The Fasting Hyperglycaemia Study: III. Randomized Controlled Trial of Sulfonylurea Therapy in Subjects With Increased But Not Diabetic Fasting Plasma Glucose

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Self-referred subjects (N = 227) thought to be at increased risk of developing diabetes who had fasting plasma glucose (FPG) values in the range of 5.5 to 7.7 mmol · L^{-1} on two consecutive occasions 2 weeks apart were randomized to sulfonylurea therapy (gliclazide, ≤160 mg · d^{-1}) or to a control group allocated either to double-blind placebo or to no tablets. Subjects were randomly allocated also to reinforced or basic healthy-living advice in a factorial design. A total of 201 subjects have been evaluated for 1 year in three English and two French hospital outpatient centers. Those allocated to sulfonylurea had a significant ($P < .001$) reduction in median FPG compared with the control group (6.0 mmol · L^{-1} to 5.6 mmol · L^{-1}, $P < .001$, *v* 6.0 mmol · L^{-1} to 6.0 mmol · L^{-1}, NS). Median hemoglobin A_{1c} (HbA_{1c}) also improved ($P < .0002$; 5.8% to 5.6%, $P < .001$, *v* 5.7% to 5.6%, NS), as did mean β-cell function (62% to 70%, $P < .01$, *v* 62% to 61%, NS). Mean body weight was unchanged in subjects allocated to sulfonylurea (81.7 kg to 82.4 kg, NS), but decreased in the control group (81.6 kg to 80.4 kg, $P < .01$). More subjects in the sulfonylurea group versus the control group reported one or more minor symptoms of hypoglycemia over 1 year (50% *v* 24%, $P < .0001$). Only two subjects reported major hypoglycemic episodes requiring assistance, both of whom were taking sulfonylurea. Insulin sensitivity did not change between groups. Sulfonylurea therapy with gliclazide improved glycemic control and β-cell function significantly in subjects with increased but not diabetic FPG levels. The study is being extended to determine whether sulfonylurea therapy prevents progression to non-insulin-dependent diabetes mellitus (NIDDM).

IMPAIRED GLUCOSE TOLERANCE (IGT) is associated with a high risk (15% to 40% per decade) of developing non–insulin-dependent diabetes mellitus (NIDDM),[1-3] and with an increased incidence of heart disease similar to that of patients with NIDDM.[3-6] The general population is not routinely screened for IGT, since there is insufficient information on the benefits of intervention in preventing either the onset of NIDDM or its complications. It would seem appropriate to diagnose and treat NIDDM at an earlier stage, before diabetic complications ensue, given that half of the newly diagnosed NIDDM subjects recruited into the UK Prospective Diabetes Study had already developed tissue damage associated with diabetes.[7] Short-term studies have raised the possibility that healthy-living,[8] sulfonylurea,[9] or thiazolidinedione[10] therapy may improve glycemia, but whether pharmacological treatment would provide a longer-term benefit or lead to unacceptable side effects is uncertain. In a long-term Swedish trial[11] comparing tolbutamide and placebo, the onset of diabetes appeared to be delayed in 20 of 49 patients who continued with the allocated tolbutamide therapy. However, on an intention-to-treat analysis, there was no significant difference between tolbutamide and placebo therapies.

A 6-month pilot study[9] comparing sulfonylurea therapy and placebo tablets in subjects with IGT showed that sulfonylurea therapy reduced glycemia and increased β-cell function with little risk of hypoglycemia. This report presents a larger, 1-year prospective study of subjects with increased fasting plasma glucose ([IFG] ie, elevated but not diabetic fasting plasma glucose [FPG] in the range of 5.5 to 7.7 mmol · L^{-1}).[12] Subjects were randomized to sulfonylurea treatment (gliclazide) or to a control group taking either placebo or no tablets. The subjects were allocated also, in a factorial design, to reinforced or basic healthy-living advice, which is detailed in the previous report in this series.[13]

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SUBJECTS AND METHODS

Recruitment, Randomization, and Testing

Local ethics committee permission was obtained to recruit subjects in two French (Lyon and Toulouse) and three English (Exeter, Leicester, and Oxford) centers. In brief, 1,580 self-referred subjects with at least one risk factor for NIDDM had FPG measured. Those with IFG were retested.[12] A total of 293 subjects had IFG on two occasions, and 227 (78%) of these were randomized into this prospective study (Fig 1). Thirty-nine (13%) did not wish to enroll in the study, and 27 (9%) met the exclusion criteria. Those who joined the study were similar to those who did not: (mean ± SD) age, 50 ± 9 versus 50 ± 10 years (nonsignificant [NS]); 41% versus 39% male (NS); and median (interquartile range) FPG, 6.0 (5.8 to 6.4) mmol · L^{-1} versus 6.0 (5.8 to 6.4) mmol · L^{-1} (NS).

Following recruitment, subjects had a standard 75-g 2-hour oral glucose tolerance test (OGTT) to assess for diabetes on the basis of World Health Organization (WHO) criteria,[14] and a continuous infusion of glucose with model assessment (CIGMA)[15] to assess β-cell function (%β) and insulin sensitivity (%S) in random order with measurement of FPG, hemoglobin A_{1c} (HbA_{1c}), insulin, triglyceride, and cholesterol (ie, total, low-density lipoprotein [LDL], and high-density lipoprotein [HDL] cholesterol). Before all OGTT and CIGMA tests, subjects were requested to have normal meals for 3 days, to avoid strenuous exercise, and to attend fasting without taking any medication. CIGMA tests consisted of a continuous intravenous infusion of glucose (5 mg · kg^{-1} ideal body weight/min) with three venous blood samples taken at 5-minute intervals at baseline and at 1 hour.

Subjects ($N = 227$) were randomized to sulfonylurea therapy (50%)

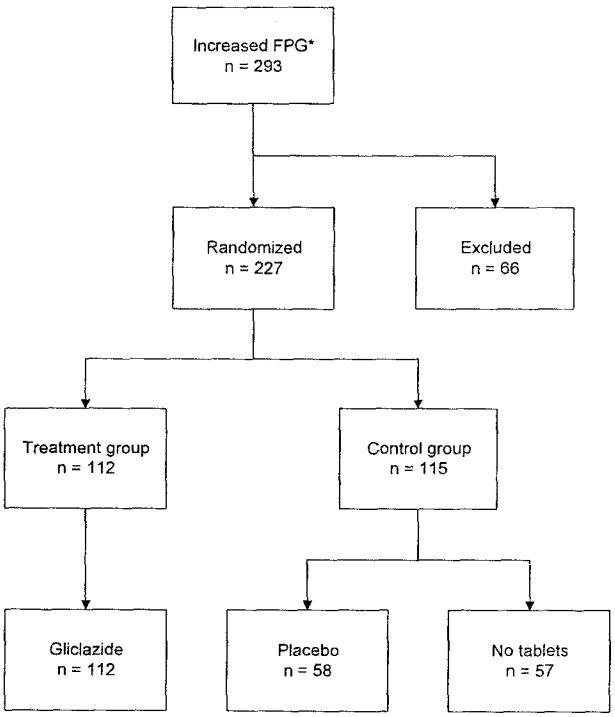

Fig 1. Recruitment and randomization of subjects. *On 2 consecutive occasions 2 weeks apart.

or to a control group (placebo 25% and no tablets 25%) and simultaneously, in a factorial design, to reinforced (50%) or basic (50%) healthy-living advice (Table 1). Those allocated to sulfonylurea began taking gliclazide 40 mg twice daily, increasing after 6 weeks to 80 mg twice daily if FPG remained at 5.5 mmol · L^{-1} or higher in the absence of symptoms of hypoglycemia. Therapy compliance was assessed by tablet count and self-reporting, and reported adverse events, including hypoglycemic episodes, were recorded. The gliclazide dose was reduced if FPG became less than 4 mmol · L^{-1} or hypoglycemia occurred.

After therapy was instituted, subjects were seen at 6 weeks, at 3 months, and thereafter every 3 months for determination of body weight, FPG, and blood pressure (BP), and for gliclazide dose adjustment. HbA_{1c}, insulin, triglyceride, and cholesterol (total, LDL, and HDL), were measured at baseline and repeated at 1 year, together with a repeat OGTT and CIGMA. A total of 201 (89%) subjects completed a 1-year follow-up evaluation.

Biochemical Methods

Clinic FPG measurements were performed by local laboratories monitored by a monthly three-level quality-assurance scheme, which

Table 1. Randomization to Treatment and Control Groups With Simultaneous Randomization to Healthy-Living Advice Groups

Group	Gliclazide Treatment*	Control*		Total
		Placebo	No Tablets	
Reinforced healthy-living advice	56	29	26	111
Basic healthy-living advice	56	29	31	116
Total	112	115		227

*Double-blind administration.

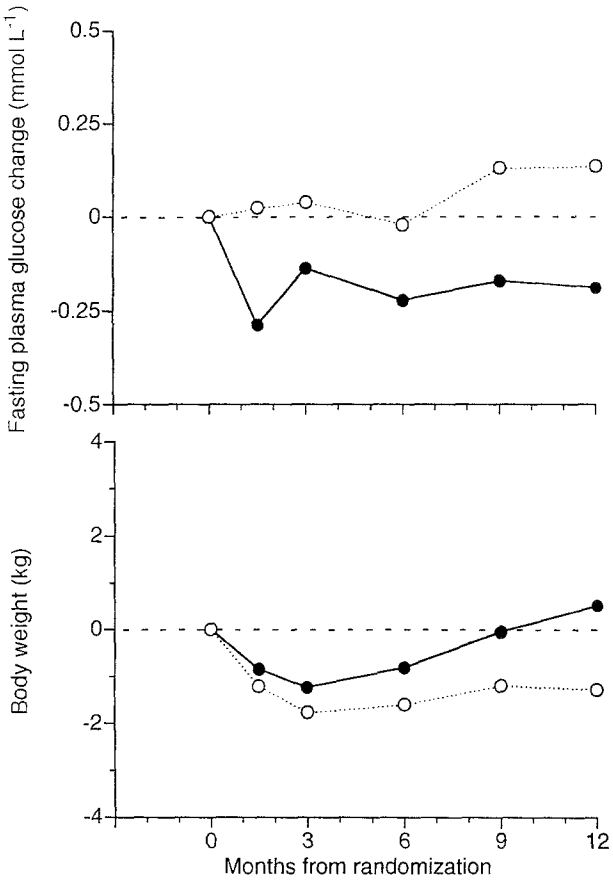

Fig 2. Mean changes in FPG and body weight at each clinic visit. (●) Gliclazide, (○) control.

maintained an overall coefficient of variation less than 4%. Blood samples for other analytes were forwarded overnight at 4°C to a central biochemistry laboratory where plasma glucose was measured during the OGTT and CIGMA in fluoride plasma by the hexokinase method, insulin by radioimmunoassay with a proinsulin cross-reactivity of 100%, C-peptide by radioimmunoassay, and HbA_{1c} by high-performance liquid chromatography with a laboratory reference range of 4.5% to 6.2%, and fructosamine was measured in heparinized plasma. Triglyceride and cholesterol levels were measured on a centrifugal analyzer by enzymatic calorimetric methods.[12,16]

Statistical Methods

Insulin sensitivity (%S) and β-cell function (%β), expressed as a percentage of normal, were calculated from the CIGMA 1-hour C-peptide and insulin levels, respectively.[15] The presence of diabetes was assessed from FPG and 2-hour OGTT plasma glucose values according to WHO criteria.[14] The area under the curve (AUC) was calculated by arithmetic trapezoidal integration. All analyses are by intention-to-treat unless stated otherwise. The data were analyzed using SAS[17] and are presented as the mean ± SD, with the median and interquartile range for glucose and HbA_{1c} and the geometric mean (1 SD range) for insulin, C-peptide, triglycerides, β-cell function, and insulin sensitivity. Within-group baseline and 1-year values were compared using the paired t test or Wilcoxon signed-rank test for continuous variables, with the sign test for categorical variables. Changes over 1 year were compared between groups using the two-sample t test or

Mann-Whitney U test for continuous variables and the Cochran-Mantel-Haenszel test with baseline adjustment for categorical variables.

Power calculations[18] showed that 214 subjects would be required to detect a 75% reduction in a 5%/yr rate of progression to NIDDM (FPG $\geq$ 7.8 mmol $\cdot$ L^{-1}) over 3 years with 80% power at $2P < .05$, assuming a withdrawal rate of 10%/yr.

RESULTS

The 227 subjects recruited into the study had a mean ($\pm$ SD) age of 50 $\pm$ 9 years, and 41% were male (Fig 1). They had a mean body mass index of 29.1 $\pm$ 4.8 kg $\cdot$ m^{-2}, median (interquartile range) FPG of 6.0 mmol $\cdot$ L^{-1} (5.8 to 6.4 mmol $\cdot$ L^{-1}), and HbA_{1c} of 5.7% (5.4% to 6.1%). There were no baseline differences between the sulfonylurea and control groups. A total of 201 subjects (89%) completed 1 year's follow-up study, with no difference between the sulfonylurea and control groups (89% v 88%, NS).

The responses in control group subjects who were randomly allocated to placebo or to no tablets were similar (data not shown) and were combined. Glycemic control as assessed by FPG improved over 1 year in the sulfonylurea group from a median of 6.0 mmol $\cdot$ L^{-1} to 5.6 mmol $\cdot$ L^{-1} ($P < .001$), while in the control group, there was no change (6.0 to 6.0 mmol $\cdot$ L^{-1}, NS, with a net difference between groups of 0.5 mmol $\cdot$ L^{-1} ($P = .0001$; Fig 2 and Table 2). A similar improvement was seen in the sulfonylurea group versus the control group for HbA_{1c} (net difference, 0.2%, $P = .0002$) and fructosamine (6 μmol $\cdot$ L^{-1}, $P = .03$). Initially, both groups decreased their mean body weight (Fig 2). However, by 1 year, there was no significant change from the baseline weight in the sulfonylurea group, while in the control group the mean body weight was 1.2 kg lower, resulting in a significant net difference of 1.8 kg ($P = .002$).

At 1 year, the OGTT glucose AUC was not different between those allocated to sulfonylurea or control (Fig 3). A trend to a greater proportion of subjects allocated to sulfonylurea with a diabetic 2-hour OGTT glucose versus the control group at 1 year was not significant. Two-hour OGTT glucose increased in the sulfonylurea group versus the control group (net difference, 1.0 mmol $\cdot$ L^{-1}, $P = .005$).

One-hour plasma glucose in the CIGMA test was significantly lower in the sulfonylurea group than in the control group (9.7 v 10.1 mmol $\cdot$ L^{-1}, $P = .006$), with no reduction in the concomitant geometric mean insulin level despite this lower glucose value. β-Cell function assessed by CIGMA increased in the sulfonylurea group but not in the control group, with a significant net difference between groups of 10% ($P = .02$). Insulin sensitivity did not change between groups.

Mean total cholesterol and LDL cholesterol decreased in both groups, with a greater net LDL cholesterol decrease in the sulfonylurea group (0.1 mmol $\cdot$ L^{-1}, $P = .02$). No significant changes were seen in mean HDL cholesterol or triglyceride levels. Systolic BP decreased in those allocated to sulfonylurea,

Table 2. Within- and Between-Group Changes From Baseline to 1 Year

	Sulfonylurea				Control				Comparison	
Parameter	No.	Baseline	1 yr	Δ (95% CI)	No.	Baseline	1 yr	Δ (95% CI)	Net Difference‖	P¶
FPG (mmol $\cdot$ L^{-1})#	100	6.0	5.6	−0.4 (−0.5-−0.2)‡	99	6.0	6.0	0.1 (−0.1-0.3)	−0.5	.0001
1-h CIGMA glucose (mmol $\cdot$ L^{-1})#	99	10.1	9.7	−0.5 (−0.7-−0.2)‡	99	10.1	10.1	0.0 (−0.2-0.3)	−0.5	.006
HbA_{1c} (%)#	94	5.8	5.6	−0.2 (−0.3-−0.2)‡	94	5.7	5.6	0.0 (−0.1-0.1)	−0.2	.0002
Fructosamine (μmol $\cdot$ L^{-1})	98	222	218	−4 (−8-0)†	97	223	225	2 (−2-5)	−6	.03
Weight (kg)	98	81.7	82.4	0.6 (−0.3-1.6)	100	81.6	80.4	−1.2 (−2.0-−0.4)†	1.8	.002
Fasting plasma insulin (pmol $\cdot$ L^{-1})§	100	73	75	0 (−10-10)	98	70	68	0 (−8-7)	0	NS
Systolic BP (mm Hg)	99	123	120	−3 (−5-0)*	100	120	121	1 (−2-3)	−4	.04
Diastolic BP (mm Hg)	99	76	76	0 (−2-1)	100	77	78	1 (−1-3)	−1	NS
OGTT 2-h glucose (mmol $\cdot$ L^{-1})#	97	8.2	9.2	0.6 (0.2-1.1)†	96	9.2	8.1	−0.4 (−0.9-0.2)	1.0	.005
OGTT AUC (mmol $\cdot$ L^{-1} $\cdot$ m^{-1})	94	468	496	28 (−1-56)	92	476	464	−12 (−44-20)	40	NS
WHO status, DM (%)	97	25	27	2	96	27	24	−3	5	NS
β-Cell function (%β)§	98	62	70	10 (4-16)†	96	62	61	0 (−4-5)	10	.02
Insulin sensitivity (%S)§	98	55	61	2 (−10-13)	97	51	57	9 (2-15)*	−7	NS
Total cholesterol (mmol $\cdot$ L^{-1})	99	5.0	4.8	−0.2 (−0.4-−0.1)†	97	4.9	4.7	−0.2 (−0.3-0.0)*	0.0	NS
HDL cholesterol (mmol $\cdot$ L^{-1})	99	1.12	1.11	−0.02 (−0.05-0.01)	97	1.12	1.12	0.01 (−0.03-0.05)	−0.03	NS
LDL cholesterol (mmol $\cdot$ L^{-1})	99	3.2	3.0	−0.2 (−0.3-−0.1)‡	97	3.1	3.0	−0.1 (−0.2-0.0)*	−0.1	.02
Triglyceride (mmol $\cdot$ L^{-1})§	99	1.21	1.16	0.00 (−0.15-0.15)	97	1.22	1.14	−0.12 (−0.28-0.04)*	0.12	NS

NOTE. Two-hour OGTT categorized by WHO criteria[15] for diabetes mellitus (DM). Data are shown as the mean difference (95% CI).

*$P < .05$, †$P < .01$, ‡$P < .001$: paired t test, Wilcoxon signed-rank test, or sign test.

§Geometric mean baseline and 1-yr values.

‖Net difference between groups (Δ sulfonylurea − Δ control).

¶t test, Mann-Whitney U test, or Cochran-Mantel-Haenszel test to compare 1-yr differences between groups.

#Median baseline and 1-yr values.

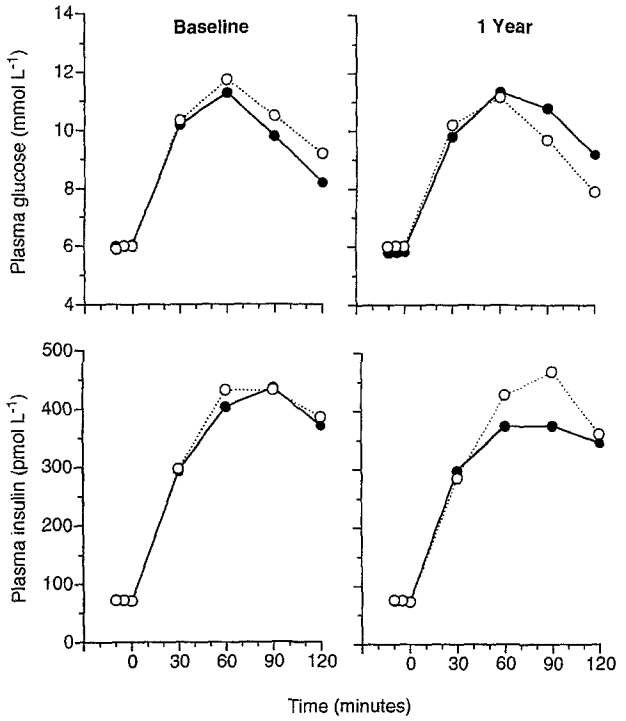

Fig 3. Baseline and 1-year OGTT median plasma glucose and geometric mean insulin values. (●) Gliclazide, (○) control.

with a net difference of 4 mm Hg at 1 year, although this was not significant after baseline adjustment.

At 1 year, 74% of subjects in the sulfonylurea group reported taking the maximum permitted gliclazide dose of 160 mg · day^{-1}, 4% 120 mg · d^{-1}, 12% 80 mg · d^{-1}, and 1% 40 mg · d^{-1}. The proportion of patients who reported taking the tablets did not differ between sulfonylurea and control groups (91% *v* 92%, NS).

Minor hypoglycemic episodes were reported more commonly by subjects in the sulfonylurea group than in the control group (50% *v* 24%, $P < .0001$; Fig 4). The number of hypoglycemic episodes reported decreased during the study, with no significant differences between the groups at 1 year. In the control group, those allocated to placebo tablets reported hypoglycemic episodes more commonly than those allocated to no tablets (33% *v* 16%, $P = .03$), but this difference was not significant after correction for baseline differences. Three major hypoglycemic episodes (requiring assistance) were reported by two subjects taking gliclazide. Two of these episodes occurred in one subject whose dietary intake was reduced.

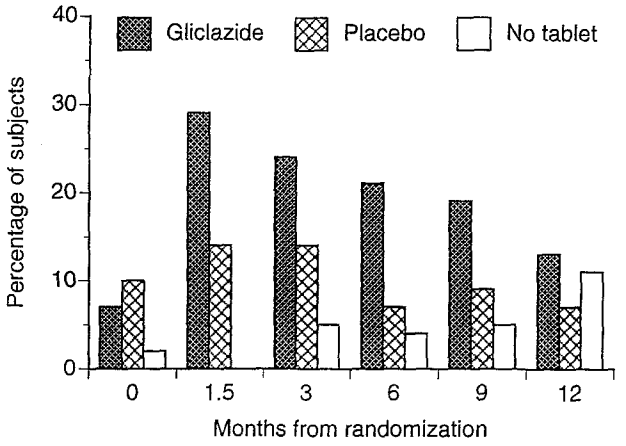

Fig 4. Percentage of subjects with self-reported minor hypoglycemic episodes.

DISCUSSION

This trial in subjects thought to be at increased risk of NIDDM and who had IFG on two consecutive occasions has shown that over 1 year sulfonylurea therapy with gliclazide improved glycemia, as assessed by FPG, HbA_{1c}, and fructosamine, and enhanced β-cell function. Compliance with therapy was high despite an increased occurrence of self-reported minor hypoglycemic episodes. Only two subjects reported major hypoglycemic events, and in one these were associated with inadequate food intake. The percentage of subjects reporting hypoglycemia decreased during the year even though the mean sulfonylurea dose had increased.

The maintained reduction of 0.5 mmol · L^{-1} FPG and 0.2% HbA_{1c} seen with sulfonylurea therapy was associated with a net increase in body weight of 1.8 kg compared with the control group, a small reduction in LDL cholesterol, but no changes in HDL cholesterol or triglyceride. Sulfonylurea therapy improved glycemia in a similar manner to that induced by tolbutamide in the Malmohus study,[11] which showed that glycemia returned to previous higher levels when tolbutamide was stopped. In the current study, the glucose response to the CIGMA test, which induces glucose concentrations similar to those following meals, was improved by sulfonylurea therapy. Although the OGTT 2-hour glucose value increased in those allocated to gliclazide compared with controls, the proportion classified as diabetic by OGTT criteria did not increase.

Only long-term studies can determine whether sulfonylurea therapy will decrease the progression to diabetes or the onset of diabetes-related tissue damage. Sulfonylurea therapy may be advantageous in enhancing β-cell secretion in subjects with IFG, since progression to diabetes is accompanied by deteriorating β-cell function.[19-21] It is conceivable that maintaining near-normoglycemia with sulfonylurea therapy might decrease glycemia-induced β-cell pathology.[22] Alternatively, long-term therapy with sulfonylurea might be disadvantageous, although the Malmohus,[1] Whitehall,[1] and Bedford[23] studies gave no indication of this. The Fasting Hyperglycaemia Study is being extended to 6 years' follow-up study to assess whether progression to diabetes is retarded.

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