United Kingdom prospective diabetes study (UKPDS) 13: relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years

United Kingdom Prospective Diabetes Study Group

The participating centres are listed at the end of this paper.

Abstract

***Objective*—To assess the relative efficacy of treatments for non-insulin dependent diabetes over three years from diagnosis.**

***Design*—Multicentre, randomised, controlled trial allocating patients to treatment with diet alone or additional chlorpropamide, glibenclamide, insulin, or metformin (if obese) to achieve fasting plasma glucose concentrations ≤6 mmol/l.**

***Setting*—Outpatient diabetic clinics in 15 British hospitals.**

***Subjects*—2520 subjects who, after a three month dietary run in period, had fasting plasma glucose concentrations of 6·1-14·9 mmol/l but no hyperglycaemic symptoms.**

***Main outcome measures*—Fasting plasma glucose, glycated haemoglobin, and fasting plasma insulin concentrations; body weight; compliance; and hypoglycaemia.**

***Results*—Median fasting plasma glucose concentrations were significantly lower at three years in patients allocated to chlorpropamide, glibenclamide, or insulin rather than diet alone (7·0, 7·6, 7·4, and 9·0 mmol/l respectively; $P<0·001$) with lower mean glycated haemoglobin values (6·8%, 6·9%, 7·0%, and 7·6% respectively; $P<0·001$). Mean body weight increased significantly with chlorpropamide, glibenclamide, and insulin but not diet (by 3·5, 4·8, 4·8, and 1·7 kg; $P<0·001$). A similar pattern was seen for mean fasting plasma insulin concentration (by 0·9, 1·2, 2·4, and −0·1 mU/l; $P<0·001$). In obese subjects metformin was as effective as the other drugs with no change in mean body weight and significant reduction in mean fasting plasma insulin concentration (−2·5 mU/l; $P<0·001$). More hypoglycaemic episodes occurred with sulphonylurea or insulin than with diet or metformin.**

***Conclusion*—The drugs had similar glucose lowering efficacy, although most patients remained hyperglycaemic. Long term follow up is required to determine the risk-benefit ratio of the glycaemic improvement, side effects, changes in body weight, and plasma insulin concentration.**

Introduction

A raised overnight basal plasma glucose concentration is characteristic of non-insulin dependent diabetes mellitus. In each person it is repeatable from night to night provided that the nutritional state is constant and the patient is in good health.[1] Fasting plasma glucose concentration is a simple and effective measure of control of diabetes.[2] Epidemiological studies suggest that the risk of diabetic retinopathy is raised in patients whose fasting plasma glucose is above 7·8 mmol/l.[3,4] Even slightly impaired glucose intolerance, in the upper 5% of the normal population distribution, is associated with increased deaths from cardiovascular disease.[5] These epidemiological data suggest that maintaining fasting plasma glucose concentration below 7·8 mmol/l may prevent microvascular complications but that fasting plasma glucose concentrations would need to be reduced to near normal to minimise the risk of macrovascular complications. The relevance of epidemiological studies to treatment of diabetes, however, is uncertain since the factors that induce macrovascular complications may be different in diabetic subjects, those with impaired glucose tolerance, and non-diabetic subjects with glucose tolerance in the upper range of the normal population.

The United Kingdom prospective diabetes study is a multicentre, prospective, randomised, intervention trial, started in 1977, which aims primarily to determine whether improved glycaemic control in non-insulin dependent diabetic patients will prevent diabetic complications and their associated morbidity and mortality.[6] The secondary aim is to evaluate whether any particular drug is better than treatment with diet alone. If diet alone is not sufficient to lower the fasting plasma glucose concentration to ≤6 mmol/l in newly diagnosed non-insulin dependent diabetes, reduction can often be achieved with a sulphonylurea (such as chlorpropamide[7] or glibenclamide[8]), metformin,[8] or a basal insulin supplement provided by ultralente insulin.[9] We report the relative efficacy of these drugs in 2520 patients.

Subjects and methods

A total of 6147 patients aged 25 to 65 years with newly diagnosed non-insulin dependent diabetes (fasting plasma glucose >6 mmol/l on two occasions) were referred to the study between 1977 and 1987. Subjects were excluded if they had severe vascular disease (myocardial infarction in the past year, current angina, or heart failure); accelerated hypertension; proliferative or preproliferative retinopathy; renal failure with plasma creatinine concentration >175 μmol/l; other life threatening diseases (such as cancer); an illness requiring systemic steroids (such as severe asthma); an occupation which precluded insulin treatment (such as bus driver); language difficulties; or ketonuria >3 mmol/l suggestive of insulin dependent diabetes. We excluded 1675 from the study but these patients had a similar mean age (52 (SD 8) years), sex distribution (58% men), and median fasting plasma glucose concentration (11·2 (interquartile range 8·2-15·1) mmol/l) to those recruited.

All patients recruited gave informed consent.

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During the three month run in period hormonal contraceptive pill or hormonal replacement therapy was stopped (if reasonable) and a loop diuretic (frusemide) was substituted for thiazides when appropriate. Subjects were seen monthly and advised to follow a diet containing about 50% carbohydrate, low saturated fat, and moderately high fibre, with reduced total energy content if obese. A further 397 patients were withdrawn because additional exclusion criteria were discovered or because of non-compliance during the run in period.

Of the 4075 remaining subjects, 560 continued to have fasting plasma glucose values above 15·0 mmol/l or hyperglycaemic symptoms, 746 successfully reduced their fasting plasma glucose to ≤6·0 mmol/l, and 2769 continued to have raised fasting plasma glucose concentrations of 6·1-14·9 mmol/l but no hyperglycaemic symptoms. These 2769 patients were entered into the randomisation. Of these, 249 were lost to follow up or died during the first three years of the study leaving 2520 subjects who are reported on here.

Subjects were stratified for obesity before randomisation to treatment in the following proportions: non-obese subjects—diet alone (30%), diet plus chlorpropamide (20%), diet plus glibenclamide (20%), diet plus insulin (30%); obese subjects (≥120% ideal body weight[10])—diet alone (24%), diet plus chlorpropamide (16%), diet plus glibenclamide (16%), diet plus insulin (24%), diet plus metformin (20%) (table I). All patients regularly received dietary advice, with most centres having a dedicated dietitian. The dietary principles published by the British Diabetic Association were followed.[11] Overweight subjects were advised to reduce their energy intake in proportion to the degree of obesity and usual food intake. Drugs were prescribed at each three monthly visit, at which time patients were asked specifically about compliance.

DIET

Patients randomised to diet only were seen every three months and received specialist dietary advice, repeated as necessary, aiming for further weight reduction if obese and weight maintenance otherwise. Patients in whom symptoms reappeared, or in whom fasting plasma glucose concentrations rose to ≥15·0 mmol/l were secondarily randomised to sulphonylurea, insulin, or biguanide in the same proportions as in the main randomisation. The doses were increased to avoid symptoms and to reduce the fasting plasma glucose concentration to below 15 mmol/l.

CHLORPROPAMIDE AND GLIBENCLAMIDE

Doses were increased once a week until the fasting plasma glucose value was ≤6·0 mmol/l or to a maximum of chlorpropamide 500 mg once daily or glibenclamide 10 mg twice daily. Once the fasting plasma glucose concentration was ≤6·0 mmol/l, or the patient was receiving maximum treatment, three monthly appointments were given. If the fasting plasma glucose rose to ≥15·0 mmol/l or symptoms developed metformin was added to a maximal dose of 850 mg three times a day if tolerated. If either of these glucose related criteria persisted the patient was transferred to insulin.

TABLE I—*Demographic details of 2520 newly diagnosed non-insulin dependent diabetic subjects after a three month run in period on diet alone. Values are mean (SD) unless stated otherwise*

	All	Non-obese	Obese*
No of patients	2520	1264	1256
Age (years)	52 (8)	53 (8)	52 (8)
No (%) men	1455 (58)	923 (73)	532 (42)†
Ethnic group No (%):			
White	2052 (81)	978 (78)	1074 (86)†
Asian	242 (10)	170 (13)	72 (5)
Afro-Caribbean	225 (9)	115 (9)	110 (9)
Median (interquartile range) fasting plasma glucose (mmol/l)	8·3 (7·3-9·9)	8·2 (7·3-9·9)	8·4 (7·4-10·0)
Glycated haemoglobin (%)	7·2 (1·5)	7·2 (1·5)	7·2 (1·4)
Body mass index	27·5 (5·1)	23·8 (2·0)	31·3 (4·5)
Body weight (kg)	76·6 (15·0)	68·1 (9·5)	85·2 (14·7)
Geometric mean (1SD range) fasting plasma insulin (mU/l)	12·6 (7·4-21·2)	10·2 (6·3-16·7)	15·4 (9·5-24·8)†
Randomisation:			
Diet alone	664	373	291
Chlorpropamide	446	259	187
Glibenclamide	472	260	212
Insulin	676	372	304
Metformin	262		262

*>120% Of ideal body weight.
†Significantly different from non-obese (P<0·0001).

INSULIN

Patients randomised to insulin were started on ultralente insulin (initially beef Ultratard MC and subsequently human Ultratard HM, Novo Nordisk, Pease Pottage, United Kingdom). The initial dose was calculated as (fasting plasma glucose −3) × 2 IU per day, with an appropriate increase if the patient was obese.[9] Patients were asked to maintain their prescribed diet but were not given specific rules on the size or timing of meals, since they usually did not require short acting insulin. Patients were seen initially once a week, when the insulin dose was adjusted until the fasting plasma glucose became ≤6·0 mmol/l. Thereafter they were seen at three monthly intervals. Any patients receiving more than 16 IU ultralente insulin a day, or proportionately more if obese, were asked to monitor their blood glucose concentration at home.[9] If blood glucose concentrations before meals or going to bed were >7·0 mmol/l additional soluble insulin two or three times a day was advised.[12] Other insulin formulations could be used if glucose control remained unsatisfactory.

METFORMIN

Patients randomised to metformin were started on 850 mg once a day. They were seen initially once a week, and the dose increased to 850 mg three times a day, or to the maximum tolerated, aiming at maintaining the fasting plasma glucose concentration at ≤6·0 mmol/l. If the fasting plasma glucose rose to ≥15·0 mmol/l or symptoms developed glibenclamide was added and the dose increased to the maximum tolerated or until the fasting plasma glucose concentration was ≤6·0 mmol/l. If the fasting plasma glucose again became ≥15·0 mmol/l, or symptoms recurred, the patient was transferred to insulin.

ASSESSMENT

All patients were asked at each three month visit whether they had experienced hypoglycaemic symptoms. The most severe episode for each period was recorded and graded as minor if the patient was able to treat the symptoms unaided or major if third party help or medical intervention was necessary. Details of all major hypoglycaemic episodes reported were audited centrally.

Fasting plasma glucose measurements were measured at the clinic with a monthly quality assurance scheme maintaining a coefficient of variation of <4%. Glycated haemoglobin concentration (HbA_{1c}) was assayed by high pressure liquid chromatography (normal range 4·5-6·2%[13]) and insulin by radioimmunoassay with 100% cross reactivity to proinsulin.[13]

STATISTICAL ANALYSES

Body mass index was calculated by dividing the weight in kilograms by the square of height in metres (kg/m^2). Annual data are presented as the median of three consecutive visits for each patient—that is, the annual visit, the preceding, and the following three monthly visit. All analyses are according to allocated treatment (intention to treat) unless stated otherwise. The Mann-Whitney U test or *t* test was used for group

comparisons and the χ^2 test for categorical comparisons with appropriate adjustments for small cell sizes. The Bonferroni method was used for multiple comparisons.

Results

At recruitment the median (interquartile range) fasting plasma glucose concentration was 11·2 (9·1-13·8) mmol/l, mean (SD) HbA_{1c} 9·1% (2·1%), mean body weight 80·4 (15·6) kg, and geometric mean (ISD range) fasting plasma insulin 13·7 (8·0-23·3) mU/l. During the three month dietary run in there was a significant reduction ($P<0·0001$) in fasting plasma glucose of mean (SD) 2·9 (3·1) mmol/l, HbA_{1c} 1·9% (2·0%), body weight 3·7 (3·5) kg, and fasting plasma insulin 1·3 (7·6) mU/l. At recruitment 1361 (54%) patients were hypertensive (systolic blood pressure >160 mm Hg or diastolic blood pressure >90 mm Hg or taking antihypertensive drugs) with a reduction to 1058 (42%) (410 (32%) non-obese, 648 (52%) obese) after two months' dietary intervention. No significant differences were seen at randomisation between the allocated groups in age, sex distribution, ethnic group, fasting plasma glucose, glycated haemoglobin, body weight, or fasting plasma insulin.

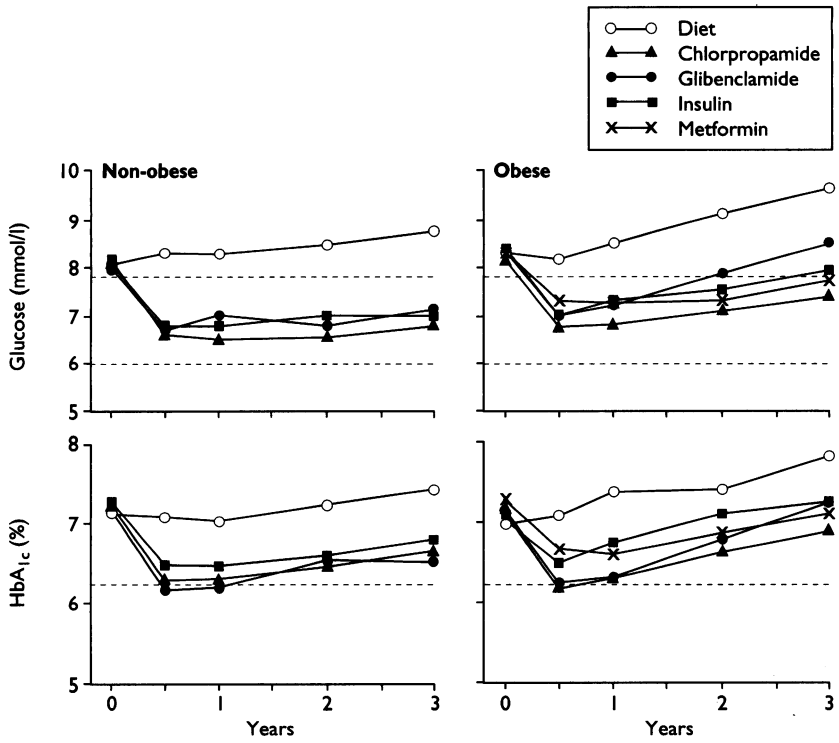

FIG 1—*Changes in median fasting plasma glucose and mean glycated haemoglobin concentration in non-obese subjects and obese subjects according to randomisation group. (The horizontal dashed lines in the upper panels indicate 6·0 and 7·8 mmol/l and in the lower panels, 6·2%.)*

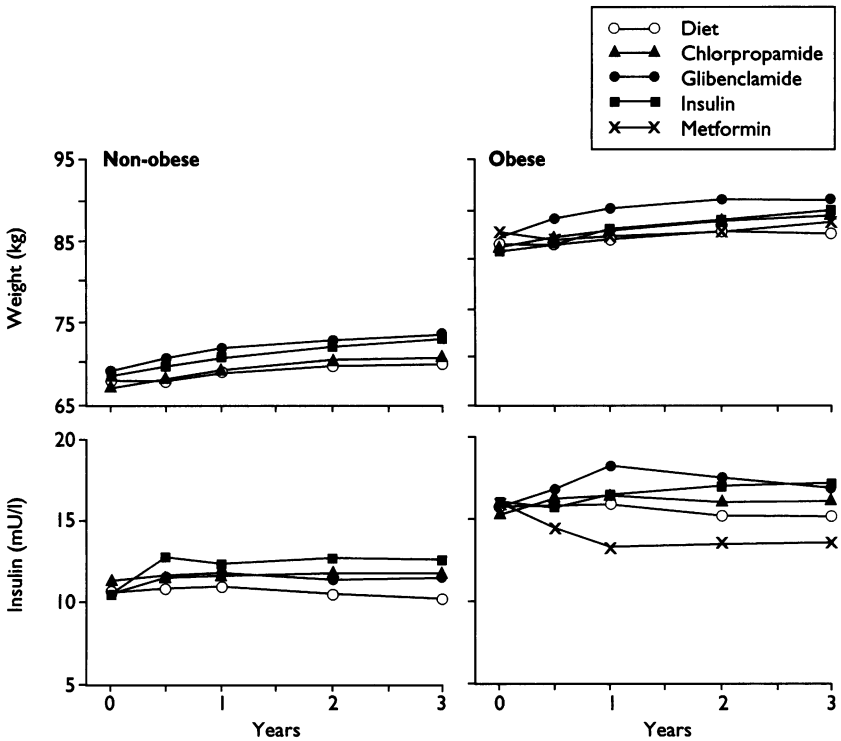

FIG 2—*Changes in mean body weight and geometric mean fasting plasma insulin in non-obese subjects according to randomisation group*

Median fasting plasma glucose concentrations fell in patients allocated to drug treatment compared with those allocated to diet alone (fig 1). Concentrations remained significantly lower ($P<0·001$) at three years: median (95% confidence interval) fasting plasma glucose concentrations (mmol/l) were 9·0 (8·8 to 9·3) for diet alone, 7·0 (6·8 to 7·2) for chlorpropamide, 7·6 (7·3 to 7·9) for glibenclamide, and 7·4 (7·2 to 7·6) for insulin. In obese patients allocated metformin fasting plasma glucose concentrations were similarly reduced but glibenclamide was significantly less effective ($P<0·001$) than chlorpropamide, with median values at three years being diet alone 9·6 (9·0 to 10·2), chlorpropamide 7·4 (7·1 to 7·8), glibenclamide 8·5 (7·9 to 9·1), insulin 7·9 (7·6 to 8·2), and metformin 7·7 (7·5 to 8·0) mmol/l.

Significantly lower mean glycated haemoglobin concentrations were seen in the patients allocated to drugs than in those allocated diet alone (fig 1). They remained significantly lower ($P<0·001$) at three years: diet alone 7·6% (7·4% to 7·7%), chlorpropamide 6·8% (6·6% to 6·9%), glibenclamide 6·9% (6·7% to 7·0%), and insulin 7·0% (6·9% to 7·1%). In non-obese subjects no significant differences were seen between the mean values obtained with chlorpropamide, glibenclamide, or insulin. In obese patients allocated metformin concentrations were similarly reduced, with mean values being diet alone 7·8% (7·6% to 8·0%) and metformin 7·1% (6·9% to 7·3%).

Mean body weight rose in all treatment groups (fig 2). At three years mean body weights (kg) were diet alone 77·1 (76·0 to 78·3), chlorpropamide 77·9 (76·5 to 79·3), glibenclamide 81·1 (79·7 to 82·5), and insulin 80·2 (79·1 to 81·4). In the obese group after three years' treatment those allocated to additional metformin were not significantly different from those allocated to diet alone (87·4 (85·3 to 89·5) *v* 86·2 (84·4 to 88·0) kg).

Geometric mean fasting plasma insulin concentrations were higher in patients allocated to drugs than those allocated to diet alone (fig 2). They remained significantly higher ($P<0·001$) at three years with geometric mean (95% confidence interval) fasting plasma insulin concentrations (mU/l) being diet alone 11·6 (11·1 to 12·2), chlorpropamide 13·0 (12·4 to 13·7), glibenclamide 13·3 (12·6 to 13·9), and insulin 14·1 (13·5 to 14·7) respectively. In obese patients allocated metformin fasting plasma insulin values (13·2 (12·4 to 14·1)) were significantly lower ($P<0·001$) than in those allocated to diet alone 14·8 (13·9 to 15·7).

COMPLIANCE

At three years 74% (275) of non-obese and 69% (214) of obese patients allocated to diet remained on diet alone (table II). Patients who developed hyperglycaemic symptoms or whose fasting plasma glucose concentrations rose to ≥15 mmol/l had higher fasting plasma glucose values at randomisation than those who were able to remain on diet alone (9·8 (8·5 to 11·7) *v* 7·8 (7·1 to 8·8) mmol/l; $P<0·0001$). Non-obese subjects who required drug treatment had a similar mean body mass index to those who remained on diet alone (23·4 (2·3) *v* 23·9 (1·8)) whereas obese subjects who required

drugs had a higher mean body mass index than those remaining on diet alone (33·0 (5·7) *v* 30·8 (4·1); P<0·001).

At three years 81% (419) of non-obese and 76% (305) of obese patients allocated to a sulphonylurea were taking sulphonylurea alone. This figure rose to 472 (91%) and 354 (89%) respectively when those taking additional metformin were included (table II). Fewer of the subjects allocated to chlorpropamide than those allocated to glibenclamide required additional drugs 39 (9%) *v* 63 (13%); P<0·05). Conversely, more subjects allocated to chlorpropamide refused to take it or had side effects, including ethanol induced flushing (57 (13%) *v* 35 (7%); P<0·01).

At three years 76% (282) of non-obese and 70% (214) of obese patients allocated insulin treatment were still taking it, the remainder having refused insulin treatment (table II). A total of 228 (61%) and 176 (58%) respectively were taking ultralente insulin alone, the remainder being on more complex insulin regimens.

At three years 79% (207) of obese patients allocated to metformin continued to take it (table II) with 88% (232) including those taking additional glibenclamide. Thirty (11%) refused metformin treatment or had unacceptable side effects.

RESPONSE TO TREATMENT

Figure 3 shows the response to treatment on the basis of intention to treat and actual treatment—that is, those who remained on their allocated monotherapy at three years. The results with the two approaches were similar, confirming that inclusion of patients who did not remain on their allocated therapy, because of non-compliance or addition of other drugs, had no important effects on the results.

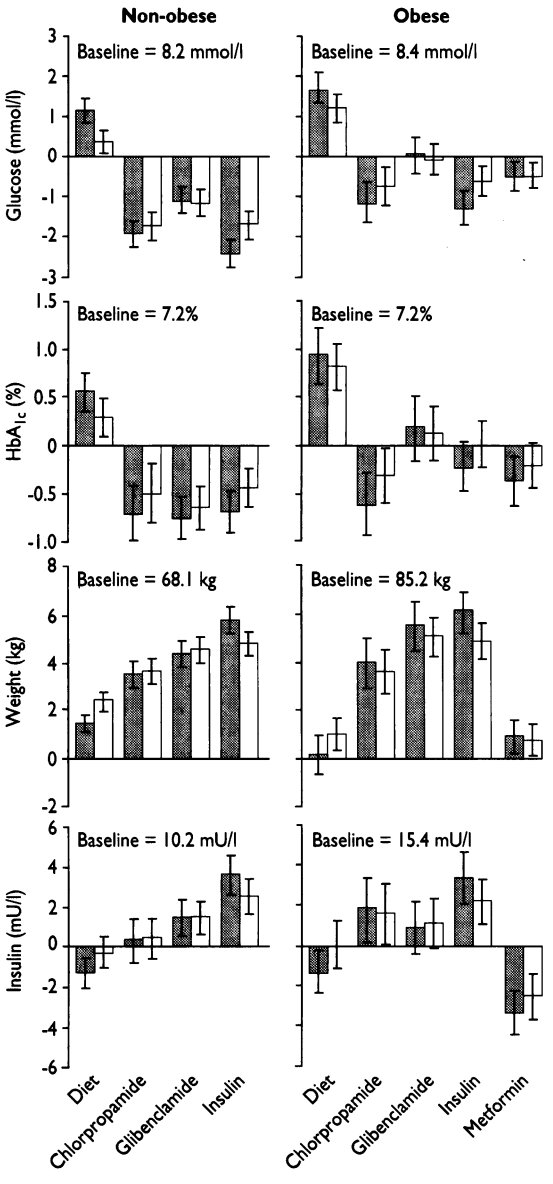

FIG 3—*Mean change (95% confidence interval) in fasting plasma glucose, glycated haemoglobin, body weight, and fasting plasma insulin from randomisation to three years in subjects remaining on their allocated monotherapy (shaded bars) or on an intention to treat basis (open bars)*

TABLE II—*Treatment at three years according to randomised treatment group*

	No (%) taking allocated monotherapy	No (%) requiring additional therapy	No (%) not taking allocated monotherapy
Diet alone (n=664):			
All subjects	489 (74)	188 (26)	
Non-obese	275 (74)	98 (26)	
Obese	214 (69)	90 (31)	
Chlorpropamide (n=446):			
All subjects	350 (78)	39 (9)*	57 (13)†
Non-obese	209 (81)	22 (8)*	28 (11)†
Obese	141 (75)	17 (9)*	29 (16)†
Glibenclamide (n=472):			
All subjects	374 (79)	63 (13)*	35 (7)†
Non-obese	210 (81)	31 (12)*	19 (7)†
Obese	164 (77)	32 (15)*	16 (8)†
Insulin (n=676):			
All subjects	404 (60)	92 (14)‡	180 (27)§
Non-obese	228 (61)	54 (15)‡	90 (24)§
Obese	176 (58)	38 (13)‡	90 (30)§
Metformin (n=262):			
Obese	207 (79)	25 (10)‖	30 (11)†

*Adding metformin and then changing to insulin if necessary.
†Tablet refusal or changed from allocated therapy—for example, because of side effects.
‡Multiple insulin.
‖Metformin failure, adding glibenclamide and then changing to insulin if necessary.
§Insulin refusal.

TABLE III—*Numbers (percentages) of patients allocated to each therapy who achieved different degrees of fasting plasma glucose control when on allocated therapy alone*

	Plasma glucose concentration (mmol/l)			
	<6·0	6·0-7·7	7·8-14·9	Not on randomised treatment
Non-obese:				
Diet alone	10 (3)	80 (21)	184 (49)	98 (27)
Chlorpropamide	73 (28)	85 (33)	52 (20)	50 (19)
Glibenclamide	53 (21)	78 (30)	77 (30)	48 (19)
Insulin	100 (27)	108 (29)	74 (20)	90 (24)
Obese:				
Diet alone	12 (4)	49 (16)	147 (48)	90 (32)
Chlorpropamide	40 (21)	52 (28)	48 (26)	46 (25)
Glibenclamide	29 (14)	38 (18)	96 (45)	48 (23)
Insulin	49 (16)	73 (24)	92 (30)	90 (30)
Metformin	29 (11)	85 (32)	93 (36)	55 (21)

The analysis of data from patients who were able to continue with their allocated treatment alone shows that, although sulphonylurea and insulin reduced fasting plasma glucose and glycated haemoglobin concentrations, they increased body weight and fasting plasma insulin concentration. In the obese subjects, however, metformin produced comparable reductions in fasting plasma glucose and glycated haemoglobin concentrations but did not induce weight gain and reduced fasting plasma insulin concentrations. Table III shows the proportion of patients receiving monotherapy at three years who were able to achieve fasting plasma glucose values <6·0 mmol/l (the study aim), <7·8 mmol/l (WHO criterion for diabetes), or <15·0 mmol/l (the study upper limit).

Hypoglycaemic episodes occurred most often in subjects taking ultralente insulin or glibenclamide (table IV). A total of 39% of non-obese and 31% of obese subjects taking complex insulin regimens reported hypoglycaemic episodes in the third year compared with 34% and 28% among those taking ultralente insulin alone. In patients with fasting plasma glucose values ≥10 mmol/l at randomisation, the incidence of hypoglycaemic attacks was twofold lower with sulphonylurea than with insulin. These patients received larger insulin doses and were more often given complex insulin regimens.

The excess of hypoglycaemic reactions with gliben-

TABLE IV—*Numbers (percentages) of patients in each year reporting one or more hypoglycaemic episodes of any severity, or one or more major episodes among those continuing to take monotherapy*

	Any hypoglycaemia				Major hypoglycaemia			
	Year 1	Year 2	Year 3	Mean %	Year 1	Year 2	Year 3	Mean %
Diet alone:								
All subjects	1 (0·6)	4 (1·6)	5 (1·6)	1·2	0	2 (0·8)	0	0·2
Non-obese	0	4 (2·8)	4 (2·3)	1·7	0	2 (1·4)	0	0·5
Obese	1 (1·4)	0	1 (0·8)	0·7	0	0	0	0
Chlorpropamide:								
All subjects	51 (15·3)	48 (14·4)	36 (10·7)	13·5	2 (0·6)	2 (0·6)	0	0·4
Non-obese	27 (13·5)	24 (12·1)	20 (9·9)	11·8	0	1 (0·5)	0	0·2
Obese	24 (18·0)	24 (17·9)	16 (11·9)	15·9	2 (1·5)	1 (0·8)	0	0·7
Glibenclamide:								
All subjects	129 (36·3)	95 (26·7)	73 (20·3)	27·8	7 (2·0)	5 (1·4)	2 (0·6)	1·3
Non-obese	77 (37·9)	54 (26·6)	43 (20·8)	28·4	4 (2·0)	3 (1·5)	1 (0·5)	1·3
Obese	52 (34·2)	41 (26·8)	30 (19·5)	26·8	3 (2·0)	2 (1·3)	1 (0·7)	1·3
Insulin:								
All subjects	131 (33·8)	136 (34·7)	126 (31·6)	33·4	5 (1·3)	6 (1·5)	6 (1·5)	1·4
Non-obese	75 (33·9)	82 (36·9)	77 (34·3)	35·0	4 (1·8)	2 (0·9)	3 (1·3)	1·3
Obese	56 (33·5)	54 (31·7)	49 (28·0)	32·2	1 (0·6)	4 (2·4)	3 (1·7)	1·5
Metformin:								
Obese	16 (8·2)	11 (5·7)	8 (4·1)	6·3	1 (0·5)	1 (0·5)	1 (0·5)	0·5

clamide compared with chlorpropamide occurred mainly in those patients with fasting plasma glucose values below 7·8 mmol/l at randomisation, with a preponderance of reactive hypoglycaemia after meals, usually late morning. In patients taking chlorpropamide, hypoglycaemic reactions tended to occur on waking. The proportion of patients taking sulphonylureas who had minor hypoglycaemic episodes fell significantly ($P<0·01$) during the study whereas the annual rate remained similar for those allocated insulin. Metformin was associated with fewer hypoglycaemic attacks than sulphonylurea or insulin but more than on diet alone. Major hypoglycaemic episodes were infrequent with all treatments.

Discussion

The subjects studied were probably representative of patients with non-insulin dependent diabetes in the United Kingdom, given the geographical spread of the centres and the eligibility for inclusion of all newly diagnosed patients referred by general practitioners. Ineligible subjects had a similar mean age, fasting plasma glucose concentration, and sex distribution as those who were recruited. Patients with a plasma glucose concentration above 6 mmol/l but who are symptom free often continue to be treated by diet alone. Our results show that it is clinically feasible to aim at achieving near normal fasting plasma glucose concentrations with the addition of sulphonylurea, ultralente insulin, or metformin. Glycaemic control was monitored by visits to a morning clinic for measurement of fasting plasma glucose, and the dose was increased if the fasting plasma glucose was raised. The treatment regimen is straightforward and could easily be used routinely in general practice.[2]

The long term aim of the study is to determine whether improved blood glucose control will prevent the complications of diabetes. Over the first three years only 23% of those allocated to diet had a fasting plasma glucose concentration below 7·8 mmol/l; values above this being associated with an increased risk of retinopathy and raised urine albumin excretion. By contrast, 53% of those taking drugs had a fasting plasma glucose concentration below 7·8 mmol/l. We found significant differences in fasting plasma glucose concentration (1·7 mmol/l) and glycated haemoglobin (0·7%) between those allocated to diet only and those allocated to drugs. Improved blood glucose control was associated with some side effects. Sulphonylureas and insulin induced weight gain and were associated with a significantly higher incidence of hypoglycaemia. It remains to be seen whether the long term benefits of tighter glycaemic control outweigh the higher incidence of side effects.

Subjects allocated to diet alone became more hyperglycaemic over the three years despite only a small increase in body weight in both obese and non-obese patients. However, if fasting plasma glucose values below 7·8 mmol/l need to be achieved to prevent complications, our data suggest that most patients with non-insulin dependent diabetes will need drug treatment.

CHOICE OF DRUG

The drugs that were studied had similar effects on fasting plasma glucose concentrations. Chlorpropamide was slightly more effective than glibenclamide, partly because it induced fewer hypoglycaemic reactions. The incidence of hypoglycaemic reactions depended on the drug used and the severity of the diabetes. Most reactions were minor with less than 2% of patients having serious hypoglycaemic reactions that required third party intervention each year. Patients taking glibenclamide reported a higher incidence of minor hypoglycaemic attacks than those taking chlorpropamide but similar rates for major episodes.

Ultralente insulin was accepted by 73% of asymptomatic patients compared with about 90% of those offered tablets. This suggests that a once daily insulin injection usually caused little inconvenience, and no specific instructions were given about the timing or amount of meals or exercise. The moderate weight gain in patients treated by insulin was similar to that in those treated with glibenclamide. These results suggest that insulin can be given to obese non-insulin dependent diabetic subjects without inordinate weight gain when it is administered mainly as a basal insulin supplement.

The obese subjects were slightly less responsive to treatments than the non-obese subjects and tended to have a greater increase in fasting plasma glucose and glycated haemoglobin. In the obese subjects metformin did not induce a weight gain but sulphonylurea or insulin was associated with an increase of 3-5 kg over three years. Metformin was slightly less effective in controlling the fasting plasma glucose concentration over the first six months, but the glycaemic reduction achieved was maintained over three years, possibly partly because of the lack of weight gain. Fasting plasma insulin concentrations increased with chlorpropamide (10·2%), glibenclamide (6·7%), and insulin (13·4%) but were reduced with metformin (16·5%), possibly due to increased expression of the glucose transporter GLUT1.[14] Epidemiological studies of the general population have shown a weak association between fasting insulin concentrations and subsequent heart disease,[15,16] but it is not clear whether the same relation pertains in diabetic subjects.

Key messages

- The most appropriate treatment for patients with non-insulin dependent diabetes is not known
- In this study after three years chlorpropamide, glibenclamide, insulin, and metformin were all more effective than diet alone with no differences in efficacy in reducing glycaemia
- Sulphonylureas and insulin tended to increase body weight, plasma insulin, and the risk of hypoglycaemia, whereas metformin did not affect weight, reduced insulin, and was associated with less frequent hypoglycaemia
- Long term follow up is required to determine the risk benefit ratio for each of these treatments

It is not possible to assess from the present data which treatment will be the most effective in the long term. While chlorpropamide and metformin seem to be the most effective in reducing hyperglycaemia with the least incidence of hypoglycaemic reactions, it is important to remember that in the only other large scale intervention study of diabetes, the University Group Diabetes Programme, the therapeutic allocations to a similar first generation sulphonylurea (tolbutamide) and a similar biguanide (phenformin) were ended because of a tendency to increase rather than decrease the incidence of major cardiovascular events.[17]

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Bottle feeding and the sudden infant death syndrome

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Abstract

***Objective*—To determine whether the risk of the sudden infant death syndrome is increased in bottle fed babies.**

***Design*—Population based case-control study matching for age and time.**

***Subjects*—All babies aged 1 week to 1 year dying of sudden infant death syndrome during November 1987 to April 1989 or February 1990 to June 1991 and two live controls.**

***Setting*—Avon and north Somerset.**

***Main outcome measures*—Breast or bottle feeding, sleeping position, maternal smoking, parental employment, and length of gestation.**

***Results*—Compared with being fully breast fed, the crude odds ratio for sudden infant death in fully bottle fed babies was 3·1 and for mixed breast and bottle fed babies 1·5. These odds ratios fell to 1·8 (95% confidence interval 0·7 to 4·8) and 1·2 (0·5 to 2·7) respectively after maternal smoking, parental employment, preterm gestation, and sleeping position had been adjusted for. Sleeping position partly masked the effect of being bottle fed on sudden infant death as breast fed babies were more likely to have slept prone than bottle fed babies.**

***Conclusions*—Bottle feeding is not a significant independent risk factor for the sudden infant death syndrome. Patterns of maternal smoking, preterm gestation, and parental employment status account for most of the apparent association with bottle feeding.**

Introduction

Over the past 25 years the effect of method of feeding on the risk of the sudden infant death syndrome has been analysed in 17 case-control studies[1-17] and one cohort study.[18] These studies were designed to investigate a variety of risk factors for the sudden infant death syndrome, including bottle feeding. Eleven studies[7-17] found an increased risk of sudden death in bottle fed babies and seven found no effect.[1-6 18] Reasons for such inconsistent results include different ways of measuring type of feeding and variations in the degree to which confounding factors were taken into account.

Bottle feeding is largely determined by social and cultural factors and is strongly associated with maternal smoking.[19 20] Of the 11 studies which found a positive association between being bottle fed and the sudden infant death syndrome, only two accounted for con-