Insulin Restriction May Cut Life Span

BY BRUCE K. DIXON
Chicago Bureau

Women with type 1 diabetes who take less insulin than prescribed may be raising their risk of complications and shortening their life spans.

Because of various psychosocial variables, more than half of adult patients do not achieve the American Diabetes Association's glycemic targets, said Ann E. Goebel-Fabbri, Ph.D., of the Joslin Diabetes Center and Harvard Medical School, both in Boston, and her associates. Chief among the implicated variables are general psychological distress, diabetes-specific distress, fear of hypoglycemia, concern about weight gain, and related eating-disorder behaviors.

In this 11-year study, the largest to examine the long-term effect of insulin restriction on the morbidity and mortality of women with type 1 diabetes, insulin restriction at baseline conveyed more than a threefold increase in the relative risk of death, said the authors (Diabetes Care 2008;31:1-5).

At baseline, the cohort included 234 women aged 13-60 years who had had a diagnosis of type 1 diabetes for at least 1 year and who agreed to be followed up. Of those, 26 died during the study period. Mean age at follow-up was 45 years (range, 24-72 years).

Women reporting insulin restriction showed distinct clinical differences from those reporting appropriate insulin use.

At baseline, insulin restricters were significantly younger (aged 32 vs. 36 years) and had higher hemoglobin A_{1c} values (9.6% vs. 8.3%). However, there were no differences between the two groups with regard to baseline body mass index (BMI) or diabetes duration, the authors said.

Predictably, insulin restricters reported significantly lower scores on the baseline measure of diabetes self-care behaviors, and they scored higher on baseline measures of diabetes distress; fear of hypoglycemia; general psychological symptoms; eating disorder symptoms, such as bulimia; and the Eating Disorders Inventory.

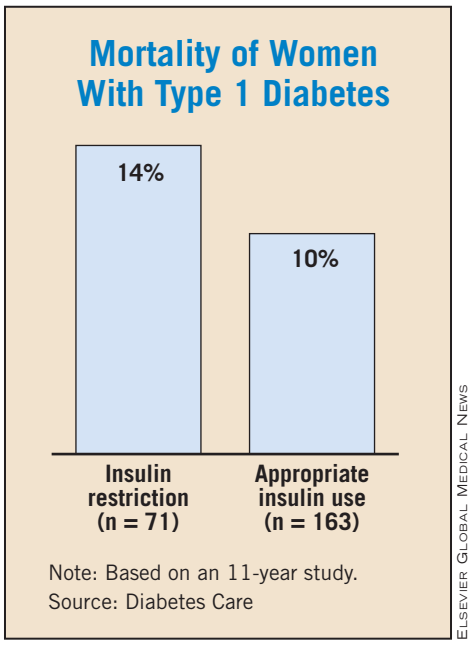
In addition, women who said at baseline that they restricted insulin were significantly more likely to report nephropathy and foot problems at follow-up, the researchers said, adding that self-reported rates of retinopathy, neuropathy, and cardiovascular complications at follow-up did not differ between groups.

Causes of death for 10 of 71 women reporting insulin restriction included perforated bowel with gastroparesis (1), cancer (1), cardiac events (3), hypoglycemia (1), renal failure (2), sepsis (1), and suicide in the context of retinopathy-related blindness (1).

Causes of death for 16 of 163 women reporting appropriate insulin use included cancer (1), cardiac events (11), diabetic ketoacidosis (1), sepsis (2), and unknown causes (1), Dr. Goebel-Fabbri noted in an interview.

Comparisons of both groups of deceased women found that those who had restricted insulin died at a significantly younger age, and had higher baseline hemoglobin A_{1c} values, poorer diabetes self-care behaviors, increased levels of diabetes-specific distress, and higher scores on measures of bulimia and other eating disorder symptoms.

Compared with their living counterparts, deceased insulin restricters at baseline had higher BMI and hemoglobin A_{1c} values and reported more symptoms of bulimia and higher levels of diabetes-specific distress.



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"These data suggest that mortality associated with insulin restriction occurred in the context of eating disorder symptoms, rather than other psychological distress," the authors said. They added that these patients require careful monitoring and would benefit from in-depth evaluations by a mental health professional, ideally one with specialized training in diabetes.

The researchers suggested physicians screen type 1 diabetes patients by routinely asking them if they follow their insulin prescriptions. "The health and wellness of women with type 1 diabetes is likely to be promoted by greater attention to the problem of insulin restriction in future research and clinical practice," they concluded. ■

For Large Doses of Insulin, Look to U-500

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — For patients who need large doses of insulin (more than 200 U/day), U-500 insulin is the best choice because of more predictable pharmacokinetics and lower cost per unit.

"[With] a huge volume of insulin—60 or 80 U—you're going to have more variability in the absorption" with conventional insulins such as U-100, lispro, or glargine, Dr. Irl B. Hirsch told a meeting sponsored by the American Diabetes Association.

Although U-500 insulin is called "regular" insulin, "it ain't like regular insulin" because it's five times more concentrated and has longer pharmacokinetics, said Dr. Hirsch, professor of medicine at the University of Washington, Seattle. This has caused confusion in some hospitals regarding dosing.

For clarity, some physicians refer to milliliter or cubic centimeter measurements when referring to U-500 insulin, but "there's no formal consensus on this," he said.

Twenty U of U-500 insulin in a U-100 syringe is 0.2 mL—the same dose as 100 U of U-100 insulin in a volume of 1 mL. U-500 insulin is available only from Eli Lilly & Co., for which Dr. Hirsch is a consultant.

The duration of action of U-500 insulin is up to 24 hours. Large doses of insulin can be given with one-fifth the volume using U-500 insulin, so there's less day-to-day variation in absorption and less variability of absorption in different body regions.

U-500 insulin can be helpful especially in those needing large depots of insulin but who have little subcutaneous tissue. A smaller volume of insulin is less painful for these patients.

The pharmacokinetic and pharmacodynamic characteristics of huge doses of either conventional or NPH insulin per injection have not been well studied since not many patients need such high doses, Dr. Hirsch noted.

With U-500 insulin, "Don't think about this as giving prandial insulin. The basal/prandial distinction we make with insulin components for a typical basal bolus sort of goes away when we're talking about U-500 insulin, since it is really both."

The National Institutes of Health published an algorithm suggesting that insulin-resistant patients who need less than 200 U/day use U-100 insulin, and that U-500 insulin be considered for severely insulin-resistant patients who need more (Diabetes Care 2005;28:1240-4).

A twice-a-day regimen of U-500 insulin would be used for patients who need 200-300 U/day, and a three-times-a-day regimen would apply to patients who need 300-750 U/day. For 750-2,000 U/day, patients would use U-500 insulin t.i.d. plus a fourth dose at bedtime. Above 2,000 U/day, an insulin pump is best, Dr. Hirsch said.

Although a 20-mL vial of U-500 insulin costs about $260, compared with $43-$89 for a 10-mL vial of U-100 insulin, lispro, or aspart, the cost per unit is cheapest with U-500—3 cents a unit rather than 4 to 9 cents "This is the economical way," he said. ■

Guide for Dosing U-500 Insulin

If the patient needs	Use
Less than 200 U/day	U-100 insulin
200-300 U/day	b.i.d. regimen of U-500 insulin
300-750 U/day	t.i.d. regimen of U-500 insulin
750-2,000 U/day	t.i.d. regimen of U-500 insulin plus a fourth dose at bedtime
More than 2,000 U/day	insulin pump

Source: National Institutes of Health

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Mull the Risks And Benefits in Older Diabetics

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — The heterogeneous nature of diabetes in the elderly makes it imperative to assess each patient individually before deciding whether to use aggressive or more conservative therapy, Dr. Hermes Florez said.

Some older diabetes patients have newly diagnosed disease and are quite functional, whereas others have long-standing disease and significant functional decline. Older adults are more likely to have multiple comorbidities and to be taking multiple medications.

It is also important to consider life expectancy, noted Dr. Florez, an endocrinologist at the University of Miami and the Miami Veterans Affairs Medical Center, at a meeting sponsored by the American Diabetes Association.

To help chart an individual's management plan, one should balance the potential benefits of aggressive glycemic control against the risks from comorbidities, medication side effects, and geriatric syndromes such as dementia, incontinence, and depression, advised Dr. Florez. He described the following sample cases to highlight treatment choices:

► **Low risk, high benefit.** Aggressive treatment was an easy decision for a 70-year-old woman with a 20-year history of diabetes who also had hypertension, lipid abnormalities, and early appearance of retinopathy but who functioned well independently and had no other comorbidities.

► **High risk, low benefit.** The opposite was true for a 68-year-old man with a 4-year history of diabetes who also had severe cardiomyopathy with ventricular tachycardia and couldn't walk. He already was taking 14 medications. Intensifying treatment for better blood pressure, lipid levels, or blood-sugar control could pose greater risks than benefits.

► **Low risk, low benefit.** Less easy to manage was a 75-year-old woman with new-onset diabetes, none of the associated cardiovascular risk factors, no other comorbidities, and no functional impairment. She's at low risk, but evidence is lacking that she would benefit from intensive therapy to lower her HbA_{1c} level below 6.5.

► **High risk, low benefit.** A 72-year-old man with long-standing diabetes of 18 years' duration, a history of multiple hypoglycemic episodes, and complications related to diabetes. Intensive therapy for blood glucose levels, lipids, and blood pressure probably would seem indicated, but he also had major cognitive deficits. Unless a relative or caregiver can monitor therapy, intensive treatment poses too much risk for side effects, falls, or further cognitive decline. Treatreat should be conservative.

Dr. Florez has received research funding from Merck & Co., a maker of diabetes medications. ■