Idiopathic Type 1 Diabetes in Dallas, Texas

A 5-year experience

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OBJECTIVE — To describe the clinical course of individuals with idiopathic type 1 diabetes after a mean of 5 years from diagnosis and to compare glycemic control between those treated with diet and/or oral agents and those treated with insulin at follow-up.

RESEARCH DESIGN AND METHODS — Medical records of patients with new-onset diabetes, who presented with unprovoked diabetic ketoacidosis, were reviewed. A total of 54 of these individuals were traceable and had relevant data collected within the past 2 years. All patients had nonsusceptibility HLA haplotypes and no serological evidence of autoimmune type 1 diabetes. Most of these patients were male (41 men and 13 women), were non-Caucasian, were obese at the time of diagnosis (BMI 31.6 ± 6.3 kg/m^2), reported weight loss (12.8 ± 9.8 kg), had a family history of type 2 diabetes, and had acanthosis nigricans. At follow-up, 33 patients were still taking insulin and 21 were on diet and/or oral-agent therapy.

RESULTS — Both treatment groups were similar in clinical presentation and demographics at diagnosis. After 4.8 ± 1.6 years of follow-up, the 33 patients that were receiving insulin had a lower HbA_{1c} than the 21 patients who were using therapies other than insulin (7.8 ± 2.4 vs. 11.1 ± 3.5%, $P = 0.009$; 95% CI 1.0–6.5%). There was a high correlation between change in weight and change in HbA_{1c} at follow-up ($r = 0.45$, $P < 0.001$, $n = 54$). There were no differences in the rate of diabetes complications or in the episodes of recurrent diabetic ketoacidosis.

CONCLUSIONS — Idiopathic type 1 diabetes occurs more frequently in male African-American patients but also occurs in other ethnic groups. Patients with idiopathic type 1 diabetes who continued to use insulin had better glycemic control than patients using therapies other than insulin. Regained weight is a good clinical marker for improvement in glycemic control. Individuals with this type of diabetes should not be switched to therapies other than insulin.

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The diabetes of young obese African-Americans has been called by different names, including atypical diabetes and Flatbush diabetes (1,2). In 1997, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus included this group of individuals in the new classification, calling it idiopathic type 1 diabetes (3). These individuals tend to have diabetic ketoacidosis as their initial clinical presentation, they lack autoimmune markers at diagnosis, and they have physical characteristics that are more typical of patients with type 2 diabetes (1,2,4). Their subsequent course is also unusual in that many of these patients after initial therapy with insulin seem to maintain acceptable glycemic control for many years by either diet or oral hypoglycemic agents.

Individuals with autoimmune type 1 diabetes usually present with unprovoked diabetic ketoacidosis. Insulin resistance does not play a major role in its pathogenesis, as the main defect is an absolute insulin deficiency (5). The vast majority of individuals are lean, young, and with autoimmune markers associated with diabetes, and most have susceptibility HLA haplotypes (6,7). They have a rapid β-cell destruction mediated by T-cells, and they need exogenous insulin to preserve life.

Type 2 diabetes is associated with obesity, insulin resistance, and chronic hyperglycemia without the development of unprovoked ketoacidosis (4,8–11). Insulin resistance is believed to play a major role in its pathogenesis, causing progressive β-cell dysfunction (12–15). At onset, diabetic individuals have two defects: insulin resistance and β-cell dysfunction (15). Because these individuals secrete some insulin, they do not require exogenous insulin to preserve life. The majority of type 2 diabetic patients are older compared with type 1 diabetic patients; most are obese and lack the autoimmune markers associated with type 1 diabetes (3).

Patients with idiopathic type 1 diabetes do not easily fit into either classification (16). It seems to be a clinically distinct type of diabetes, and there is often confusion regarding the classification and subsequent therapy of these patients (1,2,4,16–18). Its pathogenesis is largely unknown, but it is likely related to insulin resistance and transient β-cell dysfunction, perhaps because of glucose desensitization (2,4,19). Autoimmunity is not believed to be involved in its pathogenesis. There are a few case reports of point mutations in different genes, but large genetic analyses to corroborate these findings are lacking (20).

Idiopathic type 1 diabetes has been described mostly in African-Americans

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

but also in individuals from other ethnic groups (21–26). The majority of these patients are been treated as if they have type 2 diabetes (1,2,4,16). After a variable period of insulin therapy, their therapy is changed to diet and/or oral hypoglycemic agent therapy (2,4,27). However, there are no long-term or prospective randomized trials comparing continued insulin therapy with oral hypoglycemic therapy in terms of glycemic control, complications, and recurrent episodes of ketoacidosis.

This study describes the clinical course of a group of individuals with this form of diabetes who were admitted to the University Diabetes Treatment Center at Parkland Memorial Hospital in Dallas, Texas, from 1992 to 1996, at the initial presentation of their diabetes. Specifically, we compared different therapies on several outcomes, including glycemic control, the development of another episode of diabetic ketoacidosis, changes in body weight, and other metabolic parameters.

RESEARCH DESIGN AND METHODS

— We reviewed the medical records of patients with new-onset diabetes presenting with unprovoked diabetic ketoacidosis (not associated with a precipitating event such as infection, trauma, acute pancreatitis, etc.). All patients admitted with new-onset diabetes to the University Diabetes Treatment Center from 1992 to 1996 were invited to participate in a screening for autoimmune markers of diabetes and for determination of HLA haplotyping (28). To be eligible, the patients needed to have the following clinical characteristics: *1*) typical symptoms of diabetes before admission (polyuria, polydipsia, polyphagia, and weight loss); 2) diabetic ketoacidosis (anion gap >12 mEq/l plus pH <7.35 and/or HCO_3 <17 mEq/l) and urine ketones >80 mg/dl, in the absence of a precipitating event; and *3*) absence of immune markers (ICA, IAA, and GAD antibodies) or HLA susceptibility antigen (DR3 [DQA1*0501 and DQB1*0201], DR4 [DQA1*0301 and DQB1*0302] in Hispanics/non-Hispanic whites, and DR7 [DQA1*0301 and DQB1*0201] in African-Americans).

After identification of the eligible individuals, we conducted a chart review of these patients. Information collected included present diabetes therapy, body weight, HbA_{1c}, plasma lipid level, serum creatinine level, 24-h urine collections for microalbuminuria, subsequent episodes of diabetic ketoacidosis, and occurrence of other diabetes-related complications.

Table 1—*Patient demographics and clinical parameters at diagnosis*

n	54
Age (years)	34.8 ± 11.6
Sex	
Female	13
Male	41
Race	
Black	35
Hispanic	16
Native American	3
Weight at diagnosis (kg)	95.9 ± 24
BMI (kg/m^2)	31.6 ± 6.34
Reported weight-loss (kg)	12.8 ± 9.8
Arterial pH	7.30 ± 0.1
Plasma glucose (mg/dl)	609 ± 226
HCO_3 (mEq/l)	15.9 ± 6.8
Anion gap (mEq/l)	25.1 ± 7.8
Urine ketones (mg/dl)	150

Data are *n* and means ± SD.

Statistical analysis

The general statistical analysis was done using computer software (Glantz's Primer-version 3.02; McGraw-Hill, 1992). All results are expressed as means ± SD. The differences between treatment groups at diagnosis and follow-up were compared using a two-tailed *t* test for nominal values including HbA_{1c} (nondiabetic <5.6%). The differences within treatment group were evaluated using paired *t* test for nominal values. The differences between sex and ethnic group were evaluated using one-way analysis of variance. The differences in the development of complications between treatment groups were evaluated using χ^2 for categorical values. Statistical significance was defined as $P < 0.05$.

RESULTS

— A total of 80 patients fulfilled the criteria previously described. Of these 80 patients, 54 were being followed at our clinics and had pertinent data collected within the past 2 years (1998–2000). From the original sample, 26 individuals were not included: 3 had died from unrelated conditions, 12 had moved from the Dallas area, and 11 were not traceable. All of the patients reported weight loss before admission and had typical symptoms of type 1 diabetes at presentation (Table 1).

There was no difference in age, BMI, sex, or weight loss at diagnosis among ethnic groups (Table 2). The mean age at diagnosis was 34.8 ± 11.6 years, and the mean HbA_{1c} at diagnosis was 13.5 ± 1.8%. Hispanic individuals tended to have a lower HbA_{1c} than other ethnic groups. All of the patients had family history of type 2 diabetes in first-degree relatives, 44 were obese, 15 had a previous diagnosis of hypertension, and 35 had acanthosis nigricans. All of the patients reported being overweight before the onset of symptoms, but 10 were not overweight at diagnosis (BMI range 21–26) because of significant weight loss (up to 100 lbs) before admission to the hospital. There was significant male predominance, with a 3:1 male-to-female ratio (41 men and 13 women). The strong gender difference and other baseline characteristics were also present in the nontraceable patients.

Patients were initially treated with in-

Table 2—*Ethnic distribution of patients with idiopathic type 1 diabetes*

	Black				
	African	African-American	Hispanic	Native American	*P*
Sex					
Male	3	23	13	2	0.84
Female	0	9	3	1	
Age	35.3 ± 10.8		34.5 ± 13.8	30 ± 10.6	0.75
Weight loss at diagnosis (kg)	11.9 ± 9.5		11.5 ± 6.3	8.8 ± 4.6	0.83
Weight at diagnosis (kg)	98.8 ± 23.87		86.1 ± 21.5	111.7 ± 27.4	0.11
HbA_{1c} at diagnosis (%)	13.8 ± 1.9		12.5 ± 1.3	14.8 ± 1.6	0.03
BMI (kg/m^2)	31.6 ± 6.6		30.9 ± 6.2	34.0 ± 3	0.74
Follow-up (years)	4.6 ± 1.7		4.6 ± 1.4	4.7 ± 2.5	0.99

Data are *n* and means ± SD.

Table 3—*Comparison of treatment groups at diagnosis, discharge, and follow-up*

	Oral agents/diet (n = 21)		Insulin (n = 33)		
	Diagnosis	Follow-up	Diagnosis	Follow-up	P*
Age (years)	34.7 ± 12	40.1 ± 11.2	34.7 ± 11	39.4 ± 11.7	0.83
Ethnic group					
Black	13	13	22	22	0.25
Hispanic	8	8	8	8	
Native American	0	0	3	3	
Years follow-up	—	5.2 ± 1.5	—	4.5 ± 1.5	0.10
HbA_{1c} (%)	13.3 ± 1.5	11.1 ± 3.5†	13.5 ± 1.9	7.8 ± 2.4‡	0.001
ΔHbA_{1c} (%)	—	2.4 ± 3.3	—	5.7 ± 2.8	<0.0001
Weight (kg)	93.2 ± 25	92.6 ± 27§	97.2 ± 23.7	108.5 ± 28.2‖	<0.0001
ΔWeight (kg)	—	−0.69 ± 10.4	—	11.5 ± 11.1	<0.0001
BMI (kg/m^2)	31.5 ± 6.5¶	30.7 ± 7.1¶	32.7 ± 6.4	35.7 ± 7.8#	<0.0001
ΔBMI (kg/m^2)	—	−0.3 ± 3.7	—	3.6 ± 3.6	<0.0001
Insulin dose at discharge (U/kg)	0.87 ± 0.32	—	0.87 ± 0.29	0.72 ± 0.36**	—

Data are n and means ± SD. *P-value between groups at follow-up; †P = 0.003; ‡P <0.001; §P = 0.76; ‖P = 0.04; ¶P = 0.72; #P = 0.02; and **P = 0.02 for diagnosis versus follow-up.

travenous fluids and insulin for the treatment of diabetic ketoacidosis, and all of the patients were discharged on subcutaneous insulin. The mean daily insulin requirement at discharge from the hospital was 0.87 ± 0.3 U/kg. There was no difference among ethnic groups in insulin requirements at discharge. A total of 21 patients (39%) initially treated with insulin were switched to diet and/or oral agent therapy after a mean of 12.1 ± 10 months (range 1–36, median 8 months). At mean HbA_{1c} 9.5 ± 4.3%, each patient's respective personal physician changed these treatments. Patients were switched to diet and/or oral agent therapy for two main reasons: insulin-induced hypoglycemia and patient preference. Nine patients chose to discontinue insulin; they had a mean HbA_{1c} of 13 ± 2.9% at the time of therapy change. Eleven patients were switched because of frequent insulin-induced hypoglycemic episodes; they had a mean HbA_{1c} of 5.6 ± 0.35% at the time of change. One patient had hemophilia-A and chose to discontinue insulin (HbA_{1c} 6.1%). After 4.8 ± 1.6 years of follow-up (range 2.1–8.3, median 4.6), 33 patients were on insulin and 21 were using diet and/or oral agent therapy.

Table 3 shows the HbA_{1c}, body weight, and BMI in the 54 patients according to therapy at diagnosis and follow-up. Both treatment groups were similar in terms of HbA_{1c}, body weight, and BMI. Both groups had a lower HbA_{1c} at follow-up than at diagnosis. However, the change in HbA_{1c} was greater in patients using insulin than in those not using insulin at follow-up (Table 3). The average HbA_{1c} for those individuals who continued on insulin was 7.8 ± 2.5%, compared with 10.6 ± 3.5% for those not using insulin (P = 0.001; 95% CI 1.14–4.4).

The mean insulin requirement at follow-up for the patients on insulin was 0.72 U/kg, 0.15 U/kg less than at diagnosis (P = 0.02, 95% CI 0.03–0.27 U/kg), but some of the patients were also taking insulin sensitizers (three on metformin and two on troglitazone), which might explain this finding. Six patients on sulfonylureas were also taking metformin, and one was taking troglitazone (P = 0.36).

There was a significant correlation between changes in HbA_{1c} and weight changes (r = 0.45, P < 0.001, n = 54) in both treatment groups. Patients with greater improvement in HbA_{1c} had greater weight gain. Weight gain after initiation of diabetes treatment was 6.6 ± 12.5 kg, regardless of what therapy was used. However, 17 patients continued to lose weight during the years of follow-up. These patients had a follow-up HbA_{1c} of 11.4 ± 3.5%. Of the patients that lost weight during the study, 5 were on insulin and 12 were on diet and/or oral agent therapy (7 on diet therapy alone, 2 on glyburide/metformin, 2 on glyburide alone, and 1 on glyburide/troglitazone combination).

In the 37 patients who gained weight, HbA_{1c} was 8.0 ± 2.5% at follow-up. Of the patients that gained weight, 28 were on insulin and 9 were on oral agents or diet. The patients in the insulin-therapy group that gained weight had a significantly lower HbA_{1c} than the patients in the diet and/or oral agent group that gained weight (P = 0.01; difference of 2.6%, 95% CI 0.83–4.4%). There was also a significant difference of 3.4% in HbA_{1c} in patients that gained weight (regardless of therapy) compared with those that lost weight during the observational period (P < 0.0001, 1.7–5.1%). The patients on insulin therapy had a mean weight gain of 11.0 ± 11.2 kg (P < 0.0001, 6.6–18.5 kg) versus non–insulin-treated patients. Overall, the non–insulin-treated group had a mean weight loss of 1.6 ± 9.4 kg since diagnosis.

At follow-up, 37 patients gained weight, 11 developed hypertension, 8 had an infectious complication (i.e., abscess or pyelonephritis), 7 developed microalbuminuria, 6 developed diabetic neuropathy, and 2 developed hyperlipidemia. Nine patients developed another episode of diabetic ketoacidosis (four in the insulin group and five in the diet and/or oral agent group) and were hospitalized. Another two were hospitalized for hyperglycemia with ketosis without acidosis. All of the patients in the insulin-therapy group temporarily discontinued insulin use before the recurrence of diabetic ketoacidosis, and all resumed insulin therapy after the event. Other than weight gain, there was no difference in diabetes-related complications between treatment groups in this short study period.

CONCLUSIONS — Idiopathic type 1 diabetes is highly common in major cities whose populations include large numbers of African-Americans (2,4,17,22,24,29). These patients are usually treated as if they have type 2 diabetes, with diet and/or oral hypoglycemic agents, based on their physical characteristics and on the results of the few studies available in the literature (2,4,27). However, it is still unclear whether this recommendation is beneficial for patients with idiopathic type 1 diabetes, as the primary pathophysiological defect is still largely unknown.

Furthermore, there have been no prospective clinical trials to assess which therapy is better in terms of clinical outcomes or prevention of diabetes complications, and there are no guidelines to

determine whether and when to switch these patients to therapies other than insulin (16). This is the first study that compares the two major forms of therapy in patients with idiopathic type 1 diabetes.

There are only a few studies with a fairly large number of patients with idiopathic type 1 diabetes that have had an emphasis on clinical outcomes. In Brooklyn, Banerji et al. (2) studied 21 patients with idiopathic type 1 diabetes ("Flatbush diabetes"), some of whom had a previous history of type 2 diabetes. These patients were studied at variable times, from 3 to 120 months after diagnosis. They all had evidence of insulin resistance with some preservation of β-cell function. There was no comparison showing which therapy (insulin, diet, or oral hypoglycemic agents) was better in terms of glycemic control or preservation of endogenous insulin secretion.

Umpierrez et al. (27) evaluated 17 African-American patients to determine which therapy (oral hypoglycemic agents or diet) was better in avoiding episodes of ketoacidosis. After a mean follow-up of 16 months, patients in the oral hypoglycemic group had fewer relapses (episodes of diabetic ketoacidosis) than patients on diet therapy alone. There was no mention of which therapy was better in terms of glycemic control.

Our study has a longer follow-up after diagnosis than previous studies, includes other ethnic groups, and has evaluated outcomes after a longer period of treatment. This is important because in studies within the first few years after diagnosis, the HbA_{1c} may improve because of the "honeymoon period." It is not known whether patients with idiopathic type 1 diabetes have a shorter or longer honeymoon period than patients with type 2 diabetes or autoimmune type 1 diabetes.

Based on our study and others, these patients seem to have a variable response to oral hypoglycemic agents. Thus, these patients may not have the predicted pharmacological response that is usually seen in patients with type 2 diabetes who have had many years with good glycemic control on oral hypoglycemic therapy alone. The fact that these patients are phenotypically similar to patients with type 2 diabetes does not mean that they have type 2 diabetes.

In our review, we found that in most patients with idiopathic type 1 diabetes, insulin therapy was better in terms of glycemic control than either oral hypoglycemic agents or diet therapy alone and that long-term glycemic control is better maintained with insulin treatment. Based on these results, we recommend that patients with this form of diabetes not be changed to any therapy other than insulin. The response to oral hypoglycemic agents is unpredictable, and there are no randomized trials to support this commonly accepted practice.

Idiopathic type 1 diabetes is probably a heterogeneous nonautoimmune-mediated insulin-deficient form of diabetes. Because not all individuals with morbid obesity or patients with uncontrolled type 2 diabetes develop severe enough insulinopenia to have an episode of diabetic ketoacidosis, patients with idiopathic type 1 diabetes must have a severe form of accelerated β-cell failure (30,31). This β-cell failure is potentially reversible early in the disease, but recovery is shorter in duration compared with patients with type 2 diabetes. Why the β-cell failure is reversible early and then rapidly progresses is unclear.

We also noted significant weight gain associated with improvement of glycemic control, regardless of what therapy was used. Insulin-treated patients gained more weight than individuals on other therapies. Finally, we noted the significant male predominance in patients with idiopathic type 1 diabetes; this is also seen in studies by Banerji et al. (2) and Umpierrez et al. (4).

There are some limitations to this study. First, the study is retrospective and based on chart reviews. These patients were all followed by different physicians with different approaches and styles in diabetes management. The second limitation of this study is the potential for nonadherence to the different therapies by the study subjects. The main reasons for switching patients to oral agents or diet were insulin-induced hypoglycemia or patient preference. It is possible that patients treated with diet and/or oral agents were less adherent than those treated continuously with insulin. Third, the inclusion of the 26 individuals who were initially screened but whose follow-up information was not available might have changed our findings. Finally, the number of patients was relatively small, and there was no randomization process used to determine therapy.

In summary, our study suggests, with some limitations, that 5 years after diagnosis, patients with idiopathic type 1 diabetes have better glycemic control with the continuous use of insulin. The usual practice of changing these patients to therapies other than insulin has been based on noncontrolled short-term studies and should be revised. Our study also indicates that weight-gain is a good clinical marker of improved glycemic control, regardless of what therapy is used. We have noted that idiopathic type 1 diabetes can occur in obese Hispanic and Native American individuals and occurs with a significant male predominance. Randomized trials evaluating different forms of therapies in idiopathic type 1 diabetes are needed.

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