercises four times a week.

**Management approach:** After outlining the components of glucose excursions that determine the A1C level (i.e. both pre-and post-prandial glucose concentrations) and the current therapeutic regimen (targeting essentially only the pre-prandial glycemic control), he accepted the need for initial prandial coverage with a rapid-acting insulin (starting with his heaviest meal in the evening) and need for postprandial glucose monitoring. He started on 10 units of a rapid-acting insulin analog with dinner and was advised to monitor glucose before and 2 hours after his evening meal. He agreed to see a dietitian to learn carbohydrate counting so he would be able to adjust the insulin dose according to carbohydrate content of his meal(s), starting with 1 unit for each 10 g of carbohydrate intake. Understanding was reached to eventually expand his prandial coverage to other meals, which raised his glucose levels by more than 30 mg/dL.

BMI, body mass index; A1C, glycated hemoglobin concentration.

## BARRIERS TO EARLY INSULIN THERAPY

Despite the recognition that tight glycemic control is of paramount importance, both healthcare providers and patients may be reluctant to initiate insulin therapy. Concerns regarding initiation of insulin therapy among healthcare providers and patients are primarily related to possible weight gain and perceived risks of severe hypoglycemia. In addition, the physician and patient are required to make informed decisions on insulin schedules and dosing, which can appear daunting. Compared with OADs, insulin therapy also requires more frequent glucose monitoring. All of these factors may be viewed as further hassle in a disease that is already time-consuming. Distinct

issues may also exist among patients including needle anxiety, social embarrassment and stigma, and concerns regarding lifestyle changes and restrictions [34,35].

So-called “psychological insulin resistance” may be considerable, as indicated by a market research survey of 99 insulin-naïve diabetic patients in the UK and USA, in which 76% of patients revealed negative feelings about injection [36]. These issues were recently investigated in the Diabetes Attitudes Wishes and Needs (DAWN) program, which aimed to enhance the understanding of patient perceptions and attitudes of healthcare providers [37]. Results from this cross-sectional study of 2061 insulin-naïve diabetic patients and 3170 healthcare providers have highlighted the fact that self-blame is common among diabetes patients, with many patients believing that the need for insulin therapy indicates a personal failure to manage their disease appropriately through diet, exercise, and OADs. Physicians may have conveyed this impression by using insulin therapy as a punishment for poor glucose control, rather than as an effective way of replacing the body’s insulin. The DAWN study indicates that many patients remain unaware of the efficacy benefits of insulin treatment, and that healthcare providers continue to represent insulin as a treatment of last resort [37].

Concerns regarding weight gain may also play a role in both patient and physician reluctance to initiate insulin therapy, arising from knowledge of the pathogenetic and the self-perpetuating relationship between T2D, obesity and diabetes treatments [38]. Over 80% of patients with T2D are overweight, yet most glucose-lowering agents increase weight gain [39]. In particular, insulin therapy has been associated with weight gain, and several underlying reasons have been postulated for this, including conservation of ingested calories, insulin-related changes in anabolic metabolism, and a possible central effect on appetite [39]. Weight gain may also be a result of defensive eating to prevent hypoglycemic episodes.

### TOWARDS EARLY INSULIN INITIATION

The benefits of early insulin treatment need to be conveyed to both patients and healthcare professionals through targeted education. A key aim is to improve patients’ confidence in their own ability to manage their diabetes through a better understanding of their condition and its therapy options [40]. From a practical perspective, the introduction of insulin analogs and developments in delivery devices have helped to ease introduction to insulin therapy

by making it a more straightforward process. Combining modern insulins with improvements in patient education should help facilitate early initiation of insulin and make this approach more widely adopted.

### TEAMWORK IN PATIENT EDUCATION

Achieving the goals of tight glycemic control and prevention of the severe complications of diabetes requires the formation of close relationships between the patient and healthcare professionals, including physicians, nurses, diabetes educators, dietitians, and pharmacists. All members of the team should be able to help the patient with education at every level of management in order to provide seamless continuity of care. In particular, all members of the team should be aware that initiation of insulin therapy is not a last-resort approach but is an effective treatment option for early intervention that can help preserve remaining pancreatic  $\beta$ -cell function, hence slowing the progression of T2D. Because of the progressive nature of type 2 diabetes it is important that patients are made aware, from an early point in their consultations, that they are likely to require treatment with glucose-lowering medications, including insulin, over time.

### INSULIN TREATMENT OPTIONS

In a normal individual, insulin levels rise from a basal level after ingestion of food, reaching a peak concentration within an hour followed by a rapid return to baseline levels. Many of the practical barriers to insulin administration in patients with diabetes have arisen from the pharmacokinetic properties of short-acting (regular) and intermediate-acting (neutral protamine Hagedorn [NPH]) human insulin, as they have variable peaks in activity and unpredictable durations of action. Human insulins are also subject to considerable within-patient variations in blood glucose [41]. As a result, insulin analogs (rapid and long-acting) have been developed with the aim of more closely duplicating basal and mealtime physiological insulin secretions.

Treatment with long-acting insulin may be adequate as an initial approach to insulin therapy, when it is added to OADs in patients who consume small regular meals. Traditionally, the intermediate-acting NPH insulin has often been used as replacement for basal insulin. However, the development of long-acting insulin analogs (insulin detemir and insulin glargine), which show improved time–action profiles and longer durations of action, offers alternatives as basal insulin replacements.

In addition to basal insulin, some patients require additional coverage using insulin at mealtimes (in basal-bolus regimens) to counter post-prandial spikes in glucose levels. A rapid-acting insulin analog (insulin aspart, insulin lispro and insulin glulisine) is initially added at the largest meal of the day, followed by one at the second largest if necessary. In the majority of patients with T2D, prandial injections may eventually be needed with all meals and OADs may be discontinued. The basal-bolus approach is considered to be the ideal regimen that most closely approximates the physiological profile of natural insulin and achieves good glycemic control over 24 hours. Administration of regular human insulin has not been ideal for control of post-prandial glucose as it requires dosing 30 to 45 minutes before meals. Rapid-acting analogs (insulin aspart, insulin glulisine and insulin lispro) have a faster onset of action, typically within 10 to 20 minutes, a greater peak effect and a shorter duration of action and therefore may provide greater flexibility in mealtime dosing. Premixed insulin formulations are also available that contain different ratios of a protaminated rapid-acting insulin and the unmodified rapid-acting insulin, such as human insulin 70/30, insulin lispro 75/25 or insulin aspart 70/30. These can simplify the initiation of insulin therapy for some patients by delivering the equivalent of an intermediate-acting basal and a mealtime insulin in one formulation.

To date, most clinical trials comparing human insulins with insulin analogs have been designed to show noninferiority of these agents in terms of reductions in A1C levels. From this standpoint, the agents can be considered to be comparable in terms of glycemic control. However, secondary benefits of reductions in weight gain and episodes of hypoglycemia have been observed with insulin analogs, which are likely to be related to the pharmacokinetic and pharmacodynamic improvements of these agents [42434445]. For example, in a subgroup analysis of 2377 OAD-treated, insulin-naïve T2D patients enrolled in the European cohort of the Predictable Results and Experience in Diabetes through Intensification and Control to Target: an International Variability Evaluation (PREDICTIVE) study, A1C levels decreased by 1.8% and 1.9% (from 8.6% to 6.8% and from 8.5% to 6.6%) for detemir- and NPH-treated patients, respectively, at 24 weeks [44], whereas mean weight gain was 1.2 kg with insulin detemir and 2.8 kg with NPH insulin ( $p < 0.001$ ). Compared with NPH insulin, the risk for all hypoglycemia with insulin detemir was reduced by 47% ( $p < 0.001$ ) and nocturnal hypoglycemia by 55% ( $p < 0.001$ ). Similarly, in the Treat-to-Target trial, the rate of hypoglycemia was 13.9%

for insulin glargine and 17.7% for NPH ( $p < 0.02$ ) [45]. This randomized, open-label, parallel, 24-week multicenter trial examined insulin glargine or NPH once daily in 756 overweight men and women with inadequate glycemic control (A1C  $> 7.5\%$ ) on one or two OADs. In terms of weight gain, the benefits of insulin detemir have been more consistently reported than those of insulin glargine [454647].

### TREATMENT ALGORITHMS AND BLOOD GLUCOSE MONITORING

In addition to the concerns discussed above, patients and healthcare providers may be concerned that adhering to a complex insulin regimen will be too difficult or time-consuming. To address this issue, simple treatment algorithms have been developed [4548495051]. In particular, a large observational study – PREDICTIVE 303 – has examined the use and monitoring of a treatment algorithm with favorable results [455152]. The US PREDICTIVE 303 study compared the effectiveness of a simplified self-adjusted dosing algorithm with standard-of-care physician-driven adjustments in predominantly primary care settings over a period of 6 months. Insulin detemir was initiated once daily as add-on therapy to any other glucose-lowering regimen or as a replacement of pre-study basal insulin in patients with T2D [52]. Results of the study at 26 weeks showed that mean A1C decreased from 8.5% at baseline to 7.9% at 26 weeks for the 303 Algorithm group and from 8.5% to 8.0% for the Standard-of-care group ( $p = 0.011$  for difference in A1C reduction between the two groups). Mean FPG values decreased from 175 mg/dL (9.7 mmol/L) at baseline to 141 mg/dL (7.8 mmol/L) for the 303 Algorithm group, and decreased from 174 mg/dL (9.7 mmol/L) to 152 mg/dL (8.4 mmol/L) for the Standard-of-care group ( $p < 0.001$  for difference in FPG reduction between the two groups). At 26 weeks, 91% of the patients in the 303 Algorithm group and 85% of the patients in the Standard-of-care group remained on once-daily insulin detemir administration [53].

Data show that more frequent self-monitoring of blood glucose levels produces significantly better glycemic control, irrespective of the diabetes type or regimen used [54]. However, the requirement for frequent blood glucose monitoring remains an issue for many patients and providers initiating insulin therapy. ADA/EASD guidelines recommend that self-monitoring of blood glucose (SMBG) should be carried out three or more times daily for patients using multiple insulin injections or insulin pump therapy [19]. They further highlight that when prescribing SMBG, it is

important that patients receive initial instruction in, and routine follow-up evaluation of, SMBG technique as well as a clear understanding of how to use data to adjust therapy. Recent developments in devices for continuous monitoring of interstitial glucose include tools that provide information about changes in glucose levels and have alerts for hypo- and hyperglycemia. However, the costs associated with CGMS can be high [55]. Advances in log books and telemedicine systems have also been made. Such developments have aimed to improve patients' understanding of their condition by emphasizing the importance of regular monitoring and feedback [5657].

### INSULIN DELIVERY DEVICES

The inconvenience associated with vials and needles has long represented a challenge for patient acceptance of insulin therapy. This has resulted in the development of insulin analogs as pen formulations. Such devices have been designed to be lightweight with microfine needles and aim to simplify treatment regimens by making dosing more accurate, convenient, and discreet for patients. A variety of insulin pens are available, including NovoPen<sup>®</sup>, FlexPen<sup>®</sup>, OptiClik<sup>®</sup>, SoloSTAR<sup>®</sup>, KwikPen<sup>™</sup>, HumaPen<sup>®</sup> Memoir<sup>™</sup> and HumaPen<sup>®</sup> Luxura<sup>™</sup>. These devices use either replaceable insulin cartridges or prefilled nonreplaceable cartridges, which are discarded after use.

Although insulin analogs and pen devices are often favored by patients and physicians, it should be acknowledged that they have a higher cost compared with human insulins and syringes [58], with the highest cost applying to disposable pen injectors of insulin analogs. However, recent data indicate that insulin pen devices may increase medication adherence and correlate with a decrease in hypoglycemic events, and that their use is associated with a decrease in overall healthcare costs [5960]. In a Pharmetrics database survey of 1156 patients with T2D who converted to a prefilled insulin analog pen from a syringe and vial method (FlexPen<sup>®</sup>, NovoNordisk A/S), medication adherence was significantly improved after conversion to the insulin pen device (from 62% to 69%;  $p < 0.01$ ) [59]. Multivariate analysis showed that the incidence of hypoglycemic events decreased by nearly two-thirds in patients considered adherent (incidence rate ratio = 0.35; 95% CI, 0.11–0.81;  $p < 0.05$ ). In a separate observational study of 1622 patients who switched from a syringe to an insulin pen, annually-adjusted mean all-cause costs were reduced by \$1590 per patient (from \$16,357 to \$14,769) after switching to the pen ( $p < 0.01$ ), of which approximately 60% were diabetes-related costs. Therefore,

potential improvements in medication adherence and reductions in hypoglycemia and long-term healthcare cost need to be taken into account when considering the higher costs of pen delivery devices.

### CONCLUSIONS

Although glycemic control is only one of many treatment goals for patients with T2D, it remains the key element in preventing the incidence and progression of microvascular and macrovascular complications, which place a huge burden on patients, their caregivers and healthcare services. Early initiation of insulin is a valuable therapeutic tool to prevent severe and long-term complications. Through a combination of education and continued developments in insulin formulations and delivery devices, insulin treatments can be simplified and effective. Strategies to enhance healthcare services include identifying and overcoming barriers, and using a team approach in which every member of the team has a heightened awareness of the benefits of tight glycemic control and the way in which this can be achieved.

### ACKNOWLEDGEMENTS

Writing and editorial support was provided by Jackie Mayne and Caroline Pettigrew of Bioscript Stirling Ltd (UK), with funding provided by Novo Nordisk.

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