References
1. Kaplan RM, Hartwell SL, Wilson DK, Wallace JP: Effects of diet and exercise interventions on control and quality of life in non-insulin-dependent diabetes mellitus. *J Gen Int Med* 2:220–227, 1987
2. Glasgow RE, Ruggiero L, Eakin EG, Dryfoos J, Chobanian L: Quality of life and associated characteristics in a large national sample of adults with diabetes. *Diabetes Care* 20:562–567, 1997
3. Ligtenberg PC, Hoekstra JBL, Zonderland ML, Bol E, Erkelens DW: Effects of physical training on metabolic control in elderly type 2 diabetes mellitus patients. *Clin Sci* 93:127–135, 1997
4. Bradley C, Lewis KS: Measures of psychological well-being and treatment satisfaction developed from the response of people with tablet-treated diabetes. *Diabet Med* 7:445–451, 1990
5. Baron RM, Kenny DA: The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psych* 51:1173–1182, 1986
6. Blumenthal JA, Emery CF, Walsh MA, Cox DR, Kuhn CM, Williams RB, Williams RS: Exercise training in healthy type A middle-aged men: effects on behavioral and cardiovascular responses. *Psychosom Med* 50:418–433, 1988
7. Long BC: A cognitive perspective on the stress-reducing effects of physical exercise. In *Exercise Psychology: The Influence of Physical Exercise on Psychological Processes*. Seraganian P, Ed. New York, Wiley, 1993

Fatal Asymptomatic Hypoglycemia in an Elderly Insulin-Dependent Diabetic Patient Taking an Oral Beta-Blocking Medication

The largest study of the risk of serious insulin- or oral hypoglycemic–related hypoglycemia involving all classes of antihypertensives recently reported that the lowest rate of hypoglycemia over a 4-year study period in 13,559 elderly Medicaid recipients was with beta blockers. The highest rate of serious hypoglycemia was found to be with ACE inhibitors used with antidiabetic agents (1). A 1966–1998 Medline search using the terms beta blockers, insulin, and hypoglycemia produced one case report of topical timolol-associated hypoglycemic attacks in a 65-year-old insulin-dependent diabetic patient (2).

J.P. was a 68-year-old, 5-foot 4-inch, 192-lb, African-American, insulin-dependent diabetic patient who also had high blood pressure, presumed type 1 diabetes, and angina pectoris. Her diet order was 1,600 kcal (American Diabetes Association [ADA]), but her family insisted on bringing in extra food despite numerous warnings about this practice. She had gained 26 lb in the 6 months since her admission to the nursing facility. Her medications were as follows: NPH insulin 42 U subcutaneously every morning at 7:00 A.M., sublingual nitroglycerin 0.4 mg as needed (not used), and propranolol 20 mg q.i.d.. Her fasting blood sugar (FBS) had ranged between 5.7 and 6.8 mmol/l (102–122 mg/dl) weekly for the past month. Her insulin dose had been increased from 20 U on admission to 42 U over the 6-month period in response to monthly FBS readings >8.9 mmol/l (160 mg/dl). When the family went on vacation and the extra food supply was unavailable, on the 3rd day of reduced caloric intake, the patient did not care for the food of the day and was found at 4:00 P.M. semicomatose, with blood pressure (BP) = 158/88, P = 76, R = 26. Her prior weekly vital signs had ranged from BPs of 110–126/60–72 mmHg, pulses of 56–64 beats/min, and respiration rates of 12–20 breaths/min. She died by 5:00 P.M., with a fingerstick blood sugar of <1.4 mmol/l (25 mg/dl). The patient's nursing aides and roommate denied that she had any of the classic symptoms of hypoglycemia (tachycardia, sweating, excitation, nervousness, or tremors) over the prior week or on the day of her death. The nurses' daily notes for the week before death had no mention of any of these symptoms.

A 1980 study of the safety of beta-blocker usage in insulin-treated diabetic patients found, using the surrogate hypoglycemic measure of unconsciousness, that 50 insulin-treated diabetic patients using beta blockers had the same frequency of episodes (5 vs. 10) as 100 insulin-using diabetic patients matched for age, sex, and duration of diabetes who did not use beta blockers over an 8-month period (3). The latest study previously mentioned found that cardioselective beta blockers had the lowest frequency of serious hypoglycemia (<2.8 mmol/l [50 mg/dl]) in older individuals using insulin or sulfonylureas when compared with the nonselective beta blockers, thiazide diuretics, calcium channel blockers, or ACE inhibitors (1). Intensive treatment of type 1 and type 2 diabetes appears to lower the rates of renal impairment, cardiac and overall morbidity, and mortality (4–6). Insulin usage per se does, however, produce higher rates of hypoglycemia and weight gain when compared with oral hypoglycemic agents in an outpatient setting over 6 years (6) and in the nursing home over a 3-year period (7). Intensive insulin therapy for type 1 diabetes also has been found both to increase blood pressure and to adversely affect lipid profiles proportional to weight gain (8).

This patient appeared to have multiple factors that led to her weight gain: insulin use and excessive outside dietary intake. Her complete diabetes history was not obtainable. The family did state that she had tried the "sugar pill," but that she would not take the pill nor adhere to her diet. Her attending physician on admission to the nursing facility was from a different provider than her community-based physician. The nursing facility physician's therapeutic goal was tight control of blood sugar, which he defined as <6.9 mmol/l (125 mg/dl). Beta-blocker therapy for both high blood pressure and angina pectoris was preferred, because of her history of angina pectoris, for presumed secondary prevention of myocardial infarction, since the patient had complained of several episodes of severe chest pain. No electrocardiographic readings were available on this patient.

The extent to which the nonselective beta blocker propranolol masked the hypoglycemic symptoms that may have been more likely with her tight blood sugar control (i.e., <6.9 mmol/l [125 mg/dl]) is suggested by the negative findings on questioning of health care personnel involved in the care of the patient as well as by the clinical record. The patient and her roommate were both well oriented to time, place, and person and did not have clinical evidence of dementia. The roommate was very concerned with the patient's overall care and was known to have summoned help for her roommate if she suspected any problem. The patient was not known to take naps during the daytime hours. It was this roommate who noticed the patient's unusual drowsiness and sedation and reported this to the charge nurse at 4:00 P.M. on the day of death.

The ADA has recently revised its guidelines to include the category of "impaired glucose tolerance" (FPG 6.1–6.9 mmol/l [110–125 mg/dl]) and has lowered the threshold for clinical diabetes from 7.8 to 6.9 mmol/l (140 to 126 mg/dl) (9). The implications of these new guidelines, as well as recent findings on tight control of diabetes (4–6) and the recommendations that beta-blockers be used in diabetic patients at risk of myocardial infarction for secondary prevention (10), raise the concern that there may be more cases like the one reported.

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References

1. Shorr RI, Ray WA, Daugherty JR, Grifffin MR: Antihypertensives and the risk of serious hypoglycemia in older persons using insulin or sulfonylureas. *JAMA* 278:40–43, 1997
2. Silverstone BZ, Marcus T: Hypoglycemia due to opthalmic timolol in a diabetic. *Harefuah* 118:693–694, 1990
3. Barnett AH, Leslie D, Watkins PJ: Can insulin-treated diabetics be given beta-adrenergic blocking drugs? *Br Med J* 280:976–978, 1980
4. Andersson DK, Svardsudd K: Long-term glycemic control relates to mortality in type II diabetes. *Diabetes Care* 18:1534–1543, 1995
5. Hellman R, Regan J, Rosen H: Effect of intensive treatment of diabetes on the risk of death or renal failure in NIDDM and IDDM. *Diabetes Care* 20:258–264, 1997
6. United Kingdom Prospective Diabetes Study Group: United Kingdom prospective diabetes study 24: a 6-year, randomized, controlled trial comparing sulfonylurea, insulin and metformin therapy in patients with newly diagnosed type 2 diabetes that could not be controlled with diet therapy. *Ann Intern Med* 128:165–175, 1998
7. Cooper JW, Gordon JE, Parish RC: Diabetes mellitus prevalence and treatment outcomes in a geriatric nursing home population. *J Geriatr Drug Ther* 5:73–82, 1990
8. Purnell JQ, Hokanson JE, Marcovina SM, Steffes MN, Cleary PA, Brunzell JD: Effect of excessive weight gain with intensive therapy of type 1 diabetes on lipid levels and blood pressure. *JAMA* 280:140–146, 1998
9. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
10. MacDonald TM, Butler R, Newton RW, Morris AD: Which drugs benefit diabetic patients for secondary prevention of myocardial infarction? DART/MEMO Collaboration. *Diabet Med* 15:282–289, 1998

Glycosylated Hemoglobin Levels and New Diagnostic Criteria

The recent American Diabetes Association (ADA) expert committee report (1) has revised the diagnostic criteria for diabetes by lowering the fasting plasma glucose (FPG) level from 140 mg/dl (7.77 mmol/l) to 126 mg/dl (7.0 mmol/l). The ADA report has also introduced a new statistical risk group called "impaired fasting glucose" (IFG), which is based on an FPG value of 110–125 mg/dl. There are no data on HbA_{1c} levels in relation to the new diagnostic criteria.

The present study is based on an analysis of 2,635 oral glucose tolerance tests (OGTTs) and HbA_{1c} measurements done during a 3-year period from 1 April 1994 to 31 March 1997. All OGTTs were done using a 75-g oral glucose load, with World Health Organization study group recommendations (2). Pregnant women were not included in the analysis. Fasting and half-hourly venous plasma (EDTA) samples up to 2 h were used for glucose estimations, which were done within 15 min of sample collection by the glucose oxidase method, using kits provided by Boehringer Mannheim (Mannheim, Germany) on a Ciba Corning Express Plus Auto Analyzer (Medfield, MA). Quality control was done on a daily basis, and the coefficient of variation for glucose was <3.0%. HbA_{1c} was measured using a dedicated high-performance liquid chromatography system (Variant; BioRad, Hercules, CA). Our center is certified by the unity quality control program of BioRad for precision in HbA_{1c} estimation.

The new categories of glucose intolerance were based on the FPG of the individuals (1). Impaired glucose tolerance (IGT) was diagnosed based on the 2-h plasma glucose (2). Nondiabetic healthy control subjects were selected from an ongoing epidemiology study.

Table 1 presents the HbA_{1c} levels for the different categories of glucose intolerance. HbA_{1c} levels of the IFG and IGT patients were significantly different from those of control subjects and type 2 diabetic patients. The HbA_{1c} levels and the 2-h plasma glucose levels of the subjects with IFG were significantly higher than those of the subjects with IGT ($P < 0.001$).

To our knowledge, there are no data available on the HbA_{1c} levels in different categories of glucose intolerance. We report that the levels of HbA_{1c} are higher in the statistical risk classes of diabetes, namely IGT and IFG, compared with those in healthy control subjects. This suggests that even at this stage of prediabetes, hemoglobin undergoes glycosylation, though it is below the value seen in subjects with type 2 diabetes (3). Our data also suggest that in those patients with IFG, the HbA_{1c} levels and 2-h plasma glucose values are higher than in those with IGT. These data could have significance for future epidemiological studies on diabetes.

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Table 1—*HbA_{1c} levels in patients from different categories of glucose intolerance*

	Control subjects	IFG patients	IGT patients	Type 2 diabetic patients
n	303	419	509	1,053
FPG (mg/dl)*	70 ± 12	117 ± 5	105 ± 14	142 ± 27
HbA_{1c} (%)*	5.3 ± 0.49	6.8 ± 0.9	6.3 ± 0.8	7.8 ± 1.4
2-h plasma glucose (mg/dl)*	94 ± 42	199 ± 58	168 ± 17	277 ± 59

*Groups are significantly different from each other ($P < 0.001$).