Overcoming Psychological Barriers in Insulin Therapy

Nada Logan Stotland, MD, MPH
Professor of Psychiatry, Rush Medical College, Chicago, Illinois

ABSTRACT

Background: Research shows that tight glycemic control is a major factor in forestalling the microvascular and macrovascular complications that accompany diabetes mellitus (DM). Recent evidence shows that earlier use of insulin therapy is beneficial for people who are at higher risk for these complications because it provides more effective glycemic control. Yet, some patients either do not adhere to their insulin therapy or they modify their regimens in an unprescribed way.

Objective: The goal of this article was to examine the psychological barriers some patients with DM have to insulin therapy. Also discussed are strategies to overcome these barriers.

Methods: A literature search of MEDLINE was conducted for the period 1992 through 2005, using search word combinations including *psychological barriers in people with diabetes, insulin therapy, needle phobia, injection anxiety, weight gain*, and *fear of hypoglycemia*. Relevant articles relating to the topic of overcoming psychological barriers in insulin therapy were studied and summarized.

Results: The primary reasons why some patients alter their insulin intake are injection-related anxiety, concern about weight gain, and fear of hypoglycemia. Injection-related anxiety, or needle phobia, is associated with higher levels of anxiety, depression, and phobic symptoms; it can result in poor glycemic control. Such patients should be identified early in therapy so that attention can be directed to address this anxiety. Weight gain can become a circuitous problem; the patient may be overweight at the time of DM diagnosis and then fear a weight gain after the initiation of insulin therapy. This may lead to a patient's decision to skip doses of insulin therapy and sacrifice glycemic control in the process. Fear of hypoglycemia can be avoided through awareness of the causes of low blood glucose and prescribing newer insulin analogues that have lesser serum peaks and troughs over a 24-hour period.

Conclusions: Good communication between patient and clinician is the key in overcoming any psychological barriers to insulin therapy that some patients may have. The optimal use of insulin therapy is dependent on the patient's intentions to use it as prescribed. (*Insulin*. 2006;1:38–45) Copyright © 2006 Excerpta Medica, Inc.

Key words: psychological barriers in people with diabetes, insulin therapy, needle phobia, injection anxiety, weight gain, fear of hypoglycemia.

INTRODUCTION

The long-term benefits of intensive insulin therapy to control blood glucose levels have been demonstrated in prospective randomized[1–3] and epidemiologic[4] studies in patients with type 1 or type 2 diabetes mellitus (DM). These studies found a correlation between tight glycemic control and reduction in the progression of chronic complications associated with DM.

Research has demonstrated that optimum glycemic control is not routinely achieved in clinical practice.[5] Some of the psychological barriers to satisfactory insulin therapy include fear of hypoglycemia,[6] fear of

Accepted for publication October 9, 2005.
1557-0843/06/$19.00

weight gain,[7] and injection-related anxiety.[8] These problems have been associated with poor adherence to therapy, with subsequent inadequate glycemic control and the increased risk of developing microvascular and macrovascular complications that often accompany DM.

Clinicians have a key role in promoting patient adherence with insulin therapy. Patients need psychological support and practical information to increase their confidence in self-managing their DM and safeguarding their health.[9,10] In addition, clinicians should know the specific needs of their patients with DM, such as the degrees of self-motivation and physical dexterity to operate an injection device and any reservations a patient may have with regard to insulin therapy. Awareness of insulin analogues with improved pharmacokinetic profiles that can enhance glycemic control is also useful in clinical practice.

The goal of this article was to examine the psychological barriers some patients with DM have to insulin therapy. Also discussed are strategies to overcome these barriers.

METHODS

A literature search of MEDLINE was conducted for the period 1992 through 2005, using search word combinations including *psychological barriers in people with diabetes, insulin therapy, needle phobia, injection anxiety, weight gain*, and *fear of hypoglycemia*. Relevant articles relating to the topic of overcoming psychological barriers in insulin therapy were studied and summarized.

INJECTION-RELATED ANXIETY

A study of 115 patients with type 1 or type 2 DM treated with insulin therapy showed that 45% of study participants avoided injections of their prescribed insulin due to anxiety or needle phobia; 70% reported that they would be bothered if they had to inject themselves more than twice a day.[8] The study did not show any significant correlations between injection anxiety and age, sex, duration of DM, or the duration of insulin use. In another study, a small group of insulin-treated patients with DM were shown to have a severe fear of self-injecting and self-testing, characterized by emotional distress and avoidance behavior.[11] Based on a sample size of 24 insulin-treated adult patients with DM, results were extrapolated to the total study population (N = 1274), which showed that 0.2% to 1.3% of the population scored high in the severe fear of self-injecting range.[11]

The relationship between injection anxiety and glycemic control can have important therapeutic implications. In a study by Berlin et al,[12] poor glycemic control in patients with DM was associated with higher levels of anxiety, depression, and phobic symptoms. Furthermore, these patients performed fewer blood glucose measurements per day. Another study demonstrated that comorbid psychiatric illness was associated with a higher glycosylated hemoglobin (A1C) level compared with those patients with no psychiatric symptoms (10.8% vs 9.6%, respectively; $P = 0.02$).[13] Interestingly, a history of clinical depression has been found to increase the risk of developing DM by ~23% in younger adults (defined as ages 20–50 years).[14]

Patients who develop type 2 DM and are prescribed insulin therapy in combination with oral antidiabetic agents may initially resist the need for injectable therapy, even though they acknowledge the benefits of insulin use. In one study of patients with type 2 DM who did not yet require insulin therapy, participants reported negative attitudes toward the use of insulin, including anxiety about injection-associated pain, proper techniques, and the everyday necessity of administering injections.[15] For patients with negative attitudes, the clinician can identify the anxiety from the patient's perspective and address any concerns in a positive and reassuring manner.

The use of a short questionnaire (**Table I**) can help clinicians identify patients who may have injection-related anxiety.[8] Patient responses can provide the clinician with important clues relating to the success of subsequent therapy and highlight the need for more intense education and regular monitoring of DM management, including A1C levels.

For some patients with insulin-treated DM, pen devices for insulin injections have improved their quality of life. Manufacturers offer pen needles that are one third shorter (12.7 mm) than standard-length needles and have a larger gauge, with a smaller bore diameter for greater patient comfort. Because the pen needle does not puncture the stopper of an insulin vial before injection, the needle maintains its sharpness and beveled angle, thereby potentially reducing any discomfort associated with injection. Pen devices may be simpler to use for specific populations, such as older adults, children, and adolescents. A randomized, cross-

Table I. Insulin treatment questionnaire.

Patient's name _____	Male/Female _____ Age _____ Most recent A1C _____
How long have you had diabetes?	_____ years
Do you use a pen device?	Yes ____ No ____
How long have you injected insulin?	_____ years
Do you use a syringe?	Yes ____ No ____
Number of injections per day?	1 __ 2 __ 3 __ 4 __ More? __
How would you describe your feelings regarding daily injections?	Unconcerned ___ Mild anxiety ___ Moderate anxiety ___ Fear ___
Are these feelings excessive or unreasonable to you?	Yes ___ No ___
Have you avoided injections because of these feelings?	Yes ___ No ___
When you are injecting, how would you describe your feelings?	Unconcerned ___ Mild anxiety ___ Moderate anxiety ___ Fear ___
If you had to inject insulin more frequently, would this trouble you?	Yes ___ No ___
Do your feelings about injections interfere with your daily injections?	Yes ___ No ___
Have you ever developed any of the following symptoms before an injection? If so, circle as many of those as you have felt.	Palpitations Sweating Shortness of breath Nausea Dizziness Numbness Chills Out of body feeling Fainting Other _____

A1C = glycosylated hemoglobin.
Reprinted from *Diabetes Research and Clinical Practice*, Volume 46, Pages 239–246, Zambanini A, Newson RB, Maisey M, Feher MD. Injection related anxiety in insulin-treated diabetes. Copyright 1999, with permission from Elsevier.

over comparison of prefilled, disposable pens and conventional vials and syringes showed that 74% of patients indicated a preference for the pen over the vial/syringe method; 74% of the study participants considered the pen easier to use overall, and 85% of the study participants found the insulin dose scale on the pen easier to read.[16]

Research on noninjectable insulin formulations may lead to future options for patients with DM. For example, inhaled insulin is currently being assessed and has been found to maintain glycemic control comparable to that of patients taking multiple daily injections.[17] The prime benefit appears to be providing an effective alternative to subcutaneous insulin as part of a basal/bolus strategy in patients who are unwilling or unable to use preprandial insulin injections, presumably contributing to increased patient satisfaction and quality of life due to the reduced number of daily injections required.[17] However, patient satisfaction data are based on a small number of published clinical trials;

longer term pulmonary and other safety data are still needed. In one study, inhaled insulin was associated with a lower overall hypoglycemia rate compared with subcutaneously injected insulin (9.3 vs 9.9 episodes/patient-month) but a higher severe hypoglycemia rate (6.5 vs 3.3 episodes/100 patient-months).[17] Also, the lower bioavailability (and therefore higher doses of inhaled insulin required) may make inhaled insulin less cost-effective than injected insulin.

CONCERN ABOUT WEIGHT GAIN

Weight gain can be a concern for some patients with DM. For patients with type 2 DM (which is typically diagnosed from middle age onwards), weight gain can be an issue because patients are often overweight at the time of diagnosis and any further increase in weight is undesirable. The prospect of additional weight gain secondary to insulin use may be a major obstacle for some patients.[16] The anticipation of weight gain with insulin therapy and the discipline needed to compensate for it are psychological burdens that can cause negative feelings toward insulin therapy.[7] Insulin omission in women with type 1 DM is common. In one study, almost one third of the women surveyed admitted to their underuse of insulin to reduce their weight.[7] In a study of 341 women aged 13 to 60 years with type 1 DM, 31% reported intentional insulin omission.[18] The women who skipped their insulin therapy had poorer glycemic control, more DM-related hospitalizations, greater psychological distress, more fear of hypoglycemia, and higher rates of retinopathy and neuropathy.

Weight gain can be a concern for some patients when they start insulin therapy. In the United Kingdom Prospective Diabetes Study, adults initiating insulin therapy averaged a weight gain of almost 5 kg (11 lbs) over the first 3 years.[3] A weight gain for patients with type 2 DM is also associated with increased insulin resistance, thereby undermining the effectiveness of treatment.[19]

Research has found that although insulin therapy improves blood glucose control, some patients may experience changes in their blood pressure and lipid profiles.[20] In an ancillary study of the Diabetes Control and Complications Trial (DCCT), patients with type 1 DM who gained the most weight during therapy also had the highest waist-to-hip ratios, blood pressures, and levels of triglycerides, total cholesterol, low-density lipoprotein cholesterol, and apolipoprotein B compared with those in the lower weight ranges.[20]

DM management for obese patients involves glycemic control and weight reduction. These goals are particularly difficult to achieve in the obese patient with DM because progressive β-cell dysfunction and increasing insulin resistance may require the administration of increasingly higher dosages of insulin.[19]

Other research has found that insulin itself does not result in weight gain in patients with type 2 DM.[21] Insulin is often first prescribed to patients with type 2 DM after a period of poor metabolic control by oral agents, a period that may be accompanied by weight loss due to insulin deficiency and/or the poor metabolic control itself. The weight gain observed during insulin therapy may simply correspond to reexpression of the patient's physiologically controlled body weight. Onset of weight loss before the diagnosis of DM has rarely been observed, even in obese patients with type 2 DM and even though type 2 DM may remain undiagnosed for as long as 9 to 12 years.[22] Long-term studies of insulin-treated patients with type 2 DM suggest that the weight such patients reach is asymptomatic, and that most weight gain occurs during the first 3 years of treatment.[3,23]

When insulin therapy is required for the treatment of the obese patient with DM, combination therapy with oral agents that have been found to minimize the amount of exogenous insulin required may minimize weight gain. In addition, the obese patient with DM whose disease is poorly controlled with maximum oral antidiabetic therapy may benefit from weight-reducing agents, such as sibutramine or orlistat.[19]

New insulin analogues have been shown to be relatively beneficial in lessening weight gain during insulin therapy. Basal insulins precipitate when injected into subcutaneous tissues and therefore have a much slower absorption rate and extended action compared with other insulin formulations. For example, the action profile of insulin glargine shows a 24-hour constant profile compared with isophane insulin suspension, which peaks 4 to 6 hours after injection.[24] Thus, insulin glargine offers the potential of less nocturnal hypoglycemia and better fasting glucose control. This finding was confirmed in a study of patients with type 2 DM, which also showed that although A1C reductions were similar with insulin glargine and isophane insulin, less nocturnal hypo-

glycemia and significantly less weight gain were observed (0.4 kg [0.9 lbs] vs 1.4 kg [3.1 lbs], respectively; $P < 0.001$).[25]

Insulin detemir (another basal insulin) has also demonstrated relative benefits with respect to weight. Comparative studies of people with type 1 DM have consistently found that those individuals treated with insulin detemir have not gained weight on average, whereas those treated with isophane insulin have gained weight.[26–29] Insulin detemir also has been reported to incur a reduced risk of weight gain for patients with type 2 DM. In a 6-month comparative study of 505 people with type 2 DM, patients treated with insulin detemir gained 1.0 kg (2.2 lbs), whereas patients receiving isophane insulin gained 1.8 kg (4.0 lbs; $P = 0.02$).[30]

The mechanism of action in terms of weight gain observed with newer insulin analogues may be related to the reduced risk of nocturnal hypoglycemia, which perhaps leads to a reduction in the amount of "defensive eating" by the patient to guard against these episodes.[18,25]

FEAR OF HYPOGLYCEMIA

Patient behaviors commonly cause hypoglycemia,[31] a condition which is therefore generally preventable. Episodes of severe hypoglycemia, a common occurrence in patients with type 1 DM and hypoglycemia unawareness, can generate fear and anxiety.[32] Studies have found that the most frequent cause of hypoglycemia—accounting for almost two thirds of the cases—was reduction of caloric intake by patients without adjustments in DM medications.[33] Medication increases are rarely identified as the cause of hypoglycemic episodes. One study showed that a high proportion (51.2%) of stable, insulin-treated patients developed hypoglycemic episodes, but severe hypoglycemia occurred infrequently (3.4% of those who experienced hypoglycemia).[31] Patients identified a cause for 45% of these episodes: 53% of these episodes were attributed to missing a meal, 24% to exercise, and <2% followed a medication increase.

Intensified insulin therapy in the DCCT led to an improvement in the quality of DM care.[34] An ancillary study of this trial revealed that patients with less DM knowledge (and therefore lower hypoglycemic awareness) had higher A1C levels and a higher incidence of severe hypoglycemia.[34] Patients with type 2 DM—whether on insulin therapy or not, and especially if they are of advanced age and if they smoke—are more likely to have low hypoglycemia awareness.[35]

For many people with DM, the fear of hypoglycemia can lead to eating regular snacks to protect against hypoglycemic events, thus resulting in weight gain. This strategy may be used by patients who have a fear of nighttime hypoglycemia. The selection of a longer, smoother acting, and more consistently performing insulin that minimizes the number of serum troughs per 24-hour period could enable the patient to have the confidence to break a habit that may be contributing to any weight gain. For example, insulin glargine, the first clinically available basal analogue with a prolonged absorption and activity profile, has a 24-hour duration of action, no pronounced peak, and lower between-subject variability versus isophane insulin or extended insulin zinc suspension.[36] In patients with type 2 DM, insulin glargine has been found to confer at least equivalent glycemic control with a lower incidence of hypoglycemia compared with isophane insulin.[37] In one study that compared insulin glargine with isophane insulin, ~60% of patients attained A1C levels ≤7.0% with each insulin type. However, nearly 25% more patients attained this without documented nocturnal hypoglycemia using insulin glargine compared with isophane insulin (33.2% vs 26.7%, respectively; $P < 0.05$).

Further research may lead to the development of new treatments. One example of special interest is the 1-year success rate after islet transplantation in patients with type 1 DM following the Edmonton Protocol, in which donor pancreatic islets are infused into the hepatic portal vein of the recipient using radiographs.[38] This development offers the hope of good glycemic control without major surgical risks. A quality-of-life study demonstrated that the clinical success of this experimental procedure is associated with a substantial reduction in emotional burden through reduced fear of hypoglycemia.[39] Anxiety in islet-transplanted patients is reduced overall, probably because of the freedom from the requirement of exogenous insulin.

DISCUSSION AND CONCLUSIONS

Insulin is a molecule of historic proportions. It is the first molecule to be completely sequenced, and one of the first proteins to be crystallized in pure form; its structure was investigated using radiographic crystal-

lography, and it was the first protein to be chemically synthesized.[40] As the insulin molecule is refined into insulin analogues that can reduce the number of daily injections while providing superior efficacy, patients with DM stand a better chance of achieving the glycemic control needed to stave off the complications caused by DM. However, adherence remains the defining parameter; if the patient does not follow prescribed insulin therapy regimens, then the superiority of the insulin formulation is not fully realized.

For the clinician caring for patients with DM, the watchwords to use in daily clinical practice are assess, counsel, guide, and monitor (**Table II**).[41] Be aware of any cues the patient may give for not adhering to therapy. Take the initiative to ask about concerns relating to weight gain, especially if a patient with DM is overweight. Educate patients with DM that any fear of hypoglycemia can be addressed through awareness of the causes of low blood glucose, as well as adhering to prescribed insulin regimens, which may include newer insulin analogues that have lesser serum peaks and troughs over a 24-hour period. Good communication between patient and clinician can be the first step in overcoming any psychological barriers the patient may have relating to insulin therapy.

REFERENCES

1. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med*. 1993;329:977–986.
2. Ohkubo Y, Kishikawa H, Araki E, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: A randomized, prospective 6-year study. *Diabetes Res Clin Pract*. 1995;28:103–117.

Table II. Strategies for overcoming barriers to insulin therapy.

Possible Barrier	Solutions
Is the patient adherent to therapy?	Look for nonadherence markers: missed appointments, lack of response to medication (A1C levels; fasting glucose), missed refills
Does the patient have psychological problems?	Determine needle anxiety, weight concerns, fear of hypoglycemia Identify concomitant psychiatric/psychological problems, such as depression or phobias
Does the patient have trouble following the regimen?	Elicit patient's feelings about the regimen and his/her feelings about following the regimen Evaluate patient's involvement in therapy: injection technique, ability to use blood glucose monitor Encourage use of a medication-taking system, such as prefilled pens Provide simple, clear instructions and simplify regimen as much as possible
Are you listening to the patient's questions or concerns?	Listen to the patient and customize the regimen in accordance with the patient's wishes
Are caregivers involved in regimen?	If necessary, enlist help from family members, friends, and community services when needed
Are you providing feedback?	Reinforce desirable behavior and results when appropriate
Is the type of insulin appropriate?	Consider medications with long half-lives to promote adherence

A1C = glycosylated hemoglobin.
Adapted with permission from Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353:487–497.[41]

3. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33) [published correction appears in *Lancet*. 1999; 354:602]. *Lancet*. 1998;352:837–853.
4. Klein R, Klein BE, Moss SE, Cruickshanks KJ. Relationship of hyperglycemia to the long-term incidence and progression of diabetic retinopathy. *Arch Intern Med*. 1994; 154:2169–2178.
5. Turner RC, Cull CA, Frighi V, Holman RR, for the UK Prospective Diabetes Study (UKPDS) Group. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: Progressive requirement for multiple therapies (UKPDS 49). *JAMA*. 1999;281:2005–2012.
6. Mollema ED, Snoek FJ, Ader HJ, et al. Insulin-treated diabetes patients with fear of self-injecting or fear of self-testing: Psychological comorbidity and general well-being. *J Psychosom Res*. 2001;51:665–672.
7. Bryden KS, Neil A, Mayou RA, et al. Eating habits, body weight, and insulin misuse. A longitudinal study of teenagers and young adults with type 1 diabetes. *Diabetes Care*. 1999;22:1956–1960.
8. Zambanini A, Newson RB, Maisey M, Feher MD. Injection related anxiety in insulin-treated diabetes. *Diabetes Res Clin Pract*. 1999;46:239–246.
9. Pibernik-Okanovic M, Prasek M, Poljicanin-Filipovic T, et al. Effects of an empowerment-based psychosocial intervention on quality of life and metabolic control in type 2 diabetic patients. *Patient Educ Couns*. 2004;52: 193–199.
10. Banister NA, Jastrow ST, Hodges V, et al. Diabetes self-management training program in a community clinic improves patient outcomes at modest cost. *J Am Diet Assoc*. 2004;104:807–810.
11. Mollema ED, Snoek FJ, Heine RJ, van der Ploeg HM. Phobia of self-injecting and self-testing in insulin-treated diabetes patients: Opportunities for screening. *Diabet Med*. 2001;18:671–674.
12. Berlin I, Bisserbe JC, Eiber R, et al. Phobic symptoms, particularly the fear of blood and injury, are associated with poor glycemic control in type 1 diabetic adults. *Diabetes Care*. 1997;20:176–178.
13. Lustman PJ, Griffith LS, Clouse RE, Cryer PE. Psychiatric illness in diabetes mellitus. Relationship to symptoms and glucose control. *J Nerv Ment Dis*. 1986;174:736–742.
14. Brown LC, Majumdar SR, Newman SC, Johnson JA. History of depression increases risk of type 2 diabetes in younger adults. *Diabetes Care*. 2005;28:1063–1067.
15. Hunt LM, Valenzuela MA, Pugh JA. NIDDM patients' fears and hopes about insulin therapy. The basis of patient reluctance. *Diabetes Care*. 1997;20:292–298.
16. Korytkowski M, Bell D, Jacobsen C, Suwannasari R, for the FlexPen Study Team. A multicenter, randomized, open-label, comparative, two-period crossover trial of preference, efficacy, and safety profiles of a prefilled, disposable pen and conventional vial/syringe for insulin injection in patients with type 1 or 2 diabetes mellitus. *Clin Ther*. 2003;25:2836–2848.
17. Skyler JS, Weinstock RS, Raskin P, et al, for the Inhaled Insulin Phase III Type 1 Diabetes Study Group. Use of inhaled insulin in a basal/bolus insulin regimen in type 1 diabetic subjects: A 6-month, randomized, comparative trial. *Diabetes Care*. 2005;28:1630–1635.
18. Polonsky WH, Anderson BJ, Lohrer PA, et al. Insulin omission in women with IDDM. *Diabetes Care*. 1994;17: 1178–1185.
19. Albu J, Raja-Khan N. The management of the obese diabetic patient. *Prim Care*. 2003;30:465–491.
20. Purnell JQ, Hokanson JE, Marcovina SM, et al, for the Diabetes Control and Complications Trial. Effect of excessive weight gain with intensive therapy of type 1 diabetes on lipid levels and blood pressure: Results from the DCCT [published correction appears in *JAMA*. 1998;280:1484]. *JAMA*. 1998;280:140–146.
21. Larger E, Rufat P, Dubois-Laforgue D, Ledoux S. Insulin therapy does not itself induce weight gain in patients with type 2 diabetes. *Diabetes Care*. 2001;24:1849–1850.
22. Harris MI, Klein R, Welborn TA, Knuiman MW. Onset of NIDDM occurs at least 4–7 yr before clinical diagnosis. *Diabetes Care*. 1992;15:815–819.
23. Kudlacek S, Schernthaner G. The effect of insulin treatment on HbA1c, body weight and lipids in type 2 diabetic patients with secondary-failure to sulfonylureas: A five year follow-up study. *Horm Metab Res*. 1992;24: 478–483.
24. Heinemann L, Linkeschova R, Rave K, et al. Time-action profile of the long-acting insulin analog insulin glargine (HOE901) in comparison with those of NPH insulin and placebo. *Diabetes Care*. 2000;23:644–649.
25. Rosenstock J, Schwartz SL, Clark CM Jr, et al. Basal insulin therapy in type 2 diabetes: 28-Week comparison of insulin glargine (HOE901) and NPH insulin. *Diabetes Care*. 2001;24:631–636.
26. De Leeuw I, Vague P, Selam JL, et al. Insulin detemir used in basal-bolus therapy in people with type 1 diabetes is associated with a lower risk of nocturnal hypoglycaemia and less weight gain over 12 months in comparison to NPH insulin. *Diabetes Obes Metab*. 2005;7:73–82.
27. Standl E, Lang H, Roberts A. The 12-month efficacy and safety of insulin detemir and NPH insulin in basal-bolus therapy for the treatment of type 1 diabetes. *Diabetes Technol Ther*. 2004;6:579–588.
28. Vague P, Selam JL, Skeie S, et al. Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with pre-meal insulin aspart. *Diabetes Care*. 2003;26:590–596.
29. Home P, Bartley P, Russell-Jones D, et al, for the Study to Evaluate the Administration of Detemir Insulin Efficacy,

Safety and Suitability (STEADINESS) Study Group. Insulin detemir offers improved glycemic control compared with NPH insulin in people with type 1 diabetes: A randomized clinical trial. *Diabetes Care*. 2004;27:1081–1087.

30. Haak T, Tiengo A, Draeger E, et al. Lower within-subject variability of fasting blood glucose and reduced weight gain with insulin detemir compared to NPH insulin in patients with type 2 diabetes. *Diabetes Obes Metab*. 2005;7:56–64.
31. Murata GH, Duckworth WC, Shah JH, et al. Hypoglycemia in stable, insulin-treated veterans with type 2 diabetes: A prospective study of 1662 episodes. *J Diabetes Complications*. 2005;19:10–17.
32. Cox DJ, Irvine A, Gonder-Frederick L, et al. Fear of hypoglycemia: Quantification, validation, and utilization. *Diabetes Care*. 1987;10:617–621.
33. Smith WD, Winterstein AG, Johns T, et al. Causes of hyperglycemia and hypoglycemia in adult inpatients. *Am J Health Syst Pharm*. 2005;62:714–719.
34. Schiel R, Ulbrich S, Muller UA. Quality of diabetes care, diabetes knowledge and risk of severe hypoglycaemia one and four years after participation in a 5-day structured treatment and teaching programme for intensified insulin therapy. *Diabetes Metab*. 1998;24:509–514.
35. Berlin I, Sachon CI, Grimaldi A. Identification of factors associated with impaired hypoglycaemia awareness in patients with type 1 and type 2 diabetes mellitus. *Diabetes Metab*. 2005;31:246–251.
36. Lepore M, Pampanelli S, Fanelli C, et al. Pharmacokinetics and pharmacodynamics of subcutaneous injection of long-acting human insulin analog glargine, NPH insulin, and ultralente human insulin and continuous subcutaneous infusion of insulin lispro. *Diabetes*. 2000;49:2142–2148.
37. Riddle MC, Rosenstock J, Gerich J, for the Insulin Glargine 4002 Study Investigators. The treat-to-target trial: Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients. *Diabetes Care*. 2003;26:3080–3086.
38. Ryan EA, Lakey JR, Rajotte RV, et al. Clinical outcomes and insulin secretion after islet transplantation with the Edmonton protocol. *Diabetes*. 2001;50:710–719.
39. Johnson JA, Kotovych M, Ryan EA, Shapiro AM. Reduced fear of hypoglycemia in successful islet transplantation. *Diabetes Care*. 2004;27:624–625.
40. Juvenile Diabetes Research Foundation. The history of diabetes & the search for a cure. Available at: http://www.jdrf.org/au/publications/factsheets/historycure.html. Accessed October 17, 2005.
41. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353:487–497.

Address correspondence to: Nada Logan Stotland, MD, MPH, Rush Medical College, 5511 South Kenwood Avenue, Chicago, IL 60637–1713. E-mail: nadast@aol.com