Outpatient Insulin Therapy in Type 1 and Type 2 Diabetes Mellitus

Scientific Review

Dawn E. DeWitt, MD, MSc

Irl B. Hirsch, MD

Context Newer insulin therapies, including the concept of physiologic basal-prandial insulin and the availability of insulin analogues, are changing clinical diabetes care. The key to effective insulin therapy is an understanding of principles that, when implemented, can result in improved diabetes control.

Objective To systematically review the literature regarding insulin use in patients with type 1 and type 2 diabetes mellitus (DM).

Data Sources A MEDLINE search was performed to identify all English-language articles of randomized controlled trials involving insulin use in adults with type 1 or type 2 DM from January 1, 1980, to January 8, 2003. Bibliographies and experts were used to identify additional studies.

Study Selection and Data Extraction Studies were included (199 for type 1 DM and 144 for type 2 DM, and 38 from other sources) if they involved human insulins or insulin analogues, were at least 4 weeks long with at least 10 patients in each group, and glycemic control and hypoglycemia were reported. Studies of insulin-oral combination were similarly selected.

Data Synthesis Twenty-eight studies for type 1 DM, 18 for type 2 DM, and 48 for insulin-oral combination met the selection criteria. In patients with type 1 DM, physiologic replacement, with bedtime basal insulin and a mealtime rapid-acting insulin analogue, results in fewer episodes of hypoglycemia than conventional regimens. Rapid-acting insulin analogues are preferred over regular insulin in patients with type 1 DM since they improve HbA_{1C} and reduce episodes of hypoglycemia. In patients with type 2 DM, adding bedtime neutral protamine Hagedorn (isophane) insulin to oral therapy significantly improves glycemic control, especially when started early in the course of disease. Bedtime use of insulin glargine results in fewer episodes of nighttime hypoglycemia than neutral protamine Hagedorn regimens. For patients with more severe insulin deficiency, a physiologic insulin regimen should allow lower glycemic targets in the majority of patients. Adverse events associated with insulin therapy include hypoglycemia, weight gain, and worsening diabetic retinopathy if hemoglobin A_{1C} levels decrease rapidly.

Conclusions Many options for insulin therapy are now available. Physiologic insulin therapy with insulin analogues is now relatively simple to use and is associated with fewer episodes of hypoglycemia.

JAMA. 2003;289:2254-2264

www.jama.com

PRIMARY CARE PHYSICIANS PROvide diabetes care for 39% of the 16 million patients in the United States (US) with type 1 diabetes mellitus (DM) and 82% of patients with type 2 DM.[1] The greatest change in diabetes therapy in the last decade has been the introduction of insulin analogues. Currently, 6 to 7 million Americans use human insulin or insulin analogues. The availability of the new insulin analogues makes physiologic insulin therapy realistic for many patients, because the onset and duration of the action of these analogues more closely mimic human insulin secretion, thus simplifying insulin dosing and adjustment and increasing flexibility for patients. The use of physiologic insulin replacement and continuous subcutaneous insulin infusion (CSII, or pump therapy) are increasingly popular and have become the criterion standard, with more than 200 000 patients with type 1 DM using CSII therapy worldwide.[2]

The American Diabetes Association recommends a hemoglobin (Hb) A_{1C} level less than 7%.[3] Data from 1988-1995[4] show that 43% of US patients had an HbA_{1C} level greater than 8.0%, 18% had poor control with an HbA_{1C} level greater than 9.5% (24% of the insulin-treated patients had poor control). More than 50% of US patients with type 1 DM

See also p 2265 and Patient Page.

Author Affiliations: Division of General Internal Medicine, Department of Medicine, University of Washington (Dr DeWitt); and Division of Metabolism, Endocrinology, and Nutrition, Department of Medicine, University of Washington, and Diabetes Care Center, University of Washington Medical Center (Dr Hirsch), Seattle.

Corresponding Author and Reprints: Dawn E. DeWitt, MD, MSc, Rural Clinical School, University of Melbourne, PO Box 6500, Shepparton VIC 3632, Australia (e-mail: ddewitt@unimelb.edu.au).

Scientific Review and Clinical Applications Section Editor: Wendy Levinson, MD, Contributing Editor. We encourage authors to submit papers to "Scientific Review and Clinical Applications." Please contact Wendy Levinson, MD, Contributing Editor, *JAMA*; phone: 312-464-5204; fax: 312-464-5824; e-mail: wendy.levinson@utoronto.ca.

TTVI risks) and in an increase in the absolute number of donors returning to donate a year later. Although people who successfully donate in times of crisis appear to have return behaviors similar to other first-time donors, the relatively low yearly return rates before or after the attacks reinforce the need for education about the importance of regular blood donation. Additionally, improving understanding of both motivating and deterrent factors associated with donating blood will enhance the ability to ensure the adequacy of the blood supply.

Author Affiliations: Westat, Rockville, Md (Drs Glynn, Schreiber, Wright, and Kleinman and Ms Tu); and Blood Centers of the Pacific, San Francisco, Calif, and the University of California, San Francisco (Drs Busch and Murphy).

Financial Disclosures: Dr Glynn owned stock in Biotechnology General, Cephalon, Genentech, Human Genome Sciences, IFlow, Medimmune, and Novartis. Dr Busch received research grants or funding from the National Heart, Lung, and Blood Institute (NHLBI grant NO1-HB-47114) and from the Retrovirus Epidemiology Donor Study (REDS); received honoraria from Abbott Laboratories, Chiron, Gen-Probe Inc, Ortho Diagnostics Systems, and Roche Molecular Systems; consulted for Acrometrix, Gambro BCT/Navigant, Haemonetics, Ortho Diagnostics Systems (Ortho blood advisory committee member), Roche Molecular Systems (global advisory board member), and VI Technologies (Vitex) (scientific advisory board member); had lecture sponsorships from Abbott, Cambridge Healthtech Institute, Cerus Corp, DiaMed, Emory University, Johns Hopkins University, University of California, San Diego, US Centers for Disease Control and Prevention, US Food and Drug Administration (FDA), National Institutes of Health, National Cancer Institute, and NHLBI; was an advisor for Canadian Blood Services (scientific, technical, research, and advisory committee member), US Department of Health and Human Services Advisory Committee on Blood Safety and Availability (former member), FDA Blood Policy Advisory Committee (former member), University of California, San Francisco, AIDS Research Institute (executive committee member), University of California, San Francisco/Berkeley, Institute for Global Health (affiliated faculty member), American Society of Hematology (Scientific Committee on Transfusion Medicine member), America's Blood Centers (scientific, medical, and technical committee member), International Society of Blood Transfusion (scientific advisory board member), and Biomedical Excellence for Safer Transfusions (working party member); was vice president, research, Blood Centers of the Pacific (BCP), San Francisco, Calif, vice president, research, Blood Systems Inc, Scottsdale, Ariz (parent of BCP), and acting president, Blood Systems Foundation; and received honoraria for continuing medical education programs from Agouron, Cambridge Healthtech Institute, DiaMed, Florida Blood Services/University of South Florida, and Ortho Diagnostics Systems. Dr Murphy received a speaker's honorarium from Chiron Corp. Dr Kleinman received contract support from NHLBI (through REDS) for work related to transfusion-transmitted diseases and blood safety, was a paid consultant to Roche Molecular Systems and Chiron for development and assessment of blood screening assays, and received honoraria for participation on the scientific advisory board of VI Technologies, a company developing pathogen reduction technology for red blood cell transfusion.

Author Contributions: *Study concept and design:* Glynn, Busch, Murphy, Wright, Kleinman.
Acquisition of data: Glynn, Busch.
Analysis and interpretation of data; Critical revision of the manuscript for important intellectual content: Glynn, Busch, Schreiber, Murphy, Wright, Tu, Kleinman.
Drafting of the manuscript: Glynn, Busch, Wright.
Statistical expertise: Glynn, Wright, Tu.
Obtained funding; epidemiologic expertise: Schreiber.
Administrative, technical, or material support: Busch, Schreiber, Murphy.
Study supervision: Busch.
The Retrovirus Epidemiology Donor Study (REDS Study Group) is the responsibility of the following persons: *Blood Centers:* American Red Cross Blood Services, Greater Chesapeake and Potomac Region: Catharie C. Nass, PhD; American Red Cross Blood Services, Southeastern Michigan Region: Martha J. Higgins, MD; American Red Cross Blood Services, Southern California Region: George Garrally, PhD, Sheila Hutching; Blood Centers of the Pacific: Edward L. Murphy, MD, MPH (UCSF), Michael P. Busch, MD, PhD; Sylvan N. Goldman Center, Oklahoma Blood Institute: Ronald O. Gilcher, MD, James W. Smith, MD; *Medical Coordinating Center:* Westat: George B. Schreiber, ScD, Simone A. Glynn, MD, MSc, MPH, Melissa R. King, MSPH; National Heart, Lung, and Blood Institute, NIH: George J. Nemo, PhD; Steering Committee Chairman: Thomas F. Zuck, LLB, MD (Ohio Enterprises International).

Funding/Support: This work was supported by NHLBI contracts N01-HB-97077 (superseded by N01-HB-47114), -97078, -97079, -97080, -97081, and -97082.

REFERENCES

1. Honawar V. Record rise in blood donations. *Washington Times*. September 21, 2001:B4.
2. Becker C, Galloro V. An overwhelming response within hours of the disaster, medical supplies were on their way to N.Y. *Mod Healthc*. September 17, 2001: 18-19.
3. Schmidt PJ, Bayer WL. Transfusion support in a community disaster. In: Das PC, Smit S, Halie MR, eds. *Supportive Therapy in Haematology*. Boston, Mass: Martinus Nijhoff Publishers; 1985:371-377.
4. Busch MP, Guiltinan A, Skettino S, Cordell R, Zeger G, Kleinman S. Safety of blood donations following a natural disaster. *Transfusion*. 1991;31:719-723.
5. Schmidt PJ. Blood and disaster—supply and demand. *N Engl J Med*. 2002;346:617-620.
6. Advisory Committee on Blood Safety and Availability. What lessons can be learned from the events of September 11, 2001, that would strengthen the safety and availability of the United States blood supply? Presented at: Sixteenth Meeting of the Advisory Committee on Blood Safety and Availability; January 31, 2002; Washington, DC. Available at: http://www.hhs.gov/bloodsafety/transcripts/20020131.html. Accessed March 21, 2003.
7. American Association of Blood Banks. September blood donations well above average, reports NBDRC. *AABB Wkly Rep*. November 2, 2001;7(38):1-2.
8. American Association of Blood Banks Interorganizational Task Force on Domestic Disasters and Acts of Terrorism. Report and recommendations, January 31, 2002. Available at: http://www.aabb.org/Pressroom/In_the_News/idfddat013002.htm. Accessed March 21, 2003.
9. Gimble JG, Kline L, Makris N, Muenz LR, Friedman LI. Effects of new brochures on blood donor recruitment and retention. *Transfusion*. 1994;34:586-591.
10. Meckler L. Five times more blood discarded than is usual. *The Standard-Times*. September 10, 2002: A7.
11. US Food and Drug Administration (FDA). Revised preventive measures to reduce the possible risk of transmission of Creutzfeldt-Jakob disease (CJD) and variant Creutzfeldt-Jakob disease (vCJD) by blood and blood products. US Dept of Health and Human Services/FDA/Center for Biologics Evaluation and Research (CBER). January 2002. Available at: http://www.fda.gov/cber/guidelines.htm. Accessed March 21, 2003.
12. Janssen RS, Satten GA, Stramer SL, et al. New testing strategy to detect early HIV-1 infection for use in incidence estimates and for clinical and prevention purposes. *JAMA*. 1998;280:42-48.
13. Dodd RY, Notari EP, Stramer SL. Current prevalence and incidence of infectious disease markers and estimated window period risk in the American Red Cross blood donor population. *Transfusion*. 2002;42: 975-979.
14. Villarosa L. Out to do good, some first-time blood donors get bad news. *New York Times*. December 20, 2001:B6.
15. Doherty B, McMillan M. America's Blood Centers releases numbers from last week's blood collections. *America's Blood Centers News*. September 19, 2001. Available at: http://66.155.15.152/news/detail.asp?ID=97. Accessed March 21, 2003.
16. Dodd RY, Orton SL, Notari EP IV, Stramer SL. Viral marker rates among blood donors before and after the terrorist attacks on the United States on September 11, 2001. *Transfusion*. 2002;42:1240-1241.
17. Fienberg SE. *The Analysis of Cross-Classified Categorical Data*. 2nd ed. Cambridge, Mass: MIT Press; 1980:16-19.
18. SAS Institute Inc. The CATMOD procedure. In: *SAS/STAT User's Guide*. 4th ed. Cary, NC: SAS Institute Inc; 1989:405-517.
19. Wu Y, Glynn SA, Schreiber GB, et al. First-time blood donors. *Transfusion*. 2001;41:360-364.
20. Wu Y, Schreiber G, Glynn S, et al. Demographic trends in repeat whole blood donations: 1991-1998 [abstract]. *Transfusion*. 2000;40(suppl):16S.
21. Glynn SA, Kleinman SH, Wright DJ, Busch MP. International application of the incidence rate/window period model. *Transfusion*. 2002;42:966-972.
22. Edwards PW, Zeichner A. Blood donor development: effects of personality, motivational and situational variables. *Pers Individ Dif*. 1985;6:743-751.
23. Oswalt RM. A review of blood donor motivation and recruitment. *Transfusion*. 1977;17:123-135.
24. Piliavin JA. Why do they give the gift of life? a review of research on blood donors since 1977. *Transfusion*. 1990;30:444-459.
25. Glynn SA, Kleinman SH, Schreiber GB, et al. Motivations to donate blood: demographic comparisons. *Transfusion*. 2002;42:216-225.
26. Drake AW. *Public Attitudes and Decision Processes With Regard to Blood Donation: Final Report and Executive Summary*. Cambridge, Mass: MIT; 1978: 1-189.
27. *Comprehensive Report on Blood Collection and Transfusion in the United States in 1999*. Bethesda, Md: National Blood Data Resource Center; 2001.
28. American Association of Blood Banks. Recommendations of the Department of Health and Human Services Advisory Committee on Blood Safety and Availability. February 1, 2001. Available at: http://www.aabb.org/Pressroom/In_the_News/acbsarecs020102.htm. Accessed March 21, 2003.
29. Busch M, Stramer S, Caglioti S, et al. Error surveillance in blood donor infectious disease screening. In: Abstracts of the 27th Congress of the International Society of Blood Transfusion; August 24-29, 2002; Vancouver, British Columbia. Abstract 83:128.
30. Williams AE, Thomson RA, Schreiber GB, et al. Estimates of infectious disease risk factors in US blood donors. *JAMA*. 1997;277:967-972.
31. Glynn SA, Smith JW, Schreiber GB, et al. Repeat whole-blood and plateletpheresis donors. *Transfusion*. 2001;41:736-743.

ase only 1 to 2 insulin injections per day, a suboptimal, nonphysiologic approach to type 1 DM insulin therapy.[5] Importantly, even many patients with type 2 DM would not achieve adequate control using twice-daily neutral protamine Hagedorn (NPH or isophane insulin).[6]

Most physicians would agree that good diabetes control, which often requires intensive insulin therapy, is desirable for patients with type 1 DM and type 2 DM. Patients receiving intensive therapy with lower HbA_{1c} levels with type 1 DM in the Diabetes Control and Complications Trial, or with type 2 DM in the United Kingdom Prospective Diabetes Study (UKPDS), had fewer, later microvascular complications.[7,8] Interestingly, some data suggest that insulin may benefit patients with DM in other ways. For example, early insulin therapy may preserve β-cell function.[9,10] Insulin therapy can also improve lipid metabolism[11-15] and mortality after myocardial infarction.[16]

With diabetes-related medical costs of $132 billion per year (more than 12% of the US health care budget),[17] many experts question whether intensive insulin therapy (approximately $16 000-30 000 per quality-adjusted life years gained)[17] is cost-effective. In the UKPDS, the incremental yearly cost of intensive insulin therapy for patients with type 2 DM (either with sulfonylurea [SU] agents or with insulin) was $1866,[18] while in the Kumamoto trial, multiple injection therapy for patients with type 2 DM reduced costs from $31 525 for conventional therapy to $30 310, by decreasing complications.[19]

METHODS

We searched MEDLINE for all English-language articles involving insulin use in adults with type 1 DM (n=199) or type 2 DM (n=144) between January 1, 1980, and January 8, 2003. Bibliographies and experts allowed for the identification of additional relevant abstracts (n=3) and studies (n=35). Randomized controlled trials were included (28 for type 1 DM and 18 for type 2 DM) if they compared currently available human insulins, reported glucose measurements and/or rates of hypoglycemic episodes, and were at least 4 weeks long with at least 10 patients in each group. Using similar criteria, randomized controlled trials of insulin-oral agent combination therapy (n=48) were reviewed in detail. Studies with English-language abstracts or those using animal and human insulins were selected if they were included in previously published reviews or meta-analyses and met our other criteria.

The authors reviewed, summarized, and synthesized the data. We found the literature highly problematic because it lacked standardized medication protocols, methods, and end points. A large majority of trials were sponsored by the pharmaceutical industry. Given the paucity of evidence in some areas, we believe that expert clinical diabetes practice is far ahead of clinical trials.

Table 1. Currently Available Insulin Products*

Insulin†	Onset	Peak	Effective Duration, h	Cost per 10 mL per 100 U/mL‡
Rapid-acting	5-15 min	30-90 min	5	
Lispro (Humalog)				$46
Aspart (NovoLog)				$58
Short-acting	30-60 min	2-3 h	5-8	
Regular U100				$25
Regular U500 (concentrated)				$220/20 mL
Buffered regular (Velosulin)				$55
Intermediate-acting				
Isophane insulin (NPH, Humulin N/Novolin N)	2-4 h	4-10 h	10-16	$24-$26
Insulin zinc (Lente, Humulin L/Novolin L)	2-4 h	4-12 h	12-18	$24-$26
Long-acting				
Insulin zinc extended (Ultralente, Humulin U)	6-10 h	10-16 h	18-24	$25
Glargine (Lantus)	2-4 h§	No peak	20-24	$46
Premixed				
70% NPH/30% regular (Humulin 70/30)	30-60 min	Dual	10-16	$25
50% NPH/50% regular (Humulin 50/50)	30-60 min	Dual	10-16	$46
75% NPL/25% lispro (Humalog Mix 75/25)	5-15 min	Dual	10-16	$58
70% NP/30% aspart (NovoLog Mix)	5-15 min	Dual	10-16	$59

Abbreviations: L, Lente; NPH, neutral protamine Hagedorn; NPL, insulin lispro protamine (neutral protamine lispro).
*Adapted with permission from *Practical Insulin: A Handbook for Prescribing Providers*, The American Diabetes Association, 2002.[163]
†Assuming 0.1-0.2 U/kg per injection. Onset and duration vary significantly by injection site.
‡Prices are for comparison and may vary widely. Sources of prices are from Drugstore.com (http://www.drugstore.com) or retail ranges from Costco, Safeway, Rite Aid, and Walgreens.
§Time to steady state.

RESULTS

What Are the Major Types of Insulin?

Rapid-Acting Insulin. Insulin lispro and insulin aspart do not self-aggregate in solution as human (regular) insulin does, and these insulins are rapidly absorbed (TABLE 1). Insulin lispro differs from human insulin by an amino acid exchange of lysine and proline at positions 28 and 29. The substitution of aspartic acid for proline at position 28 created insulin aspart. Rapid-acting insulins are most appropriately injected at mealtime as "prandial" insulin (sometimes referred to as "bolus" insulin) or used in insulin pumps.

Short-Acting Insulin. Regular insulin has a delay to onset of action of 30 to 60 minutes (Table 1). Patients are instructed to inject regular insulin 20 to 30 minutes prior to meals (ie, lag time is the time between injecting insulin and eating) to match insulin availability and carbohydrate absorption. Regular insulin acts almost immediately when injected intravenously.

Intermediate-Acting Insulin. Neutral protamine Hagedorn (isophane insulin; NPH) insulin is slowly absorbed due to the addition of protamine to regular insulin (Table 1). Regular insulin bound to zinc, Lente insulin, has a slightly longer effective duration than

NPH. Lente and NPH are commonly used as twice-daily basal insulins. Neutral protamine lispro (insulin lispro protamine; NPL) and protamine crystalline (crystal) aspart, available in the United States only in premixed insulins, are functionally identical to NPH.

Long-Acting Insulin. Ultralente insulin (insulin zinc extended) is absorbed slowly in its zinc crystalline form. Insulin glargine, a modified human insulin that forms a microprecipitate in the subcutaneous tissue, is released slowly with a peakless delivery of about 20 to 24 hours in most patients (Table 1).

What Are the Major Adverse Effects of Insulin?

Hypoglycemia is the most common adverse effect of insulin therapy. In the Diabetes Control and Complications Trial (type 1 DM),[20] intensive therapy increased the risk of severe hypoglycemia, defined as needing the assistance of another person. Severe hypoglycemia was reported by 26% of patients with a mean of 1.9 episodes per patient per year, and 43% of episodes occurred nocturnally. In the UKPDS, patients with type 2 DM receiving insulin therapy had lower HbA_{1C} levels, but 1% to 2% more patients receiving insulin reported at least 1 episode of severe hypoglycemia per year than those patients receiving other therapies. Intensive therapy, with oral medications or insulin, has been shown to increase the risk of episodes of hypoglycemia.[8]

Generally, patients receiving insulin gain weight. As patients attempt better glycemic control, decreased glycosuria and intermittent overinsulinization can result in hypoglycemia, hunger, and increased caloric intake. In the Diabetes Control and Complications Trial, patients with type 1 DM receiving intensive insulin therapy gained 4.75 kg more than patients receiving conventional therapy during the 3.5- to 9-year study period ($P<.001$), although waist-hip ratios did not differ between groups.[21] In the UKPDS, patients with type 2 DM receiving intensive insulin therapy gained significantly more weight (1.4-2.3 kg) than those patients treated with SUs or metformin.[8] Bedtime administration of NPH produces less weight gain than daytime NPH, making bedtime administration a preferred strategy when starting insulin therapy in patients with type 2 DM.[22,23] In one study, patients gained less weight with insulin glargine than with conventional therapy with NPH.[24]

Rapid improvement in diabetes control results in progressive worsening of retinopathy in approximately 5% of patients.[25-27] Patients with proliferative retinopathy and who have an HbA_{1C} level greater than 10% are at highest risk of worsening retinopathy.[28] In these patients, we recommend reducing the HbA_{1C} level slowly (2% each year) with frequent ophthalmologic examinations (eg, every 6 months or for any symptoms) to ensure aggressive treatment of progressive retinopathy.

What Are the Major Issues Regarding Insulin Delivery?

When prescribing insulin for patients, important issues include insulin pharmacokinetics and compatibility, technological issues, and costs. Insulin absorption variability is the biggest confounder of efforts to mimic physiologic insulin secretion. The onset and duration of action of types of insulin vary greatly when different insulins are mixed, by injection site, and among patients.[29] Large doses of human insulins form an insulin depot, unpredictably prolonging the duration of action; this response is less of an issue for the insulin analogues.[30] Thus, patients injecting 40 U of NPH insulin into their abdominal region before breakfast may have a significantly different onset and peak of action than the same patients injecting 20 U of NPH in their thigh in the evening; mixing insulin lispro with the morning NPH dose and regular with the evening NPH dose would result in further variation. Insulin glargine may not be mixed with other insulins. Cloudy insulins, for example NPH, must be resuspended before administration, and if done improperly the insulin concentration may vary significantly.[31] Importantly, any strategy that increases the consistency of delivery should decrease glucose fluctuations.

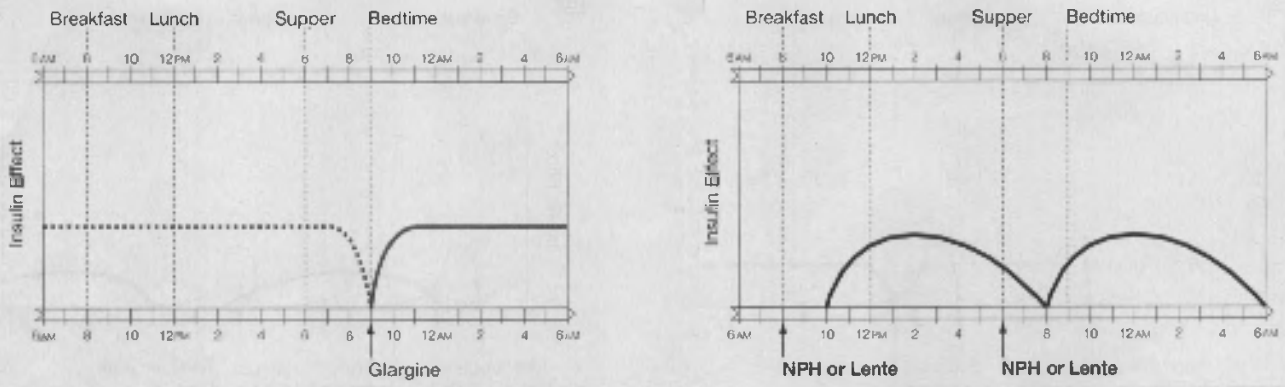
Insulin pens are convenient and may help avoid some insulin errors, but insulin cartridges for pens are more expensive than insulin in vials. Patients using insulin pumps must attend to tubing and injection site issues, must closely monitor their blood glucose level, and should have a back-up method of insulin administration.

What Are the Differences Between Physiologic and Nonphysiologic Insulin Regimens?

We refer to regimens that do not mimic normal β-cell secretion as "nonphysiologic insulin replacement" (FIGURE 1). "Physiologic insulin replacement" attempts to mimic normal insulin secretion. In general, physiologic regimens replace basal and prandial insulin (often referred to as "bolus") separately. In our experience, physicians and patients frequently misunderstand this key difference.

Traditionally, NPH was the primary basal insulin and regular was the primary prandial insulin. However, as typically used, each provides both basal and prandial effects. In conventional twice-daily NPH and regular insulin regimens (FIGURE 2), morning regular insulin is responsible for glucose disposal for breakfast, but its effective duration of 5 to 8 hours also makes it prandial insulin at lunch. After the absorption of breakfast (carbohydrate disposal is usually complete by midmorning), the regular insulin becomes, by definition, basal insulin. The morning NPH insulin is basal insulin after breakfast and lunch absorption are complete, and becomes the primary prandial insulin for lunch. But the relatively quick onset of NPH makes it functionally a component of the breakfast prandial insulin. This regimen requires strict consistency of the timing of injections and meals. Delaying lunch frequently results in hypoglycemia, at least for many patients trying to achieve meticulous glycemic control. Because NPH and regular insulin overlap in the later part

Figure 1. Examples of Nonphysiologic Insulin Replacement

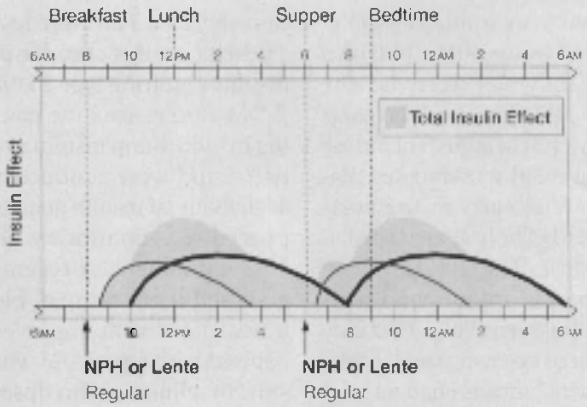


Nonphysiologic insulin replacement does not mimic normal β-cell insulin secretion. A, Once-daily, long-acting insulin glargine is released with a peakless delivery of approximately 20 to 24 hours in most patients. Glargine achieves steady state at approximately 2 hours. Dashed line indicates the effective duration of glargine continuing through the following day. B, Twice-daily, intermediate-acting neutral protamine Hagedorn (isophane insulin; NPH) and Lente (insulin zinc) are commonly used as basal insulin. Arrows indicate insulin injection.

of the morning, many patients require midmorning snacks to prevent hypoglycemia (Figure 2).

Using prandial insulin for each meal (either regular insulin, insulin lispro, or insulin aspart) with separate basal insulin (NPH, Lente, Ultralente, or insulin glargine) adds flexibility to the regimen, and glargine-lispro or glargine-aspart regimens allow patients to skip meals or change mealtimes (FIGURE 3). This approach requires more injections than with conventional twice-daily physiologic regimens, but surveys show that patients with type 1 DM are injecting insulin more frequently and they prefer the dietary freedom, with education about more complex strategies for their care, rather than simplistic rules.[1,32] In one study, 80% of patients preferred a qualitative strategy and 20% preferred a quantitative strategy to a "simple" but relatively inflexible strategy.[33] Dose adjustment is much simpler with true basal-prandial regimens (eg, glargine-lispro) than with insulins that function as both a basal and a prandial insulin (eg, NPH).

Figure 2. Example of Conventional Physiologic Insulin Regimen



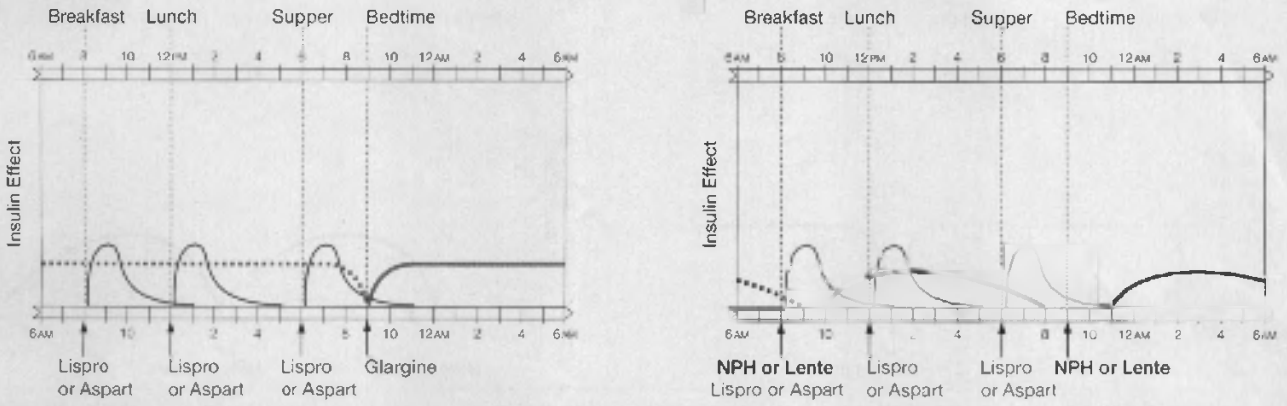
Physiologic insulin replacement with intermediate-acting neutral protamine Hagedorn (isophane insulin; NPH) or Lente (insulin zinc) and short-acting regular insulin (shown in a ratio of 70:30) attempts to mimic normal β-cell insulin secretion. Each insulin serves as both a basal and a prandial insulin. Meal timing and consistency are important for patients using this regimen. Many patients require a midmorning and bedtime snack to prevent hypoglycemia when the effect of the 2 insulins overlap at late morning and nighttime. Moving the dinnertime NPH injection to bedtime decreases the risk of nocturnal hypoglycemia. Arrows indicate insulin injection.

How Does the Patient Use Supplements and Adjustments?

Hyperglycemia correction is an important principle of insulin therapy. A supplement is a predetermined dose of rapid- or short-acting insulin used to correct hyperglycemia. Supplements are easier to determine when basal and prandial insulins are administered separately. Supplements are usually injected with the usual prandial dose of insulin. A conservative dose for patients with type 1 DM is an additional 1 U per 50 mg/dL (2.7 mmol/L) above the target blood glucose level. For patients with type 2 DM, we recommend 1 U of supplemental insulin per 30 mg/dL (1.7 mmol/L) above the target glucose level.

If patients are using insulin supplements between meals, they must beware of "insulin stacking." Injecting additional short- or rapid-acting insulin 1 hour after a dose of regular and NPH insulin would result in insulin stacking and in predictable hypoglycemia within several hours because most of the previously injected insulin has not been ab-

Figure 3. Examples of Physiologic Insulin Delivery Regimen



A, Once-daily glargine with lispro or aspart (shown in a ratio of 50:50) allows patients to skip meals or change mealtimes. Insulins lispro and aspart (rapid acting) are prandial insulins and glargine (long acting) is a basal insulin. This regimen is easier to use since it has true basal and prandial insulins. Dashed line indicates the effective duration of glargine continuing through the following day. Glargine achieves steady state at approximately 2 hours. B, Intermediate-acting neutral protamine Hagedorn (isophane insulin; NPH) and Lente (insulin zinc) are basal insulins. Rapid-acting lispro and aspart insulins are prandial insulins. This regimen (shown in a ratio of 50:50) is more difficult to adjust because NPH can act as both a basal and a prandial insulin. Dashed line indicates the effective duration of NPH or Lente continuing through the following day. Arrows indicate insulin injection.

sorbed. If patients are to inject supplements less than 3 hours after a previous insulin dose, they can decrease the supplement by 50%. Patients who exercise may be required to adjust their dose of rapid-acting insulin analogues. Patients who exercise early in the postprandial period (1-3 hours) may need to decrease their dose of rapid-acting insulin by 75%, whereas patients who exercise later in the postprandial period may require a smaller or no change in dose.[34,35]

An "adjustment" means changing the dose of any type of insulin based on a consistent pattern of blood glucose levels. For example, the adjustment for a patient receiving bedtime NPH insulin who has frequent fasting hypoglycemia would be to decrease the bedtime insulin dose. Aggressive but careful adjustments based on patients' injection timing meal patterns and activity levels are key to excellent long-term glucose control.

Why Is It Important for Patients to Self-monitor?

While there is little controversy that all patients receiving insulin should perform self-monitoring of blood glucose tests, there is disagreement about the frequency and timing of the tests. For type 1 DM, the American Diabetes Association suggests 3 or more tests per day.[29] The data are less clear for patients with insulin-requiring type 2 DM. Many type 2 DM studies exclude patients receiving insulin, lump insulin users and nonusers, and were conducted before the availability of insulin analogues and improved self-monitoring of blood glucose equipment. A recent study suggests self-monitoring of blood glucose is associated with improved control in patients with type 2 DM who use the results to adjust insulin doses.[36]

What Regimens Are Best for Patients With Type 1 DM?

Type 1, autoimmune, DM occurs in adults of all ages, including obese patients with phenotypic type 2 DM. Latent autoimmune DM (also known as LADA) of adults can be confused with type 2 DM early in diagnosis, but patients become insulinopenic relatively rapidly.[37]

Nonphysiologic Regimens. Some newly diagnosed patients with type 1 DM or latent autoimmune DM of adults who are still producing endogenous insulin may do well receiving once- or twice-daily basal insulin injections before they progress to complete β-cell failure (Figure 1). The time to complete insulin deficiency varies, but it is generally longer in adults than in children. Even with euglycemia, few physicians would recommend discontinuing insulin completely because intensive insulin therapy appears to promote β-cell preservation.[9,10,38] Data are not available to date to compare different nonphysiologic insulin regimens in this patient population.

Physiologic Regimens (TABLE 2). In patients with severe insulin deficiency, replacement of both prandial and basal insulin components is required. In patients with type 1 DM and no endogenous insulin secretion, it is very difficult to safely reach target HbA_{1c} level (<7%) with conventional insulin therapy, twice-daily NPH, and regular insulin (as shown in Figure 2). This regimen is difficult to adjust, and it is relatively inflexible because it uses both insulin components as both a prandial and a basal insulin. Moving NPH insulin from dinnertime to bedtime was first suggested in the 1980s as a strategy to optimize this conventional regimen.[39] Mixed NPH and regular insulin are given before breakfast, regular insulin is injected before dinner, and NPH is given at bedtime. A recent randomized, crossover study confirmed that this bedtime

Table 2. Available Insulin Delivery Systems and the Cost of a Physiologic Regimen With Each System

Delivery System	Advantages	Disadvantages	Cost (Comparative Examples for Initial and Monthly Cost)* Item	Amount
Syringe	Maximal ability to "freemix" insulin and adjust to patient needs	Multiple injections Need to carry bottles, syringes, and supplies Variable absorption depending on type of insulin and body injection site Lispro and glargine are both clear insulins and therefore difficult to distinguish, patients must read labels carefully	Insulin glargine 1000 U	$44
			Insulin lispro 1000 U	$46
			Syringes for 4 injections/d (120-gauge)	$36
			Total cost per month for glargine at bedtime + lispro 3 times/d	$126 Bedtime NPH + 3 times/d of prandial regular = $25 + $25 + $36 = $86
Pen	Convenient, less to carry Easy to distinguish between insulins by pen color/size Improves dosing accuracy Although not recommended, many use 1 needle per 24 h	For injection, approximately 30% more expensive per 1000 U than bottled insulin	Pen injector	Novopen 3 = $29-$32 retail
			Pen cartridges for 1000 U	NPH = $42 Glargine = $63 Lispro = $63
			Total cost per month for bedtime dose with needles	NPH/prandial lispro = $105 Glargine/lispro = $126
Pump	Fewer injections Physiologic delivery with best glycemic control and fewest hypoglycemic events overall Eliminates variable injection-site absorption	Expensive Additional training needed Patient must be aware of potential technical problems	Pump: Medtronic MiniMed	$5500/60 mo at $92 per month (assumes pump life of 5 years)
			Monthly cost of tubing/reservoirs	$150
			Insulin lispro 2000 U	$92
			Total cost per month	$334

Abbreviation: NPH, neutral protamine Hagedorn (isophane insulin).
*We estimated costs based on 0.9 U/kg for a 70-kg person at 63 U/d, 32 U of each per day, equals 1000 U/mo of each insulin type. Patients are told to discard their unused bottles at the end of the month if they use less insulin.

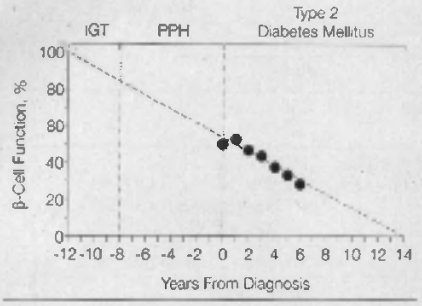
NPH strategy reduces both HbA_{1C} levels and nocturnal hypoglycemic episodes in patients with type 1 DM.[40]

Overall, patients using insulin analogues (lispro, aspart, glargine) in physiologic regimens (Figure 3A), including patients with hypoglycemia unawareness, have fewer hypoglycemic episodes than patients using traditional insulins (regular and NPH).[41-46] Because of shorter duration of action, insulin lispro (introduced in the United States in 1996) and insulin aspart are only used as prandial insulins or in CSII programs. When patients use insulins lispro or aspart, they have fewer episodes of severe hypoglycemia and nocturnal hypoglycemia than with regular insulin[47-50] (eTABLE 1[42-44,46,50-72] and eTABLE 2[12,24,27,41,53-67,72-83]; tables are published online at http://www.jama.com). Lag time depends on the onset of action of the prandial insulin used (eg, 30 minutes for regular insulin and none for insulin lispro or aspart). An inadequate lag time results in postprandial hyperglycemia and in later risk of hypoglycemia. Patient compliance with the recommended 30-minute lag time for regular insulin is 30% to 70% (patients inject insulin closer to or at mealtime.[84,85] The lack of required lag time for rapid-acting insulins and improved matching of action with carbohydrate absorption explain their clinical advantage (Figure 3).

Data on regimens using rapid-acting analogues with basal NPH are mixed (Figure 3B). Improvements in HbA_{1C} levels have not been seen when analogues are given with basal NPH provided once or twice daily, because the improvement in postprandial hyperglycemia seen with the rapid-acting analogues is negated by higher preprandial and overnight glycemia (compared with regular insulin). One study using small doses of NPH given with insulin lispro before each meal and at bedtime, to better control basal needs between meals, showed decreased HbA_{1C} levels and episodes of hypoglycemia.[62] However, in a recent study of patients with type 1 DM receiving NPH basal insulin (1-2 injections per day) with prandial lispro, adding an additional injection of NPH at lunchtime in an attempt to give smoother basal control resulted in 6.9 more episodes of severe hypoglycemia per patient-year ($P = .007$).[86] Ultralente, which is longer acting than NPH or Lente, was developed to improve basal insulin delivery. However, twice-daily Ultralente, as compared with Lente, mildly improves fasting glucose levels but increases episodes of hypoglycemia.[87]

Insulin glargine became available in the United States in 2001. Theoretically, this peakless, long-acting basal insulin analogue should reduce hypoglycemia and improve glycemic control.[88] In actuality, reductions in episodes of hypoglycemia, especially nocturnal hypoglycemia, occur consistently whereas reductions in HbA_{1C} levels have been more difficult to achieve (eTables 1 and 2; tables are published online at http://www.jama.com). A large multicenter trial of patients with type 1 DM using insulin glargine with prandial regular insulin showed no change in HbA_{1C} levels, although 25% fewer hypoglycemic episodes were noted.[42] When insulin lispro was used as the prandial insulin, no differences in HbA_{1C} levels or hypoglycemic epsisodes were observed, but patients receiving glargine gained slightly less weight.[63] When glargine and lispro were compared with NPH and regular insulin in adoles-

Figure 4. Progressive Decline in β-Cell Function and Insulin Secretion in Type 2 Diabetes Mellitus



Data show 50% of normal β-cell function at diagnosis of type 2 diabetes mellitus (year 0) and a steady decline up to 6 years following diagnosis. Clinically, most patients have had prediabetes (impaired glucose tolerance [IGT] and postprandial hyperglycemia [PPH]) for some time before clinical diagnosis of type 2 diabetes mellitus. Dotted line shows the extrapolation of β-cell function before and after diagnosis of diabetes. Adapted with permission from *Diabetes Reviews*[133] based on data from the United Kingdom Prospective Diabetes Study.[92]

cents, results of HbA_{1C} levels were similar, but the glargine-lispro regimen produced fewer hypoglycemic episodes.[61] However, in a population with a lower baseline HbA_{1C} level (7.1%), substituting insulin glargine for NPH, with prandial insulin lispro, decreased hypoglycemic episodes and HbA_{1C} levels.[89]

It may he that the main impact of physiologic insulin regimens and insulin glargine in particular is that the separation of prandial and basal components improves our understanding of insulin use, simplifies dosing adjustments, and allows patients more flexibility in meal timing. With a distinctly different basal insulin component (glargine or pump therapy), patients need approximately half of their insulin as basal insulin. When initiating a basal-prandial regimen, patients should decrease the calculated 50% basal insulin dose by 20% to avoid hypoglycemia. Using this calculation, one third of patients are receiving the correct dose, one third need more, and one third need less basal insulin.[90]

When Should Insulin Be Used in Type 2 DM?

Most patients with type 2 DM will eventually need insulin. Insulin therapy was started in patients with type 2 DM with a mean HbA_{1C} level of 10.4% in the United States,[91] and the UKPDS[92] showed that β-cell failure is progressive; 50% of normal β-cell function at diagnosis with a steady decline following diagnosis (FIGURE 4). Concomitantly, 53% of patients with type 2 DM initially treated with SUs required insulin therapy by 6 years, and almost 80% required insulin by 9 years.[93,94] Although we may he diagnosing DM earlier and thus altering this time frame, physicians should consider starting insulin therapy in patients whose HbA_{1C} level approaches 8% despite optimal oral therapy.

Improved glycemic control delays or prevents complications in patients with type 2 DM,[8,95,96] although patients often need an insulin dosage of greater than 100 U/d to achieve glycemic control.[94] Patients with type 2 DM often resist physician recommendations to start insulin therapy, partly because of misperceptions that starting insulin means the patient and physician have failed. Several unmasked studies suggest that switching from oral agents to the use of insulin in patients with type 2 DM improves treatment satisfaction, general well being, and quality of life, especially if patients previously had poor glycemic control.[22,75,79,97] When choosing an insulin regimen, the benefits of intensive therapy must be tempered by cost and ease of regimen. In general, treatment satisfaction is better with simpler regimens. Patients allocated to strict control (fasting plasma glucose level <117 mg/dL [6.5 mmol/L]) or less strict control (fasting plasma glucose level <153 mg/dL [8.5 mmol/L]) for 1 year reported improved mood and general well being if their HbA_{1C} level decreased 1% or more, but strict targets increased perceived treatment burden.[98] It has been shown that patients prefer insulin glargine to NPH,[66] twice-daily NPH to Ultralente, and insulin pen administration or premixed insulin to free-mixed insulin administered with syringes.[99-103]

What Is the Best Regimen for Patients With Type 2 DM?

Combination Oral Agent/Insulin Therapy. When using bedtime basal insulin (NPH or glargine), continuing 1 or 2 daytime oral medications is reasonable (eTABLE 3[6,8,15,94,97,104-132,134-146]; table is published online at http://www.jama.com). Metformin with insulin results in similar metabolic control, less weight gain, lower insulin doses, and fewer hypoglycemic episodes than insulin alone or insulin/SU therapy.* Thus, metformin and insulin may be the best combination for the majority of patients with type 2 DM who do not have contraindications. However, it should be emphasized that the goal is the target HbA_{1C} level, not lower insulin dose. Patients who must discontinue metformin because of increasing plasma creatinine levels should have their insulin dose increased 20% to 36% to maintain glycemic control.[147]

Combining SUs with insulin lowers insulin doses (25%-50%) with less weight gain, but increases cost.† Sulfonylureas increase endogenous insulin secretion (C-peptide) early in the disease process. Improvement of HbA_{1C} with SU use in the UKPDS was in patients whose HbA_{1C} levels were well below 10%.[93] As insulin production declines and HbA_{1C} levels approach 10%, the combination of insulin and SUs eventually becomes ineffective.[149]

Insulin secretagogues include the SUs and the glinides. Glinides are functionally short-acting SUs and may improve prandial control with or without basal insulin. Not enough data are available to date to endorse their use,[150] especially given their cost, although they may be beneficial in patients with hypoglycemia or who skip meals.

Although thiazolidinediones (TZDs) are effective insulin sensitizers, combined TZD/insulin therapy has been problematic, and TZDs are expensive. Troglitazone was taken off the market due to liver failure, but one randomized trial comparing intensive insulin monotherapy vs insulin with either metformin or troglitazone showed that all therapies lowered HbA_{1C} levels effectively.[151] Patients gained about 4.4 kg while receiv-

*References 97, 113, 114, 119, 120, 140, 144.
†References 105, 110, 119, 123-125, 127, 148.

g insulin or insulin/troglitazone, but only 0.5 kg while receiving insulin/metformin. Troglitazone significantly reduced the dose of insulin but caused the same rate of hypoglycemic episodes as insulin (2 per month), while patients receiving insulin/metformin reported no hypoglycemia. Pioglitazone and rosiglitazone should not be used with patients in New York Heart Association (NYHA) class III or IV heart failure, and patients' liver function must be monitored. Significant weight gain, pulmonary edema, and heart failure are increasingly associated with TZDs.[152] Given these issues, combination TZD/insulin therapy should be used with caution.

Insulin Therapy. The goals of insulin therapy in both type 1 and type 2 DM are to reach the target HbA_{1C} level with a low rate of hypoglycemic episodes and the least amount of weight gain (eTable 2; table is published online at http://www.jama.com). However, goals must be individualized since older patients with type 2 DM and with no complications may not benefit from intensive therapy. When starting insulin therapy in patients continuing daytime insulin secretagogues or metformin, with an HbA_{1C} level less than 9.5% to 10%, bedtime basal insulin therapy is effective, convenient, and produces less weight gain.[22,23,73] Compared with NPH, basal insulin glargine is associated with 25% fewer nocturnal hypoglycemic episodes, better postdinner control, and slightly less weight gain at twice the cost.[24,41] Both NPH and glargine are easily adjusted based on fasting blood glucose levels. Once-daily Ultralente insulin produces more hypoglycemic episodes than twice-daily NPH despite a higher HbA_{1C} level.[75] If nocturnal hypoglycemia is an issue and glargine is not an option, prandial lispro with SU lowers HbA_{1C} levels with fewer hypoglycemic episodes than NPH with SU.[146]

With progressive β-cell exhaustion, patients will be more successful in achieving glycemic control with progressively more physiologic regimens. Premixed insulins, given twice daily, (70% NPH/30% regular [70N/30R], 70% NP [neutral protamine]/30% aspart [A] [BIAsp], and 75% NPL/25% lispro [L]) are convenient but no prandial insulin is given for lunchtime. BIAsp improves postbreakfast/dinner blood glucose levels, but not HbA_{1C} levels, and decreases severe hypoglycemic episodes by 50% when compared with 70N/30R. Patients who are uncontrolled (ie, not achieving glycemic control) receiving premixed insulin regimens can often achieve control at the same insulin dose by adding lunchtime prandial insulin and by decreasing the morning insulin accordingly. Prandial insulin lispro is associated with fewer episodes of nocturnal hypoglycemia than regular insulin.[82] Another trial of lispro vs regular, with twice-daily basal Lente or Ultralente, showed a lower HbA_{1C} level with lispro at similar insulin doses.[67] Prandial therapy with lispro vs bedtime therapy with NPH lowers HbA_{1C} levels without additional hyperglycemia.[81] Importantly, patients with type 2 DM may require large insulin doses (>1 U/kg) to reach an HbA_{1C} level less than 7%.[6,153,154]

What Are the Advantages of Insulin Pump Therapy?

Patients with type 1 DM receiving CSII therapy show more improvement in HbA_{1C} levels than patients receiving intensive multiple injection therapy[155]; but it remains to be seen whether CSII will reduce the risk of microvascular complications. Compared with multiple injection therapy, CSII reduces hypoglycemic events up to 74%.[155] Intensive insulin therapy reduces costs by decreasing complications; and a study of CSII vs multiple injection therapy in peripartum patients with type 1 DM shows equal costs, but patients preferred pump therapy.[156]

An external pump is programmed to deliver individualized basal rates of short- or rapid-acting insulin (usually 0.5-1.5 U/h). Since patients receiving CSII need less insulin, it has been recommended to decrease the total daily dose by 20% to 30% and then use 50% of that reduced dose as basal insulin.[2] Prandial (bolus) insulin is given by manual activation. Rapid-acting insulins have been shown to be superior to regular insulin in a CSII program because of improved prandial control.[52,70]

The main indications for pump use in patients with type 2 DM without significant C-peptide secretion are severe hypoglycemia and wide fluctuations of glucose levels.[27,80] However, physiologic regimens with insulin glargine and lispro or aspart probably offer the same benefits at lower cost, albeit with more injections.

What Other Approaches Improve Outcomes or Reduce Costs?

While the practice of diabetes care is now increasingly precise, the complexities of care and compliance issues are overwhelming for many physicians. Improving systems of diabetes care may improve glycemic control compared with standard care as shown by (1) frequent insulin dose adjustment by nurse educators via telephone lowered the HbA_{1C} level from 9.4% to 7.8% (0.3% more than standard care)[157]; (2) "telecare" (transmitted data and telephone advice) improved HbA_{1C} levels 1% (vs 1.2%) and saved patients considerable travel time[158]; and (3) using computer decision models for adjustments of insulin doses lowered HbA_{1C} levels approximately 12% and decreased the rate of hypoglycemic episodes by 50% per week.[159,160]

COMMENT

An HbA_{1C} level less than 7% consistently reduces microvascular complications and is now the goal for most patients. Limited data suggest that reducing complications also reduces costs. A team approach with diabetes educators may be more effective at reducing complications at a similar cost. The lack of resources for efficient team care is a major barrier to diabetes care, especially in the primary care community.

Patients with type 1 DM almost always require multiple injections to attain an HbA_{1C} level less than 7%. Physiologic basal-prandial regimens are easier to use and adjust and cause fewer episodes of hypoglycemia. They also provide patients with more flexibility, and