

U.K. Prospective Diabetes Study

II. Reduction in HbA_{1c} with Basal Insulin Supplement, Sulfonylurea, or Biguanide Therapy in Maturity-onset Diabetes

A MULTICENTER STUDY

SUMMARY

Newly presenting maturity-onset diabetic subjects were put on diet and if, after 3–4 mo, their fasting plasma glucose continued >6 mmol/L, they were randomized to three therapies: (1) continuing diet alone, (2) with additional sulfonylurea, or (3) with additional basal insulin supplement provided by ultralente insulin. Obese patients were also randomized to metformin therapy. The aim was to lower the fasting plasma glucose to <6 mmol/L and the degree to which this reduced the hemoglobin A_{1c} (HbA_{1c}) concentration was studied in 195 patients over 1 yr. Sulfonylurea and insulin similarly reduced ($P < 0.001$) the fasting plasma glucose from 8.3 ± 1.9 to 6.7 ± 1.3 mmol/L (mean \pm 1 SD) and 8.6 ± 2.2 to 6.8 ± 1.4 mmol/L, respectively. This was accompanied by a significant reduction ($P < 0.001$) of the HbA_{1c} to the high normal range, from $9.1 \pm 2.1\%$ to $7.8 \pm 1.2\%$, and from $9.1 \pm 1.9\%$ to $8.1 \pm 1.3\%$, respectively, both values at 1 yr being significantly ($P < 0.05$) lower than in patients randomized to diet alone. Patients randomized to diet alone had little change in

fasting plasma glucose (8.6 ± 1.8 to 9.3 ± 2.3 mmol/L) or HbA_{1c} ($8.8 \pm 1.7\%$ to $9.1 \pm 1.6\%$, respectively). Thus, the simple therapeutic aim of trying to reduce the fasting plasma glucose to <6 mmol/L is an effective means of reducing the HbA_{1c} to a high-normal level. The HbA_{1c} and fasting plasma glucose concentrations were similarly related for all three therapies (HbA_{1c} [%] = $0.47 \times$ fasting plasma glucose [mmol/L] + 4.7). If the fasting plasma glucose concentration after dieting was >10 mmol/L, maximal-dose sulfonylurea therapy rarely reduced the fasting plasma glucose to 6 mmol/L and such patients could be started on maximum sulfonylurea therapy. Similar patients randomized to a basal insulin supplement alone required high insulin doses (mean 25 U/day), and also had mean fasting plasma glucose and HbA_{1c} levels above the normal range. DIABETES 1985; 34:793–98.

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Modification of the diet and increased exercise are accepted as the primary treatments of maturity-onset diabetes. However, most patients continue to have raised fasting plasma glucose concentrations, and there is little evidence available to determine whether one should continue with diet alone, and accept the hyperglycemia, or add sulfonylurea, biguanide, or insulin to improve diabetes control. The fasting plasma glucose is a stable, repeatable measure of control in diet-treated patients^{1–3} and sulfonylurea therapy can be used to reduce the fasting plasma glucose to <6 mmol/L^{4,5} with an accompanying reduction in HbA_{1c}.^{5,6} An alternative therapy is to lower the fasting plasma glucose with a basal insulin supplement provided by the long-acting ultralente insulin.⁷ Ultralente insulin and sulfonylurea therapies have been shown to be similarly effective in reducing the fasting plasma glucose to <6 mmol/L.^{4,8}

This article investigates the extent to which diet, insulin, sulfonylurea, and biguanide therapies reduce the HbA_{1c} to normal. The degree to which, with these different therapies, the fasting plasma glucose is a reliable indicator of diabetes control is assessed. The efficacy of sulfonylurea and insulin

TABLE 1

Fasting plasma glucose and HbA_{1c} measurements (mean ± 1 SD) in 179 nonobese and obese main randomization patients at the therapy decision when the different therapies were started, and between 6 and 12 mo later

Randomized therapy allocation	N	Fasting plasma glucose (mmol/L)		HbA _{1c} (%)	
		Therapy decision	Mean + 6, 9, and 12 mo later	Therapy decision	Mean + 6, 9, and 12 mo later
Diet only	57	8.6 ± 1.8	9.3 ± 2.3 NS	8.8 ± 1.7	9.1 ± 1.6 NS
Sulfonylurea	72	8.3 ± 1.9	6.7 ± 1.3 P < 0.001	9.1 ± 2.1	7.8 ± 1.2 P < 0.001
Insulin	50	8.6 ± 2.2	6.8 ± 1.4 P < 0.001	9.1 ± 1.9	8.1 ± 1.3 P < 0.001

The 16 patients randomized to metformin are not included. The significance of the changes is from paired *t*-tests.

therapy in patients with different degrees of hyperglycemia is reported.

MATERIALS AND METHODS

Entry to study.

Patients aged 25–65 yr inclusive with recently diagnosed diabetes (main criterion fasting plasma glucose >6 mmol/L on two occasions) were asked if they wished to participate in a prospective study. They were told that there is uncertainty which therapy is best if diet alone fails to control their diabetes, and that the decision would then be randomized. Exclusions were patients with ketonuria, myocardial infarction in the previous year, angina, heart failure, more than one major vascular episode, serum creatinine >175 µmol/L, severe retinopathy requiring photocoagulation, malignant hypertension, an uncorrected endocrine abnormality, an occupation that would not allow randomization to insulin therapy (e.g., heavy goods vehicle driver), a severe intercurrent illness likely to limit life (e.g., cancer) or requiring extensive systemic treatment (e.g., ulcerative colitis), and inadequate comprehension to allow cooperation. If reasonable, diuretics and estrogen therapy were stopped before assessment.

Patients were advised to take a "prudent" diet, containing approximately 50% carbohydrate, low saturated fat, and moderately high fiber, of energy content to attain ideal body weight. They were initially seen at monthly intervals, usually by a dietitian as well as a doctor.

Main randomization. At 3 mo, three fasting plasma glucose estimations were taken for a "therapy decision." If the mean was >7 mmol/L, patients were randomized according to a decision in a sealed envelope with stratification according to whether the weight was < or >20% of ideal weight.⁹ If the fasting plasma glucose was borderline (6–7 mmol/L), the patient was kept on diet alone for a further month and then randomized if a mean of two fasting plasma glucose concentrations was >6 mmol/L. In this "main randomization," nonobese patients were randomized: 30% to diet alone, 30% to insulin, 20% to chlorpropamide, and 20% to glibenclamide. Obese patients had the same proportional allocation with an additional group randomized to metformin (proportions: 24% to diet alone, 24% to insulin, 16% to chlorpropamide, 16% to glibenclamide, and 20% to metformin).

The patients in the main randomization were mean age 52 yr, 64% being male with a mean 118% overweight, and 36% female with a mean 136% overweight. The mean fasting plasma glucose was 11.8 mmol/L, 83% having a fasting

plasma glucose at presentation >8 mmol/L. The article reports 118 normal weight (<120% ideal weight) and 77 obese (>120% ideal weight) patients in the main randomization.

Insulin therapy. Patients randomized to insulin were started on ultralente insulin (beef Ultratard MC, Novo), the initial dose being calculated by subtracting three from the fasting plasma glucose in mmol/L, and multiplying by two to give the dose in U/day, with an increase of $x [(2.5 \text{ actual wt/ideal wt}] - 1.5)$ if the patient was obese.⁷ Patients were asked to maintain their normal prudent diet, but were not given specific rules on the size or timing of meals as usually required with short-acting insulin therapy. Patients were provided with dispos-

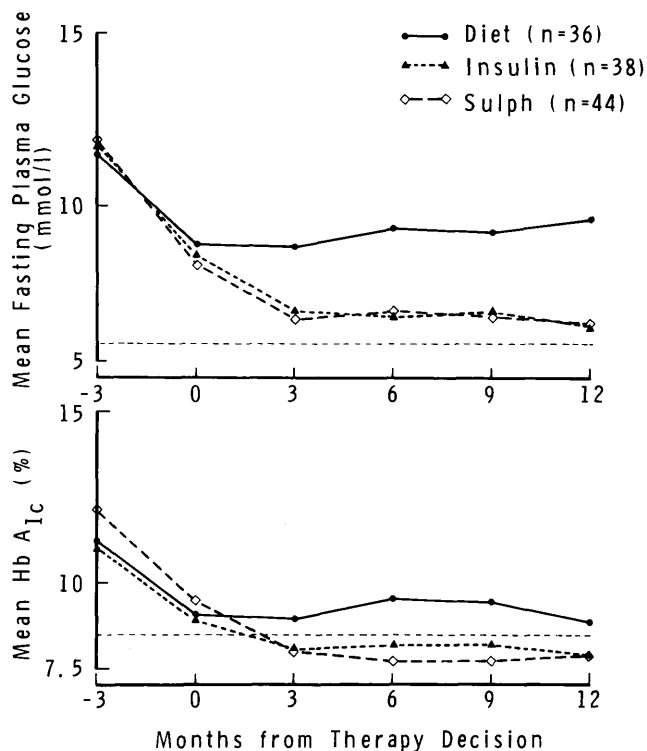


FIGURE 1. Mean fasting plasma glucose (top) and HbA_{1c} (bottom) of the 118 patients who were normal weight (<120% ideal weight) at therapy decision, with mean values at presentation, after 3-mo diet at therapy decision, and subsequently at 3-mo intervals during the next year. Those randomized to diet (●—●) had higher levels (P < 0.05) than those randomized either to insulin therapy (▲-----▲) or sulfonylurea (◇-----◇).

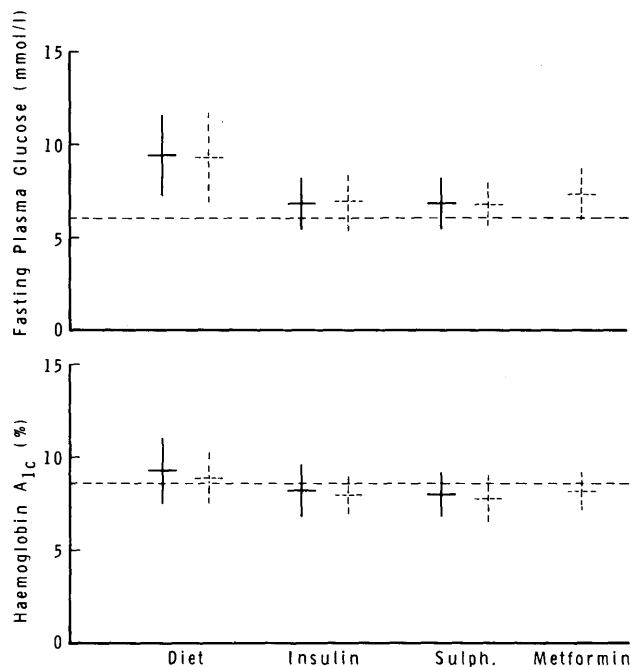


FIGURE 2. Fasting plasma glucose concentration (top) and HbA_{1c} (bottom) of the 195 patients after 1 yr on the different therapies (mean \pm 1 SD of 6-, 9-, and 12-mo values). The patients who were normal weight (<120% ideal body weight) at therapy decision are shown in continuous lines, and the obese (>120% IBW) in dotted lines. Insulin, sulphonyurea, or metformin therapy significantly reduced the fasting plasma glucose concentration and the HbA_{1c}, reducing the mean HbA_{1c} to the upper-normal range (5–8.5%).

able insulin syringes, and seen at once or twice-weekly intervals when the insulin dose was adjusted until the fasting plasma glucose became <6 mmol/L, and thereafter at 3-mo intervals. If the patient was receiving more than 12 U/day ultralente insulin, he was asked to do home blood glucose monitoring. If the premeal or prebed blood glucose concentrations were >7 mmol/L, the patient was put onto an ultralente and twice-daily soluble insulin regimen, although other insulins could be used if glucose control was not satisfactory.

Oral hypoglycemia agents. Doses were increased at once- or twice-weekly intervals, until the fasting plasma glucose became <6 mmol/L, to a maximum for chlorpropamide 500 mg once daily, for glibenclamide 10 mg twice daily, and for metformin 1700 mg at breakfast and 850 mg at the evening meal. Once a patient had a fasting plasma glucose of <6 mmol/L, or was on maximum therapy, 3-mo appointments were given. If on a sulphonyurea regimen either the fasting plasma glucose became >15 mmol/L or symptoms developed, metformin was added. If either of these criteria persisted, the patient was put onto insulin therapy. Patients randomized to metformin, who became poorly controlled by the same criteria, had additional glibenclamide therapy before transferring to insulin.

Diet therapy. All patients were seen every 3 mo, and continued to receive dietary advice, particularly if they remained overweight. Most patients were unable to comply and those randomized to insulin or sulphonyurea therapy increased their weight by a mean 2 kg over 1 yr, compared with no change in mean weight in those randomized to diet alone.⁸

Primary diet failure. After diagnosis, during the initial 3 mo

on diet before the main randomization, if either the fasting plasma glucose remained >15 mmol/L or symptoms (e.g., polyuria or thirst) persisted, a therapy decision termed "primary diet failure" was made using a separate series of randomization envelopes from the main randomization. The same obesity stratification and proportional allocation to therapies applied, except for the absence of a "diet only" group.

Recruitment to the clinical study started in 1977, and since 1980 venous blood samples, taken after an overnight fast, have been sent from the centers to Oxford for HbA_{1c} analysis at diagnosis, at therapy decision after 3–4 mo on diet, and subsequently at 3-mo intervals during the first year for HbA_{1c} analysis. The tubes were labeled with computer preprinted labels giving the number of the center, the patient's study number, and duration in the study, so that no accompanying paperwork was needed. The samples were sent in specially designed racks in expanded polystyrene boxes, with contents kept at -4°C with icepacks. The container was sent by Datapost or Securicor to Oxford with a guaranteed 24-h delivery.

This article examines all 195 patients who had HbA_{1c} assayed at therapy decision and at least twice out of the possible three visits at 6, 9, and 12 mo after the main randomization allocation to different therapies. All patients randomized to a therapy were analyzed for that allocation, even if a few patients were on a different therapy. Of those

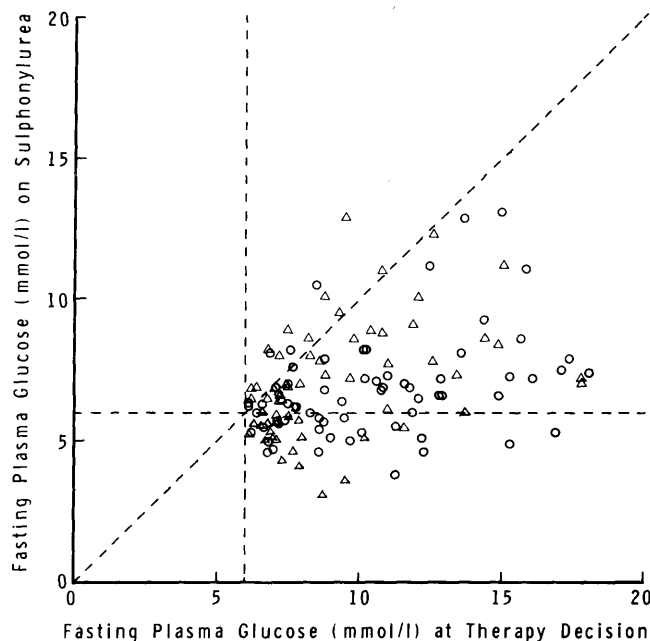


FIGURE 3. Comparison of the fasting plasma glucose responses in all patients randomized at either main randomization or primary diet failure to chlorpropamide (N = 71, \circ) and glibenclamide (N = 73, Δ) therapies. The abscissa shows the fasting plasma glucose at therapy decision (after 3-mo diet) and the ordinate shows the fasting plasma glucose concentration at 12 mo (or earlier if therapy was subsequently changed). If therapy had been ineffective and the fasting plasma glucose response had not changed, the individual patients' results would have been along the 45° line. The control criterion of fasting plasma glucose of 6 mmol/L is shown by the dotted lines. Nearly all patients have a reduced fasting plasma glucose concentration with therapy, but, if initial fasting plasma glucose concentrations were >10 mmol/L, it was unusual for the fasting plasma glucose to fall to <6 mmol/L with either therapy.

TABLE 2

The fasting plasma glucose and HbA_{1c} values for 179 patients randomized to diet, insulin, or sulfonylurea at 6, 9, and 12 mo after therapy decision, according to whether, at therapy decision before randomization, the diabetes control was stratified by the fasting plasma glucose (<8, 8–10, or >10 mmol/L) or the HbA_{1c} (<8, 8–10, or >10%) respectively

Stratification by glucose control at therapy decision before randomization	Fasting plasma glucose, mmol/L (N)			HbA _{1c} , % (N)		
	Diet	Insulin	Sulfonylurea	Diet	Insulin	Sulfonylurea
By fasting plasma glucose						
6–8 mmol/L	8.2 ± 2.2* (26)	6.4 ± 0.9 (27)	6.3 ± 0.7 (41)	8.6 ± 1.5 (26)	7.6 ± 0.8 (27)	7.3 ± 0.8 (41)
8–10 mmol/L	9.6 ± 1.8 (20)	6.5 ± 1.6 (11)	7.4 ± 1.6 (15)	9.1 ± 1.7 (20)	7.4 ± 1.1 (11)	8.2 ± 1.3 (15)
>10 mmol/L	11.4 ± 1.5 (11)	8.1 ± 1.6 (12)	7.4 ± 1.6 (16)	10.4 ± 1.3 (11)	9.6 ± 1.3 (12)	8.4 ± 1.4 (16)
By HbA _{1c}						
<8%	8.4 ± 2.3 (21)	6.2 ± 1.0 (19)	6.8 ± 1.3 (21)	8.1 ± 1.2 (21)	7.4 ± 0.8 (19)	7.6 ± 1.1 (21)
8–10%	9.7 ± 2.2 (23)	7.0 ± 1.4 (16)	6.5 ± 1.1 (25)	9.2 ± 1.6 (23)	8.2 ± 1.2 (16)	7.5 ± 1.2 (25)
>10%	10.2 ± 1.8 (13)	7.3 ± 1.7 (15)	6.9 ± 1.5 (26)	10.6 ± 1.3 (13)	8.7 ± 1.5 (15)	8.2 ± 1.2 (26)

*Mean ± 1 SD.

randomized to sulfonylurea, 2% had had metformin added and 2% had been transferred to insulin. Of those randomized to diet, 13% had been randomized as “secondary diet failures” to insulin, sulfonylurea, or biguanide. Nine percent of those randomized to insulin refused to take it and were continued on diet alone.

To assess the fasting plasma glucose response to sulfonylurea therapy at all levels of glycemia, all patients randomized to sulfonylurea (71 chlorpropamide, 73 glibenclamide) followed for 1 yr were studied, including patients classified as primary diet failure at therapy decision because of symptoms or a fasting plasma glucose >15 mmol/L after dietary therapy. To examine the efficacy of sulfonylurea alone, if a patient’s therapy was changed (either metformin added or changed to insulin) the fasting plasma glucose on the last occasion on the sulfonylurea alone was used for calculations.

For HbA_{1c} analysis, heparin blood samples were diluted 1:9 with normal saline and kept 5 h at 37°C to reverse short-term glucose adducts of HbA_{1c}.¹⁰ After centrifugation, the cells were hemolysed by addition of 0.01 M potassium cyanide, and the proportion of hemoglobin that had been glycosylated was assessed by isoelectric focusing.¹¹ The normal range (mean ± 2 SD) was 5–8.5%. Samples were assayed in duplicate (intraassay, coefficient of variation* assessed from duplicates 6.1%) and the between-assay coefficient of variation of quality control samples was 7.7%. Fasting plasma glucose measurements in the different centers were assessed by each center assaying four quality control plasma samples every month. The coefficient of variation was 5.2%, with the bias of individual centers being between –5.7% and +6.7%.

Statistics include: mean ± 1 SD, paired and nonpaired *t*-tests, and correlation coefficient *r*. The response of the fasting

plasma glucose to therapies in relation to the Therapy Decision value, the change in % ideal body weight, and dose was assessed by partial correlation analysis.

RESULTS

During the initial dietary period, before randomization to therapies, the percent ideal weight fell from 124 ± 21% to 117 ± 20%, the fasting plasma glucose fell from 11.8 ± 3.2 mmol/L to 8.5 ± 1.9 mmol/L, and HbA_{1c} from 11.4 ± 2.6% to 8.9 ± 1.9%. After therapy decision, there was little further change in either fasting plasma glucose or HbA_{1c} in the patients randomized to dietary therapy (Table 1). Sulfonylurea and insulin therapies similarly reduced both the fasting plasma glucose concentrations and the HbA_{1c} (*P* < 0.001). Figure 1 shows the change in mean fasting plasma glucose and HbA_{1c} concentrations in the normal weight diabetic subjects in the main randomization group. The values in each patient for the samples taken at 6, 9, and 12 mo showed little variation even though there were some changes in glucose control and therapy. The mean of the coefficients of variation of these results in each patient was 12.5% for the fasting plasma glucose in 116 patients with mean <8 mmol/L, and was 14.0% HbA_{1c} in the 105 patients with a mean <10%, the variation being very similar in patients on diet, insulin, or sulfonylurea.

Figure 2 shows that there was no difference between the achieved fasting plasma glucose and HbA_{1c} values of patients who were normal weight or obese (>120% ideal weight) at randomization. Both sulfonylurea and insulin therapies re-

TABLE 3

The relationship between the fasting plasma glucose (x) and HbA_{1c} (y) in 179 patients on diet, insulin, or sulfonylurea therapy, for a mean of the values at 6, 9, and 12 mo after therapy decision

Diet	y = 0.44x + 5.0	N = 57	r = 0.29
Insulin	y = 0.49x + 4.7	N = 50	r = 0.27
Sulfonylurea	y = 0.55x + 4.1	N = 72	r = 0.17

*Coefficient of variation (CV) from difference (diff) between N pairs of duplicates.

$$CV = (100 \times \sqrt{\sum \text{diff}^2 / 2N}) / \text{mean.}$$

duced the mean HbA_{1c} to the upper normal range, significantly ($P < 0.05$) better values than those obtained in patients randomized to continue on diet alone. On sulfonylurea, 81% (58/72) had a HbA_{1c} in the normal range, compared with 74% (37/50) on insulin and 40% (23/57) on diet. In the 16 obese subjects randomized to metformin therapy, the fasting plasma glucose was reduced ($P < 0.01$) from 8.6 ± 1.6 mmol/L to 7.2 ± 1.4 mmol/L and HbA_{1c} ($P < 0.05$) from $8.8 \pm 1.8\%$ to $8.0 \pm 1.0\%$. The fasting plasma glucose at 1 yr in patients randomized to metformin was significantly less ($P < 0.01$) than in obese patients randomized to diet alone and greater ($P < 0.05$) than those randomized to sulfonylurea.

Chlorpropamide and glibenclamide were equally successful in reducing fasting plasma glucose and HbA_{1c} results. Figure 3 shows the reduction in fasting plasma glucose concentrations in individual patients, in relation to their fasting plasma glucose value at therapy decision. There was considerable variation in the degree to which these sulfonylureas lowered fasting plasma glucose in different patients, which may partly be because of different adherence to diet during the study period. Thus, partial correlation analysis, taking into account the dose of drug and initial fasting plasma glucose concentration, showed a statistically significant correlation between the reduction of the fasting plasma glucose concentration and the change in weight during the first year ($r = 0.17$, $P < 0.02$). Only 9 of 57 patients with a fasting plasma glucose concentration of >10 mmol/L at therapy decision achieved a fasting plasma glucose concentration <6.0 mmol/L on sulfonylurea therapy, and no hypoglycemic reactions were reported.

The response of patients with different degrees of hyperglycemia was assessed by stratifying them by either their fasting plasma glucose or their HbA_{1c} at therapy decision. There was a very similar response to the different randomized therapies as judged by either variable at the end of 1 yr (Table 2). If the HbA_{1c} at therapy decision was stratified $<8\%$, $8-10\%$, and $>10\%$, respectively, compared with dietary therapy, the additional sulfonylurea or insulin therapies lowered it on the average by 0.6%, 1.3%, and 2.1% HbA_{1c}, respectively. The mean sulfonylurea doses for the patients with fasting plasma glucose >10 mmol/L, $8-10$ mmol/L, and <8 mmol/L were 15.9, 9.9, and 4.9 mg/day glibenclamide and 396, 238, and 199 mg/day chlorpropamide, respectively. Patients in the same glycemia groups who were randomized to insulin were treated by 24.7, 14.5, and 10.4 U/day, respectively. On the different therapies, the relationship between the fasting plasma glucose concentration and the HbA_{1c} concentration was similar (Table 3). If patients were stratified according to the fasting plasma glucose concentrations achieved by the therapies, there was similar stratification of their HbA_{1c} concentrations (Table 4).

DISCUSSION

These results confirm that the use of a simple fasting plasma glucose criterion of control of maturity-onset diabetic subjects, and aiming to reduce it to <6 mmol/L, is effective in lowering the HbA_{1c} concentration. This underlines the large part played by the raised fasting plasma glucose concentration of diabetes in determining the glycemic exposure,^{2,12} and the concordance between the height of fasting plasma

TABLE 4

The HbA_{1c} values at 6, 9, and 12 mo after therapy decision for 179 patients randomized to diet, insulin, or sulfonylurea stratified according to whether, at that time, the fasting plasma glucose concentration on different therapies was <6 , $6-8$, or >8 mmol/L

		Fasting plasma glucose (mmol/L) on different therapies		
		<6	$6-8$	>8
Diet	Mean (1 SD) HbA _{1c}	6.8	7.9 (0.9)	9.7 (1.6)
(N)		1	18	38
Insulin	Mean (1 SD) HbA _{1c}	7.5 (0.9)	8.0 (1.2)	9.4 (1.3)
(N)		16	25	9
Sulfonylurea	Mean (1 SD) HbA _{1c}	7.3 (1.1)	7.7 (0.9)	9.4 (1.3)
(N)		25	38	9

glucose concentration and the degree of postprandial glycemia.^{3,13} A significant correlation between the fasting plasma glucose and HbA_{1c} has previously been shown in diet-treated patients, but not in patients treated with oral agents or a basal insulin supplement.^{13,14} These results suggest that non-insulin-dependent diabetes can be monitored easily and effectively by fasting plasma glucose estimations at a clinic visit at only 3-mo intervals. This method applies equally to therapy with diet, sulfonylurea, biguanide, or a basal insulin supplement.

Reduction of the fasting blood glucose concentration to <6 mmol/L by sulfonylureas has been reported to give a mean HbA_{1c} (8.7%) just above the normal range.^{5,6} The different aim in this study of reducing the fasting plasma glucose to <6 mmol/L has reduced the mean HbA_{1c} to within the normal range, and the better control can be accounted for by the stricter criterion of plasma rather than blood glucose concentrations. The near-normal HbA_{1c} with a slightly high mean fasting plasma glucose of 6.3–6.5 mmol/L may partly be because the stress of coming to a clinic slightly raises the fasting plasma glucose above the true, overnight basal level.^{3,4} In addition, as HbA_{1c} measurements are moderately imprecise, the quoted normal range is likely to be larger than the actual normal range. As the prevalence of coronary heart disease rises markedly at the upper end of the normal glycemic range,^{15,16} one cannot be certain that the obtained degree of reduction of glycemia achieved by either sulfonylurea or a basal insulin supplement is sufficient to prevent the increased risk of coronary artery disease in diabetic subjects.¹⁷ It is doubtful if the glycemia could be much further reduced with the current medications without an unacceptable incidence of symptomatic hypoglycemia.

There is little available data concerning the degree of response of diabetic subjects to sulfonylurea or a basal insulin supplement. This study suggests that if the fasting plasma glucose concentration is >10 mmol/L in a patient who has dieted and who has no intercurrent infection, it is reasonable to start with the maximal sulfonylurea dose, as in most patients the fasting plasma glucose will not be reduced to <6 mmol/L, and there is minimal chance of provoking a hypoglycemic episode. If the fasting plasma glucose on diet alone is <10 mmol/L, or the HbA_{1c} $<10\%$, then usually either sulfonylurea or a basal insulin supplement reduces the HbA_{1c} to a high-normal range. If the levels are >10 mmol/L or

>10%, respectively, then neither therapy alone is effective in producing normoglycemia. The glycemia is too marked to respond to sulfonylurea, and neutral insulin to cover meals is needed in addition to a basal insulin supplement.¹⁸

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