Exploring The Quality-Of-Life Benefits With Insulin Analog Use
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Citation

Abstract
Purpose: The need for early insulin treatment in patients with type 2 diabetes and the quality-of-life benefits provided by insulin analogs compared with human insulins are reviewed. Summary: Despite the proven efficacy of insulin therapy, patients with type 2 diabetes are often reluctant to start treatment with insulin. This can stem from the inconvenience of having to plan administration relative to meals, fears of self-injecting, and concerns about hypoglycemia and weight gain. Treatment dissatisfaction among insulin users can also hinder treatment adherence and negatively impact health-related quality of life (HRQoL). The development of new insulin therapies and delivery devices has focused on improving patient satisfaction and HRQoL in order to improve adherence and ultimately treatment outcomes. Insulin analogs allow more dosing flexibility and are associated with lower risks of hypoglycemia, and, in some cases, a reduced risk of weight gain compared with human insulin. The availability of pen devices has also facilitated easy and accurate subcutaneous injection. Numerous clinical trials have reported improved HRQoL and greater patient satisfaction with insulin analogs versus human insulin and pen devices over vial and syringe. Although analog insulins are associated with higher direct costs than human insulins, for most insurance plans, co-pays costs are equivalent for these different formulations. In addition, insulin analogs and pen devices represent a cost-effective insulin treatment due to improved adherence and dosing accuracy, reducing the number of diabetes-related complications and the need for hospitalization. Insulin analog preparations therefore provide a cost-effective treatment option that improves HRQoL and is associated with a high level of patient satisfaction compared with human insulins. Conclusion: Clinical studies have shown improved HRQoL and greater patient satisfaction with insulin analogs versus human insulin. Insulin analog preparations should be considered as an option for all patients using insulin therapy.

INTRODUCTION
Diabetes is an increasingly important public health concern. Nearly 24 million people in the United States have the condition, corresponding to nearly 8% of the population, an increase of more than 3 million in approximately 2 years. Moreover, recent projections of diabetes in the United States estimate that the total diabetes burden will be 13.5% (32.6 million) of the population in 2021 and 14.5% (37.7 million) of the population in 2031.

Diabetes is known to have a detrimental impact on health outcomes, including health-related quality of life (HRQoL), and this has been demonstrated in a number of trials. The Centers for Disease Control and Prevention (CDC) highlight that the concept of HRQoL refers to a person or group’s perceived physical and mental health over time. Today’s definition of HRQoL is a direct descendent of the World Health Organization definition of health from over 50 years ago—“a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”—and is thought to encompass three fundamental domains: (1) biological functioning, (2) psychological functioning, and (3) social functioning. The medical community’s interest in HRQoL, rather than the mere presence or absence of disease, has been growing at a remarkable rate over the past few decades. An increasing number of studies incorporate assessments of HRQoL to measure the effects of chronic illness on the patient’s day-to-day life.

The magnitude of the impact of diabetes on HRQoL has been reported to be comparable to that experienced by patients with cardiovascular conditions, cancer, and chronic respiratory disease. Data from the CDC illustrate the far-reaching effects of diabetes on mental and physical well-being. In 2004, almost two-thirds (63.1%) of adults with diabetes reported having poor mental or physical health for at least 1 day in the past 30 days, and almost one-third
(32.8%) of the diabetes population were unable to perform a usual activity during this timeframe. Similarly, data from 2007 showed that 58.4% of adults with diabetes reported limitations in their mobility, such as walking a quarter mile; climbing up 10 steps; standing for 2 hours; or stooping, bending, or kneeling.

The negative impact of diabetes on quality of life is an important issue not only for the emotional and physical well-being of the patient, but also because it can interfere with treatment compliance and have a detrimental impact on treatment outcomes. This review examines the need for early insulin treatment in patients with type 2 diabetes, and assesses the quality-of-life benefits provided by insulin analogs compared with human insulins.

INSULIN THERAPY—THE MOST EFFECTIVE AGENT TO CONTROL GLYCEMIA

The benefits of intensive glycemic control on microvascular and macrovascular complications are well established for type 1 and type 2 diabetes. Comprehensive interventions targeted at glycemic control are therefore essential for the long-term health of patients with diabetes.

Because type 1 diabetes (T1DM) is associated with absolute insulin deficiency, all patients with this condition require intensive insulin therapy from initial diagnosis. In contrast, patients with type 2 diabetes (T2DM) may initially be treated with lifestyle changes, either alone or in combination with oral and/or injectable glucose-lowering drugs. However, given the progressive nature of the disease and the limited glycemic control that can be achieved with non-insulin agents, most patients with T2DM will eventually require insulin therapy. It is estimated that by the time a patient is diagnosed with T2DM, they have actually had the disease for 9–12 years. It is also projected that 50–80% of β-cell function is lost by this time; therefore pharmacotherapy that preserves β-cell function is warranted.

NEED FOR EARLY INSULIN THERAPY

Despite the clear benefits of insulin therapy in achieving good glycemic control, patients do not always receive insulin early or in a timely manner. The stepwise approach to therapy, which consists of lifestyle modifications and sequential addition of non-insulin glucose-lowering agents, followed by insulin as necessary, may result in delays in initiating insulin. In other cases, psychological resistance on the part of both healthcare providers and patients can delay insulin therapy.

Early utilization of insulin can help lower insulin resistance (physiological and psychological), reverse glucotoxicity, and preserve β-cell function for longer than is possible with most oral glucose-lowering drugs, alone or in combination. Indeed, results from a number of recent trials suggest that aggressive lowering of hyperglycemia with insulin therapy in newly-diagnosed T2DM patients can result in extended normoglycemia without the need for glucose-lowering medications. The most recent of these trials, in 382 patients with newly-diagnosed T2DM, showed that target glycemic control was attained more quickly with intensive insulin treatment (either continuous subcutaneous insulin infusion [CSII] or multiple daily insulin injections [MDI]) than with oral agents. Treatment was stopped after normoglycemia was maintained for 2 weeks; patients were then followed up on diet and exercise alone. More patients achieved target glycemic control in the insulin groups (97.1% in CSII and 95.2% in MDI) in less time (4.0 days [SD 2.5] in CSII and 5.6 days [SD 3.8] in MDI) than those treated with oral hypoglycemic agents (83.5% and 9.3 days [SD 5.3]). After 1 year, remission rates were significantly higher among patients in the insulin groups compared with patients receiving oral glucose-lowering agents (51.5% vs. 26.7%; p = 0.0012). In addition, the increase in acute insulin response was sustained in the insulin groups but declined significantly in the oral glucose-lowering drug group at 1 year.

The potential advantages of early insulin therapy with a basal insulin analog before patients become unresponsive to oral therapy have also been demonstrated in the Canadian Implementing New Strategies with Insulin Glargine for Hyperglycemia Treatment (INSIGHT) trial. Patients with T2DM and receiving no, one or two oral glucose-lowering agents were randomized to receive evening insulin glargine or conventional oral therapy. Patients receiving insulin glargine were 1.68 times more likely to achieve two consecutive A1C levels <6.5% and had significantly lower mean A1C levels compared with those receiving conventional oral therapy (p = 0.0007).

DEVELOPMENT OF INSULIN ANALOGS

The goal of insulin therapy is to mimic normal physiologic secretion of insulin as closely as possible in order to control both fasting plasma glucose (FPG) and postprandial plasma glucose (PPG). Although human insulin formulations (short-, intermediate-acting, and premixed) have been used extensively for the treatment of diabetes, their ability to achieve tight glycemic control is limited by their
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pharmacokinetic and pharmacodynamic profiles. For example, human insulins have variable peaks in activity and unpredictable durations of action, and are also subject to considerable within-patient variations in blood glucose. 
Insulin analogs (rapid, long-acting, and premixed) have been developed with the aim of more closely replicating physiologic insulin profiles. Insulin analogs have the added benefit of not requiring resuspension prior to injection—a step that can often be overlooked by patients, exacerbating the poor reproducibility with NPH (neutral protamine Hagedorn) insulin. Recognition of the benefits of insulin analogs versus human insulins are reflected in the recent guidelines published by the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE), which recommend the use of insulin analogs over human insulins. Table 1 provides a summary of currently available insulin analog treatments. Use of both types of insulin analogs in a basal-bolus regimen is considered to be the ideal regimen that most closely mimics the physiologic profile of endogenous insulin and achieves good glycemic control over 24 hours.

**Figure 1**

Table 1. Onset of action, peak action and duration of activity of available insulin analogs

<table>
<thead>
<tr>
<th>Insulin analog</th>
<th>Onset of Action</th>
<th>Peak</th>
<th>Duration of Action (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-acting</td>
<td>10-20 min</td>
<td>60-90 min</td>
<td>3-5</td>
</tr>
<tr>
<td>Long-acting</td>
<td>15-30 min</td>
<td>15-90 min</td>
<td>2-6</td>
</tr>
<tr>
<td>Glargine</td>
<td>10-30 min</td>
<td>No significant peak</td>
<td>≤2</td>
</tr>
<tr>
<td>Lispro</td>
<td>0-2 h</td>
<td>No significant peak</td>
<td>≤2</td>
</tr>
<tr>
<td>Detemir</td>
<td>0-2 h</td>
<td>No significant peak</td>
<td>≤2</td>
</tr>
</tbody>
</table>

The time course of action of any insulin may vary in different individuals or at different times in the same individual. Because of this variation, periods indicated here should be considered general guidelines only.

Two long-acting basal insulin analog preparations are available: insulin glargine and insulin detemir. These analogs have been designed to provide consistent, relatively flat, and protracted basal insulin levels. Rapid-acting insulin analogs—insulin lispro, aspart, and glulisine—are most appropriate at mealtimes to counter postprandial spikes in glucose levels. Compared with regular human insulin, rapid-acting insulin analogs show faster absorption, a more rapid onset of activity, and a shorter duration of action. These pharmacokinetic properties mean that rapid-acting analogs can be injected within 15 minutes of mealtimes, compared with the 30-minute timeframe required for regular human insulin.

Three types of fixed-ratio insulin analog premixes are also available: a 75% insulin lispro protamine suspension with 25% insulin lispro, a 50% insulin lispro protamine suspension with 50% insulin lispro, and a 70% insulin aspart protamine suspension with 30% insulin aspart. Premixed insulin analogs are derived from rapid-acting insulin analogs and consist of a mixture of a rapid-acting insulin analog and its intermediate-acting protaminated form. Accordingly, biphasic insulin regimens provide prandial and basal insulin requirements in a single insulin injection. These formulations have been developed to minimize the errors that can occur when patients self-mix insulin combinations. Premixed combinations may also simplify the insulin regimen and reduce the number of daily injections.

**GLYCEMIC CONTROL**

Results from a number of key clinical trials have shown that insulin analogs and human insulins have similar efficacy in terms of glycemic control. This conclusion was reiterated in two Cochrane reviews that reported only minor benefits with regard to efficacy of short- and long-acting insulin analogs over human insulins.

When assessing glycemic control, it is necessary to measure FPG and PPG levels in addition to measuring A1C levels. Increasing emphasis has been placed on integrating PPG levels into routine diabetes care, with evidence suggesting that PPG contributes as much as, or even more than, FPG to overall glycemic burden as A1C values approach near-normal levels <7%. Rapid-acting analogs have resulted in greater reductions in PPG levels than human insulins in a number of trials carried out in patients with T1DM. In addition, premixed insulin analogs have improved benefits in terms of PPG control compared with premixed human insulin. For example, a recent 3-month trial of biphasic insulin aspart 70/30 and premixed human insulin 70/30 reported slightly better control of FPG (7.82 vs. 7.36 mmol/L) and PPG (decrease of 6.30 vs. 4.34 mmol/L) with biphasic insulin aspart 70/30 compared with the premixed human insulin.

**IMPROVEMENT OF QUALITY OF LIFE WITH**
INSULIN ANALOGS VERSUS HUMAN INSULINS
The improvements in glycemic control observed with insulin treatments do not necessarily translate into comparable improvements in psychological outcomes. The evaluation of other endpoints, in particular HRQoL and treatment satisfaction, is therefore an important part of the assessment of insulin therapy. Determination of the impact of insulin therapy on HRQoL must take into account not only the impact of treatment on diabetes HRQoL, but also that the insulin therapy itself can impair HRQoL through fears of hypoglycemia, weight gain, and other potential adverse effects.

QUALITY OF LIFE AND TREATMENT SATISFACTION
A limited number of studies have assessed quality of life as an endpoint in comparative studies of insulin analogs and human insulins. Quality of life and treatment satisfaction were compared in a 6-month, open-label trial of 424 patients with T1DM receiving basal-bolus treatment with either insulin aspart or human insulin as the prandial insulin component. Insulin aspart was associated with significantly greater improvement in treatment satisfaction than human insulin (p < 0.01). The improvement in patient satisfaction was mainly due to increased flexibility regarding diet and leisure time (p < 0.0001). Small, but significant, improvements in total HRQoL were achieved in 23% of patients in the insulin aspart group versus 14% in the human insulin group. The benefits in HRQoL with insulin aspart compared with human insulin are summarized in Figure 1.

A separate switching study has examined the effects of glargine on disease-specific HRQoL in T1DM patients. In a study of teenagers with T1DM, those not meeting glucose control goals through multiple daily insulin injections of regular human insulin were given the option of switching to insulin lispro. After 12 months, subjects who received insulin lispro experienced a similar degree of metabolic control compared with controls, as assessed by measurement of A1C levels. However, they found that coping with diabetes was less difficult, there was a reduced negative impact of diabetes on HRQoL, and fewer diabetes-related worries were reported compared with those using regular insulin. Similarly, a questionnaire survey regarding the use of insulin lispro and insulin aspart in children and adolescents revealed that the majority of patients (305/389; 78%) experienced an improvement in HRQoL after switching to a rapid-acting insulin analog. Quality of life in this study was estimated based on the opinions of the attending physician rather than on assessment by the patients.

Figure 2
Effects of treatment with insulin aspart or human insulin on health-related quality of life (HRQoL). Changes from baseline in DSQOL scores after 6 months of treatment with insulin aspart or human insulin. â– , Insulin aspart; â–¡, human insulin. Reproduced with permission from , 2003;20(8):626-34.
Forty-seven patients with suboptimal glucose control under intensive insulin treatment (IIT) were switched from NPH to glargine. Forty patients maintained on IIT were used as controls. Diabetes-related HRQoL was assessed using the Well-being Enquiry for Diabetics (WED), before and after a 6- to 8-month switch to glargine. Results showed that patients treated with glargine showed several improvements in WED scores (discomfort, \( p = 0.020 \); impact, \( p = 0.0002 \); total score, \( p = 0.0005 \)). WED changes were associated with a lower perceived risk of hypoglycemia and fewer problems in daily life with glargine. Patients also showed improved glycemic control following treatment with insulin glargine (A1C decreased by 0.7%, treatment vs. baseline, \( p < 0.001 \)).

HRQoL effects of basal-bolus therapy using an all-analog insulin regimen have also been compared with an all-human insulin regimen. Fifty-six T1DM patients were randomized to a regimen of glargine plus lispro or NPH insulin plus unmodified human insulin for 32 weeks. At study endpoint, insulin glargine plus insulin lispro both reduced the negative impact of diabetes on HRQoL and improved HRQoL, compared with the human insulin regimen. Treatment satisfaction, assessed using the WHO Diabetes Treatment Satisfaction Questionnaire (DTSQ), was also markedly greater with glargine plus lispro compared with NPH plus human insulin (32.2 ± 3.4 vs. 23.9 ± 7.2, 86. [6.5–10.6]; \( p < 0.001 \)), with notable improvements in flexibility and convenience.

Additional studies have also reported a higher level of treatment satisfaction among patients receiving an insulin analog compared with those using regular human insulin regimens, the findings of which are summarized in Table 2. All trials evaluated treatment satisfaction using the DTSQ assessment. Significantly greater treatment satisfaction was reported for mealtime intensification with insulin aspart and once-daily insulin glargine than for the corresponding treatment with human insulin, despite small differences in A1C with the insulin analogs. An open-label study of 481 patients with T2DM in which insulin treatments were used in combination with once-daily glimepiride also showed a pronounced treatment satisfaction improvement with glargine versus NPH (\( p < 0.02 \); full analysis). Crossover trials, in which either insulin lispro or human insulin were used for bolus treatment, also reported significantly greater treatment satisfaction with the rapid-acting insulin analog than with human insulin (Table 2). Interestingly, one trial also assessed patient treatment preference at baseline and study end for human insulin or insulin lispro. At baseline, the majority of patients did not have a preference for either treatment; however, by the end of the trial there was a significant shift in preference towards insulin lispro (\( p = 0.001 \)). Among the insulin analogs, improvements in the DTSQ flexibility and convenience items were most notable.

**CONVENIENCE**

As highlighted above, the increased flexibility of dosing afforded by insulin analogs has been one of the major reasons cited for greater patient satisfaction with insulin analogs compared with human insulins. Because of the faster absorption, more rapid onset of activity, and shorter duration of action of rapid-acting insulin analogs, treatments can be administered closer to meals rather than the typical 30 minutes prior to eating required with regular human insulin. This ability to adjust insulin regimens to accommodate individual differences in eating and activity patterns is both flexible and convenient for the patient.

Aside from the insulin preparation, the method of delivery has also been a barrier to patient acceptance of insulin therapy. The inconvenience associated with vial and syringe administration has long represented a challenge for the uptake of insulin treatment. Attempts to address these issues have led to the development of insulin administration using pen devices. Pens offer the advantages of being discreet, portable, and accurate, and their ease of use makes them attractive to both patients and healthcare providers. Comparative clinical trials have demonstrated that patients not only prefer pen devices over syringe/vial delivery but also experience an improvement in HRQoL compared with the traditional syringe/vial delivery method. The dimensions that contributed most to a preference for the pen device were ease of use, activity interference, and social acceptability (\( p \leq 0.001 \)).
WEIGHT GAIN

Weight gain is a concern for many patients taking insulin therapy, particularly considering that many T2DM patients are already overweight. However, the introduction of the long-acting insulin analog, insulin detemir, means that weight gain is no longer an inevitable side effect of insulin therapy.

Data from a number of clinical trials in T1DM and T2DM patients have shown that insulin detemir is associated with significantly less weight gain compared with NPH insulin. In a multinational, open-label, prospective, observational study (n = 20,531) assessing the safety and efficacy of insulin detemir in clinical practice, there was a reduction in mean body weight (–0.7 kg; p < 0.0001), which was most apparent in patients with a higher body mass index (BMI) at baseline. The weight-sparing effects seem to be unique to insulin detemir, as data with insulin glargine have shown less consistent effects on weight gain, with two recent comparative studies showing significantly less weight gain in patients treated with insulin detemir compared with those treated with insulin glargine. Although the changes in weight are often small, knowing that a treatment will not cause significant weight gain can make a big difference psychologically to a patient’s acceptance of treatment. Furthermore, evidence clearly shows that even modest amounts of weight loss can have an important clinical impact in T2DM patients.

HYPOGLYCEMIA

Fear of hypoglycemia is a major barrier to effective insulin therapy and intensive glycemic control, and can impact on patient quality of life and adherence to treatment. Insulin analog treatments are associated with a reduced risk of hypoglycemia compared with human insulins.

In a 26-week, treat-to-target trial comparing twice-daily insulin detemir with NPH insulin, the risk for all hypoglycemia and nocturnal hypoglycemia with insulin detemir was reduced by 47% (p < 0.001) and 55% (p < 0.001), respectively. Similarly, in a meta-analysis comparing once-daily insulin glargine with NPH insulin, there was a significant reduction in hypoglycemia risk associated with insulin glargine, in terms of overall symptomatic hypoglycemia (11%; p = 0.0006) and nocturnal hypoglycemia (26%; p < 0.0001). The Cochrane review of rapid-acting insulin analogs also found a lower median incidence of severe hypoglycemic episodes per 100 patient-years compared with regular insulin (21.8 vs. 46.1).

Similarly, the Cochrane review of basal insulin analog trials showed significantly lower risks of symptomatic and nocturnal hypoglycemia with insulin glargine and insulin detemir compared with NPH insulin. A recent observational and non-interventional study of 2923 patients with T1DM and T2DM reported that switching from an all-human to an all-analog insulin regimen significantly reduced the incidence of both overall (mean difference –22.10; p < 0.0001) and nocturnal (mean difference –9.88; p < 0.0001) hypoglycemia.

COST-EFFECTIVENESS OF INSULIN ANALOGS VERSUS HUMAN INSULINS

In terms of direct prescription costs, insulin analogs and pen devices are more expensive than human insulins and syringes; although for insured patients, co-pays are typically the same regardless of the type of insulin or device used. Pharmacoeconomic modeling studies have consistently shown that insulin analogs provide gains in quality-adjusted life-years at costs well below accepted cost-effectiveness limits. The additional acquisition costs were offset by reductions in complications. Retrospective analyses of healthcare databases have also shown cost-effectiveness for analogs versus human insulins, primarily because of lower inpatient care costs as a result of decreased length of stay in
Emerging data also indicate that the improved adherence made possible through the administration of insulin using a pen device has the potential to reduce diabetes care costs (not including cost of insulin) when compared with delivery by syringe/vials, despite higher prescriptions costs for pen delivery. It has also been demonstrated that patients find insulin administration easier using a pen device, and that the dose delivered is more accurate than equivalent administration using a vial and syringe.

**CONCLUSIONS**

Assessment of glycemic control is a key means for determining the effect of diabetes treatment. However, it is now becoming apparent that the success of diabetes treatment is affected not only by the clinical efficacy of the treatment but also by a range of additional factors. In order to obtain a comprehensive understanding of the potential value of a diabetes intervention, it is therefore important to evaluate treatment outcomes in a broader context of treatment-related factors and adherence issues, particularly those that may impact on patient satisfaction and quality of life.

Relative to human insulins, analogs provide a better balance between glycemic control and tolerability. They can alleviate patient fears of hypoglycemia and concerns about weight gain. In addition, the greater flexibility and convenience afforded by their pharmacokinetic characteristics and associated pen devices can contribute to improved HRQoL. Such benefits do not need to come at an increased cost; it has been shown that the overall cost of insulin analog treatment and pen devices can be lower than that for human insulins and syringes due to reductions in complications. In addition, the ability of analogs to achieve improved HRQoL may result in improved adherence to therapy and consequently lower expenses related to poor compliance with or delayed adoption of insulin therapy.

In conclusion, insulin analog preparations should be considered as an option for all patients using insulin therapy. However, there is a need for ongoing education and reassurance to enable patients to accept their condition and gain the skills, self-confidence, and motivation necessary to achieve optimum control with insulin therapy.
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