Long-Term Normoglycemic Remission in Black Newly Diagnosed NIDDM Subjects

Mary Ann Banerji, Rochelle L. Chaiken, and Harold E. Lebovitz

We have defined and characterized the natural history of spontaneous near-normoglycemic remission off of antidiabetic medication in 79 black NIDDM subjects. They had initially presented with plasma glucose levels of 37.8 ± 19.3 mmol/l. Baseline clinical metabolic and 8-year prospective data were obtained (51 men and 28 women, mean age 45 ± 10 years, islet-cell or GAD antibody negative). After hospitalization and intensive outpatient treatment, near-normoglycemic remission (fasting plasma glucose 6.1 ± 0.83 mmol/l and HbA_{1c} 0.95 ± 0.10 of upper limit of normal) occurred within 8 ± 10 months of insulin or sulfonylurea therapy. This was unrelated to the resolution of stress or significant weight loss (1.9 ± 4.97 kg). Metabolic studies performed during remission showed 17% normal, 33% impaired, and 50% diabetic glucose tolerance. Glucose disposal (1 mU · kg^{-1} · min^{-1} euglycemic insulin clamp with D-[3-^{3}H]glucose) was higher in the normal glucose tolerance group compared with the impaired and diabetic groups (37.8 ± 10.2 vs. 26.1 ± 10.7 and 26.7 ± 12.0 μmol · kg^{-1} · min^{-1}; $P < 0.05$) despite similar BMIs in all three groups (28.8 ± 3.7 kg/m^2). Insulin secretion was below the normal range. Of 79 patients, 27 relapsed. A Kaplan-Meier survival analysis gives a median time of 40 months to relapse. Higher presenting plasma glucose and male sex predicted earlier relapse. Near-normoglycemic remission may occur in up to 30% of black new-onset NIDDM patients. It appears to be associated with intensive initial glycemic regulation and may be a method of decreasing the development of microvascular complications in NIDDM. *Diabetes* 45:337–341, 1996

Long-term complications of diabetes are correlated with the magnitude of chronic hyperglycemia as estimated by mean HbA_{1c} levels and duration of hyperglycemia (1–3). This leads to two potential strategies for decreasing or eliminating microvascular, neuropathic, and macrovascular complications: tight glycemic control and a decrease in the number of years during which hyperglycemia is present. Considerable data are available for IDDM patients both to determine the effects of various levels of glycemic control on complications and to extrapolate the benefits of delaying the development of hyperglycemia. While fewer data are available, they suggest similar effects in NIDDM (1,4).

Several years ago, we reported spontaneous near-normoglycemic remissions in a small cohort of black NIDDM patients who initially presented with acute severe hyperglycemia (5). Recently, we have demonstrated that remissions can be significantly prolonged with low-dose sulfonylurea therapy (6). Thus, one strategy for decreasing complications in NIDDM could be to maximize the induction and prolong the duration of near-normoglycemic remission.

Implementing this strategy requires identifying the factors involved in the induction and maintenance of near-normoglycemic remission. This report describes our studies in 79 patients, 71 of whom have been followed prospectively from the onset of their original hyperglycemia and the inception of their near-normoglycemic remission.

RESEARCH DESIGN AND METHODS

Population. A total of 79 black NIDDM subjects with near-normoglycemic remission from the diabetes service at Kings County Hospital and State University of New York Health Science Center at Brooklyn were studied. The selection criteria were as follows: *1*) presentation with plasma glucose ≥16.7 mmol/l with symptoms of hyperglycemia usually requiring hospitalization, *2*) a defined outpatient treatment period, and *3*) a 2-month period of normoglycemia off of antidiabetic medication before any study. Near-normoglycemia was defined as fasting plasma glucose (FPG) ≤6.4 mmol/l and/or HbA_{1c} within the normal range. Patients have been followed at 1- to 6-month intervals or until relapse. Relapse is defined as a single FPG level of >7.8 mmol/l with symptoms of hyperglycemia or three consecutive weekly FPG values of >7.8 mmol/l.

Of the subjects, 63 could be included in an analysis of the natural history and predictors of near-normoglycemic remission (subjects who developed near-normoglycemic remission after 1985). The patients were followed for nearly 8 years. This excluded eight subjects who were in remission for varying periods of time before baseline study and eight subjects who received low-dose sulfonylurea treatment in a preliminary intervention trial.

During the initial outpatient treatment, the goal was to achieve excellent glycemic control through diet and diabetes education, self monitoring of blood glucose, and medication. During near-normoglycemic remission, patients were able to occasionally indulge in barbecued food, ice cream, or cake without relapsing.

Procedures

Glucose tolerance and insulin secretion. A standard oral glucose tolerance test (OGTT) was performed after an overnight fast, using 75 g of oral glucose. Plasma was obtained at 0, 30, 60, 90, and 120 min for glucose and insulin measurements, and the results were interpreted using the World Health Organization criteria (7). Glucose and insulin areas were calculated using trapezoidal estimation.

Insulin-mediated glucose disposal. Insulin-mediated glucose disposal was measured using the euglycemic hyperinsulinemic clamp with 1 mU · kg^{-1} · min^{-1} insulin and D-[3-^{3}H]glucose infusion (8–10), as previously described (11,12). Insulin resistance was defined as glucose disposal ≤27.8 μmol · kg^{-1} · min^{-1} (12).

Subjects had constant body weights for at least 2 months before the study and had consumed at least 150 g of carbohydrate for 3 days before any study. No patient had significant renal, hepatic, or cardiac disease,

From the Department of Medicine, State University of New York Health Science Center at Brooklyn, Brooklyn, New York.

Address correspondence and reprint requests to Dr. Mary Ann Banerji, SUNY Health Science Center at Brooklyn, 450 Clarkson Ave., Box 1205, Brooklyn, NY 11203.

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FPG, fasting plasma glucose; HPLC, high-performance liquid chromatography; OGTT, oral glucose tolerance test.

TABLE 1
Clinical features of patients in remission

n	79
Sex (M/F)	51/28
Age (years)	45.4 ± 10.4
Family history of diabetes	62 (78.5%)
Glucose in remission (mmol/l)	6.05 ± 0.83
BMI in remission (kg/m^2)	28.82 ± 3.72
Presenting plasma glucose (mmol/l)	37.8 ± 19.3 (16.7–133.3)
Presenting in diabetic ketoacidosis	21 (26.6%)
Precipitating events	3

Data are means ± SD or *n* (%).

and none were using agents known to affect glucose metabolism. The udy was approved by the institutional review board. All patients gave written informed consent and were studied in the Clinical Research Center.

Analytical method. Plasma glucose was measured by a glucose oxidase method. Serum insulin was measured with a double-antibody radioimmunoassay technique with a lower limit of detection of 15 pmol/l. The cross-reactivity with proinsulin is 30%. HbA_{1c} was determined by an automated high-performance liquid chromatography (HPLC) technique with an upper limit of normal range of ≤4.9% or the Miles DC 2000 with an upper limit of normal of ≤6.3%. All values are expressed as the ratio to the upper limit of normal for the particular assay used. Evidence for autoimmune disease was assessed by anti–islet-cell (13) or GAD (14) antibodies.

Materials. Human insulin was supplied by Lilly (Indianapolis, IN). D-[3-^{3}H]glucose (13.5 Ci/mmol) was purchased from Du Pont-NEN (Boston, MA) and had been chromatographed to 98% purity by HPLC.

Statistical analysis. Group means were compared using Student's *t* test and analysis of variance. Data are expressed as means ± SD. A Kaplan-Meier survival analysis and Cox hazard proportion analysis determined the time to hyperglycemic relapse and variables predictive of long-term near-normoglycemic remission (15).

RESULTS

Clinical characteristics at the time of near normoglycemia. A total of 79 patients were near-normoglycemic on no pharmacological therapy (Tables 1 and 2). Their FPG was 6.05 ± 0.83 mmol/l, and their HbA_{1c} was 0.95 ± 0.10 of the upper limit of normal. Although the FPG and HbA_{1c} levels indicated normoglycemia (all had FPG levels <6.4 mmol/l and/or normal HbA_{1c} levels), OGTTs performed in 72 of 79 cases showed normal tolerance in 12 patients (16.7%), impaired tolerance in 24 patients (33.3%), and diabetic tolerance (mean 2-h plasma glucose 13.3 mmol/l) in 36 patients (50%).

The mean BMI was 28.8 ± 3.7 kg/m^2, and the mean age was 45 ± 10 years. Men predominated at a ratio of 2:1. There were no differences in FPG, age, or BMI between men and women. A positive family history for diabetes was present in 62 of 79 patients (78%), and a history of hypertension was present in 28 of 79 patients (35%). Islet-cell or GAD antibodies were absent in all in whom they were measured (70 of 79) except one patient, who had borderline positive GAD antibodies. The origins of our black patients were 60% African-Caribbean, 37% African-American, and 3% native African.

Clinical characteristics at time of initial presentation with hyperglycemia. All patients were newly diagnosed, presenting with symptoms of hyperglycemia with a mean plasma glucose of 37.8 ± 19.3 mmol/l (range 16.7–133.3 mmol/l; men 36.6 ± 14.3, women 39.9 ± 26.2 mmol/l) (Table 1). Eleven patients presented with plasma glucose of >55.6 mmol/l. Of 79 patients, 74 required hospitalization for intravenous fluid and insulin treatment. Of 79, 21 (26.6%) presented in ketoacidosis (pH <7.3; positive serum ketones; all GAD antibody negative).

Characteristics of the development of near-normoglycemic remission. Table 2 lists the clinical features associated with the development of near-normoglycemia in the patients. The duration of outpatient treatment before near-normoglycemic remission was similar regardless of whether the patient had normal, impaired, or diabetic glucose tolerance after near-normoglycemic remission occurred. Most patients were treated with insulin acutely, but subsequent treatment was equally likely to be with insulin or sulfonylureas. Pharmacological treatment was tapered gradually by the physician, usually when the patient complained of hypoglycemic symptoms (or it was discontinued by patients because of hypoglycemic symptoms).

During the development of near-normoglycemic remission, weight change was determined from the time of the first clinic visit to the onset of near-normoglycemic remission. The time of the first clinic visit (usually within 2 weeks of hospital discharge) was chosen to minimize the effect of the catabolic and dehydrated state associated with the presenting hyperglycemia. Weight change ranged from a loss of 20 kg to a gain of 14.5 kg, with a mean ± SD loss of 1.9 ± 4.97 kg. A total of 17 of 79 (22%) subjects lost >5% of their initial body weight, 43 of 79 (54%) subjects lost 0–5%, 12 of 79 (15%) subjects gained <5%, and 6 of 79 (7.5%) subjects gained >5% of their initial body weight. The normalization of glucose tolerance was associated with the greatest amount of weight loss (4.9 ± 6.0 kg) compared with those with impaired and diabetic glucose tolerance (1.7 ± 6.2 and 0.88 ± 3.28 kg) ($P < 0.08$).

TABLE 2
Outpatient course and clinical characteristics during remission

Glucose tolerance	*n*	Mean duration of treatment to remission (months)	Mean weight change to remission (kg)	FPG (mmol/l)	Fasting plasma insulin (pmol/l)	HbA_{1c}	Treatment (*n*)
Normal	12	7.0 ± 5.3	−4.90 ± 6.00	5.2 ± 0.7	66 ± 42	0.93 ± 0.08	Sulfonylurea (3) Insulin (4) Both (4) Diet (1)
Impaired	24	6.6 ± 8.2	−1.70 ± 6.20	6.1 ± 0.6	84 ± 54	0.96 ± 0.10	Sulfonylurea (11) Insulin (6) Both (7)
Diabetic	36	9.5 ± 14.6	−0.88 ± 3.30	6.4 ± 0.7	96 ± 60	0.95 ± 0.12	Sulfonylurea (15) Insulin (16) Both (5)

Data are means ± SD. HbA_{1c} is given as percentage of the upper limit of normal.

TABLE 3
Metabolic characteristics during remission

OGTT	n	BMI (kg/m^2)	Glucose area 0–120 min (mmol · min^{-1} · l^{-1})	Insulin area minus basal 0–120 min (pmol · min^{-1} · l^{-1})	Glucose disposal (n) (μmol · kg^{-1} · min^{-1})
Normal	12	27.8 ± 1.9	836 ± 98*	24,726 ± 19,878†	37.78 ± 10.2 (8)‡
Impaired	24	28.2 ± 4.8	1,073 ± 92*	30,156 ± 13,734†	26.1 ± 10.7 (18)
Diabetic	36	29.7 ± 3.2	1,361 ± 167*	30,654 ± 22,452†	26.7 ± 12.0 (28)

Data are means ± SD. Nondiabetic control subjects: insulin area minus basal 43,758 ± 22,356 pmol · min^{-1} · l^{-1}; glucose disposal 42.2 ± 4.7 μmol · kg^{-1} · min^{-1}. *P < 0.001, normal vs. impaired vs. diabetic OGTT. †P < 0.05 vs. nondiabetic control subjects. ‡P < 0.05, normal vs. impaired or diabetic OGTT.

Metabolic characteristics in near-normoglycemic remission

OGTT and insulin secretion. The glucose area in response to oral glucose differed significantly, as expected in the normal, impaired, and diabetic glucose tolerant groups (Table 3). The absolute insulin response (insulin area minus basal) to oral glucose was lower in all three groups as compared with nondiabetic control subjects (n = 15, age 43.9 ± 8.0 years, BMI 26.14 ± 2.18 kg/m^2). There was no significant difference in the frequency of hypertension among the three groups.

Insulin-mediated glucose disposal. Of 79 subjects, 52 (66%) had glucose disposal measured during the euglycemic insulin clamp. Of the 52, 43 (83%) subjects had a BMI of ≤30 kg/m^2 and 9 had a BMI of >30 kg/m^2. Of those subjects with a BMI of ≤30 kg/m^2, half (22 of 43) had normal sensitivity to insulin and half (21 of 43) were insulin-resistant (mean ± SD, 40.33 ± 5.0 and 18.9 ± 3.9 μmol · kg^{-1} · min^{-1}, respectively; P < 0.0001). The insulin-resistant subjects were more obese than the insulin-sensitive subjects (BMI 27.13 ± 2.3 and 25.1 ± 2.16 kg/m^2, respectively; P < 0.005). Of the obese subjects (BMI >30 kg/m^2), most (7 of 9) were insulin resistant. In terms of glucose tolerance, glucose disposal was significantly higher in the group with normal glucose tolerance compared with the groups with impaired or diabetic glucose tolerance (37.78 ± 10.17 vs. 26.1 ± 10.7, 26.7 ± 12.0 μmol · kg^{-1} · min^{-1}, respectively; P < 0.05) and was not different from nondiabetic control subjects (42.2 ± 4.7 μmol · kg^{-1} · min^{-1}, n = 8, age 45 years, BMI 25.2 ± 3.01 kg/m^2) (Table 3). Of 8 subjects with normal glucose tolerance, 7 were normally insulin sensitive, while only half the subjects with impaired or diabetic glucose tolerance were insulin sensitive (6 of 14 and 10 of 21; P < 0.05).

Hyperglycemic relapse and final study. A total of 71 patients (45 men and 26 women) in near-normoglycemic remission not treated with antidiabetic agents were followed long-term. Of the 71, 6 (8.5%) patients remained in remission for a mean of 8.8 years (5.8–12.2 years). Twenty-seven (10 women and 17 men) patients relapsed into hyperglycemia, while 44 (17 women and 27 men) remained in near-normoglycemic remission at the time of their last follow-up visit (Table 4). One-third of both men and women relapsed. Nine individuals who had a major medical or surgical illness did not relapse during the event (mean FPG during remission 5.86 ± 0.57 mmol/l and during illness 5.62 ± 0.65 mmol/l; NS). Relapse was not associated with weight gain during the near-normoglycemic remission phase (relapse versus near-normoglycemic remission: 0.90 ± 4.22 vs. −1.3 ± 4.0 kg), and their final BMIs were similar (28.5 ± 4.2 vs. 29.04 ± 3.9 kg/m^2). Those individuals who remained in near-normoglycemic remission showed no significant change from their initial near-normoglycemic remission data.

Longitudinal studies. A Kaplan-Meier survival analysis was performed on the 63 subjects in near-normoglycemic remission whom we had followed from the initial outset of hyperglycemia (after 1985) and who had received no antidiabetic therapy from the onset of near-normoglycemic remission until relapse. Figure 1 shows that the median time to relapse was 39.72 months.

A survival analysis with covariates using the Cox models showed that the duration of near-normoglycemic remission was not significantly related to glucose tolerance, initial near-normoglycemic remission, FPG, insulin or glucose response to oral glucose, BMI, insulin action, or weight gain or loss from the onset of near-normoglycemic remission until the time of relapse or last follow-up visit. The data suggest that a lower presenting plasma glucose positively affected the duration of near-normoglycemic remission, while male sex adversely affected it (odds ratio 1.0027 for each 0.055 mmol/l of presenting plasma glucose, 95% CI 1.004–1.013, P < 0.001; odds ratio 4.529 for men, 95% CI 1.413–14.519, P < 0.001). Thus, a presenting plasma glucose of 33.3 mmol/l increased the risk of relapse twofold compared with one of 16.7 mmol/l, all other variables being equal; and similarly, male sex conferred a 4.5-fold risk for relapse.

DISCUSSION

The present report extends our previous observations that near-normoglycemic remission after treatment of newly presenting severe hyperglycemia in black NIDDM subjects is a significant phenomenon (5). It occurs more commonly in men than in women (almost 2:1) and in normal weight to moderately obese individuals with a younger age of onset (≤60 years). Near-normoglycemic remission is most likely to occur within the first year of treatment and is not associated with marked weight loss. The median duration of near-normoglycemic remission is 40 months. As many as 10% may have

TABLE 4
Characteristics at relapse or final visit

	Relapse	Remission	P
n (F/M)	27 (10/17)	44 (17/27)	
Initial FPG (mmol/l)	6.1 ± 0.7	6.1 ± 0.9	NS
Final FPG (mmol/l)	12.5 ± 7	4.9 ± 3.1	<0.0001
Weight change after remission (kg)	0.48 ± 4.10 (24)	−1.3 ± 4.0 (30)	NS
Final weight (kg)	82.2 ± 15 (24)	84.15 ± 12.5 (30)	NS
Final BMI (kg/m^2)	28.5 ± 4.2 (24)	29.0 ± 3.9 (30)	NS

Data are means ± SD (n).

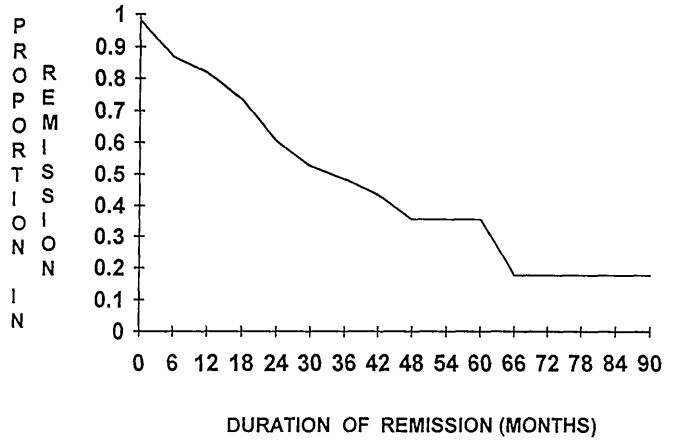

FIG. 1. A Kaplan-Meier survival curve showing the proportion in remission over 90 months.

a near-normoglycemic remission that lasts for 5–10 years. Near-normoglycemic remission occurs in both insulin-sensitive and insulin-resistant NIDDM variants. During near-normoglycemic remission, glucose homeostasis is not disturbed by stressful medical illness or occasional dietary indiscretion. These subjects are considered to have NIDDM because of residual insulin secretion, positive family histories of diabetes, absent autoimmune markers, and clinical course.

The frequency of near-normoglycemic remission in NIDDM is not known. A retrospective analysis of self-selected newly diagnosed patients who attended diabetes education classes and had intensive glucose management showed that 20 of 67 (30%) patients went into near-normoglycemic remission as compared with 3 of 91 (3%) patients who did not participate in such a program (16). Preliminary prospective data from an ongoing study of all consecutive newly diagnosed diabetic subjects admitted to Kings County Hospital with severe hyperglycemia and treated intensively supports this estimate (17). These data suggest that with appropriate management, the frequency of near-normoglycemic remission in this population can be quite significant.

There is little data in the literature with which to compare our results. Pirart and Lauvaux (18) described a series of 280 European NIDDM subjects in remission. Their patients had presented with mild hyperglycemia of 16.7 mmol/l; 104 of 280 lost >10% of their body weight, and 50% relapsed within the first year of remission (18). Our population differs remarkably from theirs, and no comparison seems valid.

The relationship of weight loss and the development of near-normoglycemia was reported by the U.K. Prospective Diabetes Study (19): 2,597 newly diagnosed NIDDM patients were treated initially for 3 months and 823 subsequently for 12 months with diet only. Of those presenting with an FPG of 6–8 mmol/l, 50% achieved a FPG <6 mmol/l after 3 months of a weight-reducing diet. The mean weight loss was 10 kg. Only 10% of those with an FPG of 14–16 mmol/l achieved an FPG of <6 mmol/l; the mean weight loss was 26 kg after 3 months of diet treatment. Only 54% of those who were normoglycemic at 3 months were able to maintain it for 1 year. Thus, achieving normoglycemia required a large amount of weight loss and was a function of the starting blood glucose. These data from whites are very different and are not comparable to ours.

The etiology of near-normoglycemic remission in our patients is not clear. It does not represent recovery from an identifiable precipitating event. It cannot be related to weight loss. It is not the honeymoon phase of IDDM (14). It occurs within months and appears to be associated with very good glycemic control in the early phases of new-onset diabetes.

Two studies describe that a significant percentage of subjects with good glycemic control on chronic sulfonylurea therapy were able to remain euglycemic when switched to placebo for periods up to and beyond 1 year (20,21). In contrast, in this series, insulin and sulfonylureas were used equally frequently for similar durations, making the association of a specific type of treatment with near-normoglycemic remission unlikely.

One hypothesis is that the acute hyperglycemia is caused by an abrupt but reversible decrease in insulin secretion. Hyperglycemia impairs the ability of the β-cell to recover, while very good glycemic control over weeks to months allows for appreciable β-cell recovery (17,22–25). The relapse may represent a progressive decline in insulin secretory capacity. Preliminary analysis of serial studies on glucose-mediated insulin secretion in our subjects suggests that near-normoglycemic remission is associated with the maintenance of insulin secretory capacity, while relapse is associated with a 50–75% decrease in insulin secretion (12).

It is not known whether near-normoglycemic remission is unique to black individuals. Physicians caring predominately for black and Hispanic patients are familiar with this phenomenon. The five cases of remission reported in the literature were black individuals. Rendell's series of 11 remission patients did not specify the race (26–30).

The ability to induce and prolong near-normoglycemic remissions in NIDDM is likely to decrease complications. NIDDM subjects in near-normoglycemic remission have normal glycemic control (HbA_{1c} and FPG) with little effort or hypoglycemia. Normoglycemic remission for 40 months is estimated to decrease proliferative retinopathy by 50–60% 10 years after the diagnosis of NIDDM in those presenting at age 45 (31). Prolonging near-normoglycemic remission, as we have reported, with the addition of low-dose glipizide could reduce complications further (6).

In conclusion, knowledge of the existence of long-term near-normoglycemic remission and development of strategies to increase its rate and duration are potentially important approaches to decreasing complications in NIDDM. This is clearly possible now in black NIDDM patients and remains to be explored in other groups.

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