Management of Newly Diagnosed Non–Insulin-Dependent Diabetes Mellitus in the Primary Care Setting: Effects of 2 Years of Gliclazide Treatment—The Diadem Study

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Five thousand five hundred seventy-two newly diagnosed non–insulin-dependent diabetes mellitus (NIDDM) patients (3,225 men and 2,347 women; mean age, 58.5 years) were recruited through the General Practitioners (GPs) network in France. All had persistent hyperglycemia after a preliminary 3-month period with dietary and life-style modification. Gliclazide (80 to 320 mg/d) was then prescribed as diabetic pharmacotherapy for 2 years. Additional therapy for hypertension and dyslipidemia was started if necessary. The aim of the study was mainly to determine the feasibility of a GP-directed protocol for the monitoring and treatment of newly diagnosed NIDDM patients, and to assess the effectiveness of diabetic therapy in this cohort. Diabetes was diagnosed in 78% of the cohort during routine screening. Among the women, 6.5% had a history of gestational diabetes. Eighteen percent of the patients had a parental history of diabetes, and the dominant maternal role in the genesis of NIDDM was confirmed. High blood pressure (Joint National Committee V criteria) was found at inclusion in 38.8% of the whole cohort. Hyperlipidemia was known in 44.6%. A history of stroke was present in 1.6% of the patients, and coronary heart disease (CHD) in 6.3%. These data support the relationship between the atherogenic state and development of NIDDM. Microalbuminuria defined as urinary albumin excretion (UAE) of at least 20 mg/L was found in 29.6% of the patients, and retinopathy in 9.8%. Among the included patients, 23% did not complete the study and were excluded from the efficacy analysis. Of these, 14% (808 patients) had only baseline evaluation data and 9% (499 patients) withdrew later. Comparison of mean baseline and final results in study completers uncovered a significant improvement in fasting blood glucose ([FBG] 182 ± 48 *v* 137 ± 40 mg/dL), post prandial blood glucose ([PPBG] 209 ± 68 *v* 162 ± 52 mg/dL), and hemoglobin A_{1c} ([HbA_{1c}] 8.7% ± 2.5% *v* 7.3% ± 2.0%). A slight improvement in total cholesterol (228 ± 44 *v* 222 ± 41 mg/dL), body mass index ([BMI] 28.5 ± 4.7 *v* 27.9 ± 4.5 kg/m^2), and waist to hip ratio (0.99 ± 0.1 *v* 0.98 ± 0.1) was observed. There was a decrease in the percentage of patients with high blood pressure (38.5% *v* 30.7%). A mild increase in the prevalence of retinopathy (10.2% *v* 11.8%) was noted during the study, while the incidence of microalbuminuria remained unchanged (30.2% *v* 29.5%). In conclusion, the data indicate that the GPs involved in this study were able to successfully monitor and manage NIDDM patients in accordance with a standardized protocol. Gliclazide appeared to be an effective and well-tolerated treatment. The high prevalence of chronic diabetic complications at diagnosis emphasizes the delay encountered in reaching the diagnosis of NIDDM and the problems associated with this delay. In addition to the classic risk factors for NIDDM exhibited in this patient cohort, we have identified CHD and a maternal genetic component as further potential predicting factors.

EARLY DETECTION AND MANAGEMENT of diabetic complications is recognized as being of great importance in the prevention of disease progression.[1,2] It is generally acknowledged that in most countries non–insulin-dependent diabetes mellitus (NIDDM) patients experience difficulty in receiving specialized diabetes care. Long-term follow-up evaluation by General Practitioners (GPs) is a normal occurrence. Meanwhile, the need for early detection and management of diabetic complications is emphasized, and the traditional care model for diabetes at the secondary and tertiary level is recognized as being expensive. Diabetes Control and Complications Trial data have confirmed the importance of hyperglycemia control in the primary and secondary prevention of microangiopathy in insulin-dependent diabetes mellitus.[3] The effects of such metabolic factors on the chronic complications of NIDDM remain to be demonstrated.[4]

These problems prompted us to question whether a new more efficient and highly cost-effective model of NIDDM healthcare could be designed. Few studies have examined whether a disease management model based at the primary care level could be effective for NIDDM patients. To address this question, we conducted a study in 5,572 NIDDM patients recruited and monitored by 1,772 GPs in metropolitan areas of France. The specific aims of the Diabetes Diamicron Etude Multicentrique (Diadem) Study conducted between 1992 and 1995 were to assess (1) the feasibility of performing such a GP-based protocol, (2) the effectiveness of gliclazide therapy, (3) the prevalence of diabetic complications at diagnosis, and (4) baseline patient characteristics to propose predictive factors for NIDDM.

PATIENTS AND METHODS

Patients

Fifty-five hundred seventy-two patients (3,225 men and 2,347 women) with newly diagnosed NIDDM defined according to World Health Organization criteria as fasting plasma glucose of at least 140 mg/dL were recruited by 1,772 GPs from metropolitan areas of France. Sixty percent were unemployed or retired. Type I diabetic patients were excluded, as were patients with significant cardiac, renal, or hepatic impairment. All patients provided informed consent before study inclusion.

Methods

After a 3-month dietary treatment adapted to the patients' life-style, patients with persistent hyperglycemia were enrolled in the study. They were treated with gliclazide for a period of 2 years, with the dose adjusted according to clinical and biological results throughout the

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study. The mean daily dose was 160 mg (range, 80 to 320 mg). Dietary modifications were maintained during the study. Furthermore, pharmacological treatment for hypertension was started if supine diastolic blood pressure was above 90 mm Hg, using angiotensin-converting enzyme inhibitor as a first-line treatment.

Patients were assessed at 0, 3, 6, 12, 18, and 24 months during the period of study. The study protocol required collection of demographic and clinical characteristics using a standardized questionnaire. Fasting (FBG) and postprandial (PPBG) blood glucose, hemoglobin A_{1c} (HbA_{1c}), and serum cholesterol and triglyceride levels were measured at baseline and every year. The body mass index (BMI) waist to hip ratio, and blood pressure were determined at each visit. Macroangiopathy lesions were diagnosed by recording symptoms, auscultation of the main arterial vessels, and electrocardiogram. Assessment of retinopathy was performed by an ophthalmologist using direct ophthalmoscopy. Urinary albumin excretion (UAE) was measured, with elevated UAE defined as 20 mg/L or greater.

Statistical Evaluation

A comparison of the prevalence of microangiopathic lesions at baseline and final evaluation was performed using the McNemar test. The comparison of biological and anthropometric parameters before and after 2 years was performed using the Student *t* test for paired data. Results were expressed as the mean ± SD.

RESULTS

Feasibility of the Study

Of the initial 5,572 patients, 1,307 (23%) did not complete the study: 808 (14%) had only baseline evaluation data, and a further 499 (9%) withdrew later. Reasons for study withdrawal included being lost to follow-up study (50%), a lack of compliance (9%), intercurrent disease (31%), side effects (6%), primary or secondary failure of treatment (16%), and other causes (18.4%). There may have been more than one reason for withdrawal. Of the side effects leading to study withdrawal, one third were hypoglycemic episodes. The baseline evaluation was made on the whole cohort (N = 5,572), and a statistical analysis of the efficacy was performed on the study completers (n = 4,265, 77%).

Baseline Evaluation

The mean age of the patient population was 58.5 ± 10 years. Table 1 illustrates the distribution of patients in relation to age and sex. Seventy-five percent of the cohort were aged 50 to 70 years, and 6% were older than 70 years.

The diabetes duration since diagnosis was 1.2 ± 2.8 years. NIDDM was diagnosed on routine screening in 78% of the patients. The remaining 22% were symptomatic on presentation, half of whom were exhibiting symptoms of hyperglycemia such as polyuria and polydipsia. A parental history of diabetes was found in 18% of the patients, with mothers implicated 1.5 times more frequently than fathers ($P < .001$) in both the index of female patients (17.1% *v* 10%) and the index of male patients (13.8% *v* 10.9%). Among women, 6.5% reported a previous gestational history of hyperglycemia (Table 2).

Table 1. Distribution (%) of 5,572 NIDDM Patients in Relation to Age and Sex

Age (yr)	Men (n = 3,255)	Women (n = 2,347)	Total (N = 5,572)
<50	20.8	15.9	18.3
50-59	30.7	26.3	28.5
60-70	43.1	50.9	47.0
>70	5.4	6.9	6.2

Table 2. Parental History and Type of Diabetes in Newly Diagnosed NIDDM Patients According to Sex

Group	Men		Women	
	Father	Mother	Father	Mother
Insulin-treated	1.6	2.3	1.4	2.3
Non–insulin-treated	10.9	13.8*	10.0	17.1*
Treatment unknown	2.7	2.6	2.1	4.0
Total	15.2	18.7	13.5	23.4

NOTE. The results are percentages.
*$P < .001$.

High blood pressure (defined as systolic blood pressure ≥130 mm Hg and diastolic blood pressure ≥85 mm Hg according to Joint National Committee V criteria) was present in 38.8% of the whole cohort. Hyperlipidemia was known in 44.6%. Peripheral arteriopathy was diagnosed in 6.8%, and a history of stroke in 1.6%. Coronary heart disease (CHD) was diagnosed in 6.3%. Myocardial infarction affected men 4.5 times more frequently than women ($P < .001$). Microalbuminuria (UAE ≥20 mg/L) was found in 29.6% of the patients, and retinopathy in 9.8%.

Final Evaluation

Comparing mean baseline values and final evaluation results in completers (Fig 1), there was a notable improvement in FBG (182 ± 48 *v* 137 ± 40 mg/dL, $P < .001$), PPBG (209 ± 68 *v* 162 ± 52 mg/dL, $P < .001$), and HbA_{1c} (8.7% ± 2.5% *v* 7.3% ± 2%, $P < .001$). Total cholesterol (228 ± 44 *v* 222 ± 41 mg/dL), triglycerides (1.66 ± 0.97 *v* 1.46 ± 0.66 mg/dL, $P < .001$), BMI (28.5 ± 4.7 *v* 27.9 ± 4.5 kg/m^2), and waist to hip ratio (0.99 ± 0.1 *v* 0.98 ± 0.1) were slightly improved (Table 3 and Fig 2).

Supine systolic and diastolic blood pressure changed from a baseline (month 0) of 143.0 ± 14.0 mm Hg to 140.5 ± 12.4 mm Hg at 24 months and from to 82.3 ± 6.7 mm Hg baseline to 80.5 ± 7.7 mm Hg at 24 months. The percentage of patients with high blood pressure as defined previously decreased from 38.5% to 30.7% ($P < .001$; Table 3). Concurrently, a mild increase in the prevalence of retinopathy was noted (10.2% *v* 11.8%). UAE was found to be unchanged (30.2% *v* 29.5%; Fig 2).

Some variables were not measured as rigorously as others throughout the course of the study. For example, FBG and blood pressure had a low rate of missing data at baseline (1% and 0.7%, respectively) and final evaluation (5% and 0.6%). Other parameters such as PPBG, HbA_{1c}, and lipid profiles had baseline missing-data rates of 14%, 25%, and 2.5%, respectively, and final evaluation missing-data, rates of 24%, 28%, and 10%.

DISCUSSION

The data presented in this study clearly indicate the ability of GPs to manage a cohort of newly diagnosed NIDDM patients according to standardized procedures. Both the clinical results and the rate of compliance with the protocol for patients

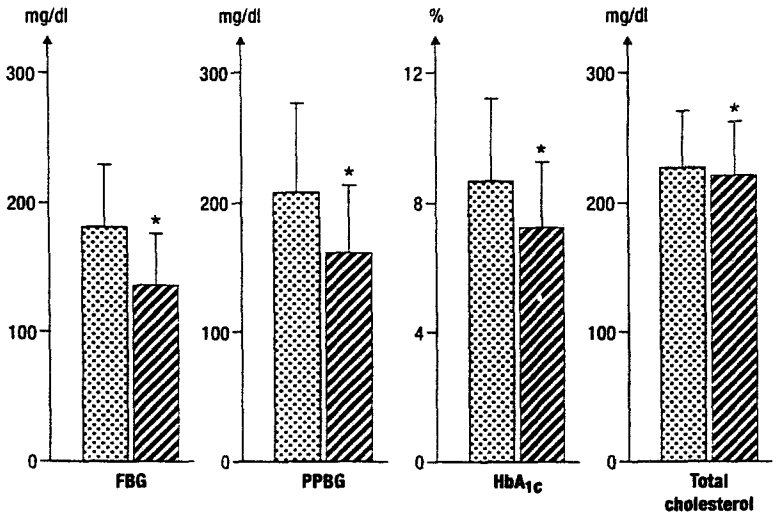

Fig 1. Metabolic characteristics (mean ± SD) at baseline (▒) and final evaluation (▨) in the Diadem Study population. *$P < .001$.

receiving gliclazide over 2 years were satisfactory. The withdrawal rate of 23% of the initially recruited patients was consistent with rates observed in other studies.[5,6]

In the assessable patients, mean values for FBG, PPBG, and HbA_{1c} were significantly reduced. The mean BMI decreased to a small extent. These results are in agreement with other studies[7-9] in which improved metabolic control of diabetes was achieved without weight gain in NIDDM patients. Some investigators[7,10,11] have emphasized the role of gliclazide in the increased sensitivity of peripheral tissues to insulin. However, these effects are probably due, in part, to changes in the life-style of patients, including an increase in physical activity and better dietary habits. The rate of side effects during the study was low, with a low incidence of hypoglycemic episodes even in elderly patients. Similar results have been observed by others,[12,13] and may characterize a specific effect of gliclazide on the release modalities of pancreatic insulin.[13,14]

Our data highlight the significant prevalence of microvascular and macrovascular diabetic complications at the time of diagnosis, together with the high percentage of patients with risk factors for CHD. The prevalence of retinopathy at diagnosis was estimated in our study to be 9.8%, whereas in other studies in Australia and Wisconsin the figures were 9.9% and 20.8%, respectively.[2] In a recent report from the United Kingdom Prospective Diabetes Study (UKPDS) group, 37% of newly diagnosed NIDDM patients had retinopathy in one eye and 18% had it in both eyes at the time of diagnosis.[15] The mild progression of retinopathy in our study may reflect the natural evolution of retinopathy as observed in the UKPDS. UAE was elevated in 29.6% of our patients, consistent with abnormal UAE rates of 20%[16] and 40%[17] found in similar recent prospective studies.

These findings highlight the problem of delayed diagnosis in NIDDM, which is an important factor in the development of diabetic vascular complications.[2,18] Early detection and management of NIDDM has become a major target for healthcare systems, where it is rapidly being realized as a costly and growing public health problem. In the United States and United Kingdom, diabetes accounts for approximately 13% and 5%, respectively, of healthcare expenditures.[19,20] This justifies the investigation of a new model for NIDDM management based in the primary care network and including GPs, nurses, dieticians, and social workers. GPs must be informed and trained to manage NIDDM patients according to protocols or national guidelines. A number of such schemes already exist.[21-23] In implementing such schemes more widely, it would be hoped to

Table 3. Cardiovascular Risk Factors in the Diadem Study Population at Baseline and 2 Years After Treatment (n = 4,265)

Risk Factor	Baseline	2 Years	*P*
BMI (kg/m²)*	28.5 ± 4.7	27.9 ± 4.5	.001
Waist to hip ratio*	0.99 ± 0.1	0.98 ± 0.1	.001
Hypertension (%)	38.5	30.7	.001
Duration of hypertension (yr)*	6.4 ± 5.5	—	—
Hyperlipidemia (%)	44.7	—	—
Duration of hyperlipidemia (yr)*	3.9 ± 4.4	—	—

*Mean ± SD.

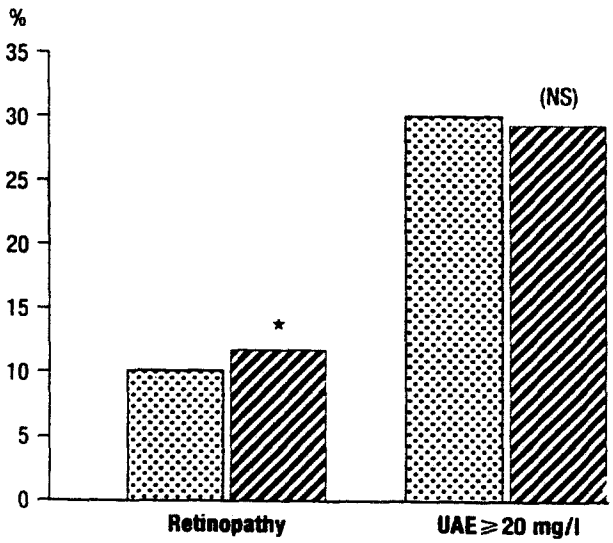

Fig 2. Prevalence (%) of microangiopathic complications at baseline (▒) and final evaluation (▨) in the Diadem Study population. *$P < .01$; NS, nonsignificant.

decrease the level of missing data and increase the quality of care for NIDDM patients.

Extending diabetes screening to the whole population would have low cost-effectiveness. The wider use of patient screening must be targeted to at-risk populations. Indeed, it has been proven that certain factors related to the insulin resistance syndrome are associated with diabetes. In this study, hypertension, hyperlipidemia, and obesity were found in nearly half of the patients and CHD was reported in 6.3% at the time of diagnosis. Our findings and those of other studies[24-26] thus allow us to propose these factors as predictors of diabetes. The dominant maternal role in the genesis of NIDDM[27,28] has also been confirmed by this study. Furthermore, the reported 6.5% incidence of women with a gestational history of hyperglycemia is probably not an incidental feature. Currently, there is no consensus on the diagnostic criteria of gestational diabetes. More investigation in this area may be necessary to evaluate whether it is one of the predisposing factors to NIDDM.[29]

In conclusion, management of NIDDM can be integrated into the regular activities of GPs, while the classic risk factors for NIDDM should be extended to include CHD and the maternal genetic component. Gliclazide treatment appears to be effective and well tolerated.

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