The Fasting Hyperglycaemia Study: I. Subject Identification and Recruitment for a Non–Insulin-Dependent Diabetes Prevention Trial

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Subjects at increased risk for developing non–insulin-dependent diabetes mellitus (NIDDM) were encouraged via a public awareness campaign, general practitioners, or a direct approach (in the case of women with previous gestational diabetes) to attend one of three English and two French centers for fasting plasma glucose (FPG) measurement. Of 1,580 subjects (mean ± SD age, 47 ± 10 years), 29% were male, 56% had a diabetic relative, 20% had a history of elevated blood glucose or glycosuria, and 9% previously had gestational diabetes. Thirty-one percent (493) had an initial increased fasting glucose ([IFG] 5.5 to 7.7 mmol · L^{-1}), 3% (41) a diabetic fasting glucose ([DFG] ≥ 7.8 mmol · L^{-1}), and 66% (1,046) a normal fasting glucose ([NFG] < 5.5 mmol · L^{-1}). Four hundred forty-one of the 493 returned for a second FPG measurement, and 67% (293) of these had a similar value on repeat testing 2 weeks later. A 75-g, 2-hour oral glucose tolerance test (OGTT) in 223 of these subjects showed that 37% (83) had impaired glucose tolerance (IGT), 26% (58) diabetes mellitus (DM), and 37% (82) normal glucose tolerance (NGT). Seven percent of self-referred patients had NIDDM by World Health Organization (WHO) criteria. Eighty-eight percent of those with an initial DFG had an increased glycated hemoglobin (>6.2%), and 75% an increased fructosamine (>282 μmol · L^{-1}). While these two glycemic measures provided good discrimination for diabetes, neither were reliable in detecting those with increased but not diabetic FPG values. In conclusion, 293 (19%) of 1,580 self-referred subjects were identified as having persistently increased FPG, and 227 have been entered into a randomized NIDDM prevention trial evaluating healthy-living advice and sulfonylurea therapy.

NON–INSULIN-DEPENDENT diabetes mellitus (NIDDM) has an insidious onset, with hyperglycemia often remaining unrecognized for many years until symptoms develop or health checks reveal glycosuria or elevated blood glucose. Half of the newly diagnosed diabetic subjects recruited into the UK Prospective Diabetes Study (UKPDS) already had evidence of diabetes-related tissue damage.[1] Subjects with impaired glucose tolerance (IGT) have an increased risk of cardiovascular disease similar to those with NIDDM.[2-6] Earlier identification of individuals at risk of NIDDM may be advisable, since preventative measures could retard the progress to diabetes and may prevent or diminish the associated high morbidity and mortality.

Large-scale screening for potentially diabetic subjects poses significant practical and logistic problems. The oral glucose tolerance test (OGTT) is relatively complex and time-consuming and has poor reproducibility (coefficient of variation [CV], 15% to 20%[7,8]). Measuring fasting plasma glucose (FPG) is a simple alternative that provides an inexpensive and reproducible glycemic index in nondiabetic and diet-treated diabetic subjects.[9] We have defined increased fasting glucose (IFG) as a plasma glucose level of at least 5.5 mmol · L^{-1} but less than 7.8 mmol · L^{-1}, the World Health Organization (WHO) fasting criterion for diabetes.[10] This report describes the identification of subjects with IFG on two consecutive FPG measurements 2 weeks apart for inclusion in the Fasting Hyperglycaemia Study (FHS), a randomized intervention trial designed to determine whether progression to diabetes mellitus (DM) can be delayed or prevented. FHS subjects are allocated to basic or reinforced healthy-living advice[11] and, in a factorial design, to therapy with a sulfonylurea (gliclazide) or placebo.[12]

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SUBJECTS AND METHODS

Subject Recruitment

Ethics committee approval was obtained in three English and two French clinical centers. Subjects aged 30 to 65 years were recruited from groups believed to have an increased risk of developing NIDDM (ie, first-degree relatives of patients with NIDDM, women with a history of gestational diabetes, moderately obese people, and those with a history of hyperglycemia or glycosuria). General practitioners were invited to refer any potentially suitable subjects for glycemic testing. Permission was sought from general practitioners to approach their female patients who had previously recorded gestational diabetes. Patients with NIDDM attending outpatient clinics were asked to encourage their first-degree relatives to come forward. Dedicated weekend mornings for blood glucose testing were advertised in prominent public places, in newspapers, on buses, and on local radio.

Subjects attending for glycemic testing were asked to fast from 10 PM the previous night. Venous blood was taken for FPG determination, and in the three English centers, additional blood was taken for measurement of hemoglobin A_{1c} (HbA_{1c}) and fructosamine levels. Subjects and their general practitioners were informed of the result in writing within 1 week. Those with IFG (ie, 5.5 to 7.7 mmol · L^{-1}) were asked to return for a repeat FPG measurement; those with FPG in the diabetic range ([DFG] ≥ 7.8 mmol · L^{-1})[10] were informed that there was a likelihood of diabetes and advised to consult their general practitioner; and those with normal FPG ([NFG] < 5.5 mmol · L^{-1}) were informed that the result was normal and were referred back to their general practitioner (Fig 1).

Subjects who re-attended and were found to have IFG on two consecutive occasions were invited to join the FHS. They were excluded if they had severe hypertension (diastolic blood pressure [BP] > 105 mm Hg), significant renal or hepatic impairment (eg, serum creatinine > 175 μmol · L^{-1} or aspartate aminotransferase activity more than twice the upper limit of normal), symptomatic vascular

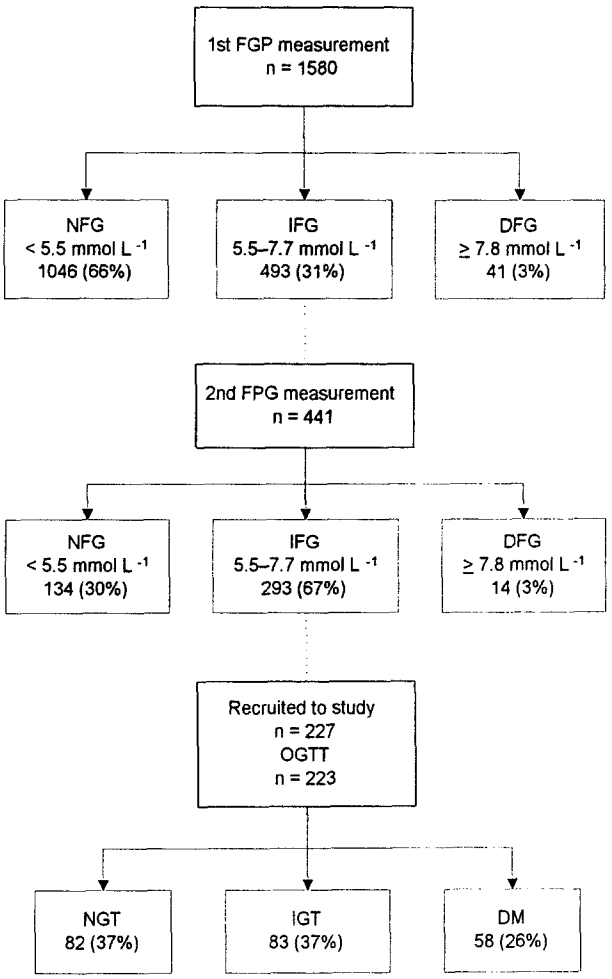

Fig 1. Procedure for identification of subjects for entry into the FHS. OGTT results per WHO criteria.[10]

disease (ie, angina or intermittent claudication), significant respiratory illness, severe intercurrent illness that either reduced the life expectancy (eg, cancer) or required extensive systemic treatment (eg, ulcerative colitis), treatment with any drugs likely to affect glucose homeostasis or weight (eg, thiazide diuretics, steroids, or appetite suppressants), or any medical condition that would limit participation in an aerobic exercise program (eg, severe generalized arthritis). Women of childbearing age not using contraception were also excluded; the use of oral contraceptives did not preclude entry to the study. Subjects who consented to join the study underwent clinical examination, biochemical risk factor assessment, and a 75-g 2-hour OGTT.[10]

Biochemical Methods

Venous blood for plasma glucose measurement was collected into fluoride oxalate vacutainers and then centrifuged within 2 hours, and the plasma was stored at 4°C. In the three English centers, additional heparinized whole blood was obtained for HbA_{1c} and fructosamine measurement. Samples from Exeter and Leicester were transported at 4°C overnight to the central biochemistry laboratory in Oxford for determination of glucose the following day and the other two analytes within 5 days. In the two French centers, glucose levels were measured in the hospital laboratories. A glucose quality-assessment scheme monitored performance at all sites. Glucose levels were measured in the central biochemistry laboratory by the hexokinase method (Gluco-quant glucose; Boehringer Mannheim, Sussex, UK) on a centrifugal analyzer (Cobas Bio; Roche Diagnostica, Herts, UK) with a CV of 1.8% at 10.5 mmol · L^{-1}. HbA_{1c} levels were measured by high-performance liquid chromatography (Biorad Diamat Analyser; Biorad Laboratories, Herts, UK) with a CV of 1.9% at 5.5%, and fructosamine levels by the Fructosamine Test Plus Kit (Roche Diagnostica, Herts, UK) on a centrifugal analyzer (Cobas Bio) with a CV of 3.1% at 272 μmol · L^{-1}. The central biochemistry laboratory normal reference range (central 95th percentile) for HbA_{1c} is 4.5% to 6.2%, and for fructosamine, 203 to 282 μmol · L^{-1}.[13] BP measurements were taken as the mean of three readings at 2-minute intervals (after discarding an initial reading) using a quality-assured electronic sphygmomanometer (Takeda).

Statistical Methods

All data were entered twice using a key-to-disk checking algorithm to avoid miskeying. Descriptive statistics were applied to check for outliers, anomalies, or nonparametric distribution of values. Two-hour 75-g OGTT plasma glucose values were categorized according to WHO criteria[10] as normal glucose tolerance (NGT), IGT, or DM. Subjects were classified as hypertensive if they had a BP of 150/90 mm Hg or above or were taking antihypertensive medication. Data were analyzed using the Statistical Analysis System (SAS)[14] with cross-tabulation, parametric or nonparametric comparison tests as required, and analysis of covariance, with correction for gender and ethnic group if appropriate.

RESULTS

Of the people who presented for glycemia testing, 1,580 (29% male) individuals aged 47 ± 10 years (mean ± SD) had an initial FPG measurement (Table 1). Of these, 67% were self-referred, 20% were encouraged to attend by a relative, and 11% had been referred by their general practitioner. Their reasons for coming forward were having a known relative with NIDDM (56%) or a history of elevated blood glucose or glycosuria (20%), being overweight (12%), or having experienced gestational diabetes (9%). Some subjects gave more than one reason for attending.

Categorization of the initial FPG measurement showed that 493 (31%) had IFG, 41 (3%) DFG, and 1,046 (66%) NFG (Table 1). Subjects with IFG and DFG were more commonly male ($P < .001$) and tended to be older than those with NFG ($P < .001$). Of 493 subjects with IFG, 441 (37% male) attended for a second FPG measurement that classified them as 293 IFG (67%), 14 DFG (3%), and 134 NFG (30%). Thus, 19% of the self-referred subjects evaluated had IFG on two occasions. Of the 293 subjects with IFG on two consecutive measurements, 227 fulfilled the FHS entry criteria and agreed to join the study, 39 were unwilling to enroll, and 27 were excluded. The 227 subjects recruited into the study had a mean age of 50 ± 9 years and 41% were male, similar to the 66 excluded subjects, who had a mean age of 50 ± 10 years and 39% were male.

There was a significant correlation of initial HbA_{1c} ($r_s = .42$, $P < .001$) and fructosamine ($r_s = .22$, $P < .001$) with concomitant FPG values in the 1,472 subjects tested (ie, excluding those in France) (Fig 2). Although relatively few subjects had an elevated HbA_{1c} (>6.2%) or fructosamine (>282 μmol · L^{-1}) value (7% and 5%, respectively), the majority of those with DFG had an elevated HbA_{1c} or fructosamine value (88% and 75%, respectively), in contrast to a minority of those with IFG (15% and 8%, respectively). The correlation of HbA_{1c} and fructosamine with FPG and the proportion of subjects with

Table 1. Baseline Data for Subjects With at Least One Risk Factor for NIDDM

Characteristic	All (N = 1,580, 100%)	NFG (n = 1,046, 66%)	IFG (n = 493, 31%)	DFG (n = 41, 3%)	*P*
Male gender (%)	29	24	37	51	<.001
Age (yr)*	47 ± 10	46 ± 10	49 ± 10	50 ± 10	<.001
FPG (mmol · L^{-1})†	5.2 (4.8-5.6)	5.0 (4.7-5.2)	5.8 (5.6-6.3)	8.8 (8.2-10.5)	N/A
HbA_{1c} (%)*	5.5 ± 0.7	5.3 ± 0.4	5.7 ± 0.6	8.1 ± 2.1	<.001
>6.2 (%)	7	1	15	88	<.001
Fructosamine (μmol · L^{-1})*	238 ± 31	233 ± 23	243 ± 27	340 ± 84	<.001
>282 (%)	5	1	8	75	<.001

NOTE. *P* values are for a trend test across groups. HbA_{1c} and fructosamine data are for a subset of 1,472 subjects at the English centers.
Abbreviation: N/A, not applicable.
*Mean ± SD.
†Median (interquartile range).

DFG and IFG who had elevated HbA_{1c} and fructosamine were similar on the first and second attendance for FPG measurement (data not shown).

Clinical and biochemical characteristics for 227 subjects included in the FHS are listed in Table 2. Forty-one percent were male, 91% were Caucasian, and the mean age was 50 ± 9 years, mean body mass index (BMI) 29.1 ± 4.7 kg · m^{-2}, and median FPG 6.0 mmol · L^{-1} (interquartile range, 5.8 to 6.4). HbA_{1c} was increased in 17% and fructosamine in 2%, fasting plasma insulin was greater than 15.5 mU · L^{-1} in 19%, fasting plasma triglyceride exceeded 2.85 mmol · L^{-1} in 6%, and high-density lipoprotein cholesterol was reduced (men, <0.69 mmol · L^{-1}; women, <0.78 mmol · L^{-1}) in 4%.

Of 223 subjects included in the FHS who had OGTT data, WHO criteria showed that 37% had IGT, 26% DM, and 37% NGT (Table 2). Thus, 7% of self-referred subjects had NIDDM by WHO criteria, 41 at the first FPG, 14 at the second FPG, and 58 at the OGTT. Of the subjects with NGT, 73% continued to have IFG, elevated HbA_{1c}, or both at the time of the OGTT, compared with 80% of the subjects with IGT and 93% of those with DM. No significant differences were seen in the proportion of males and females or Caucasians and Afro-Caribbeans

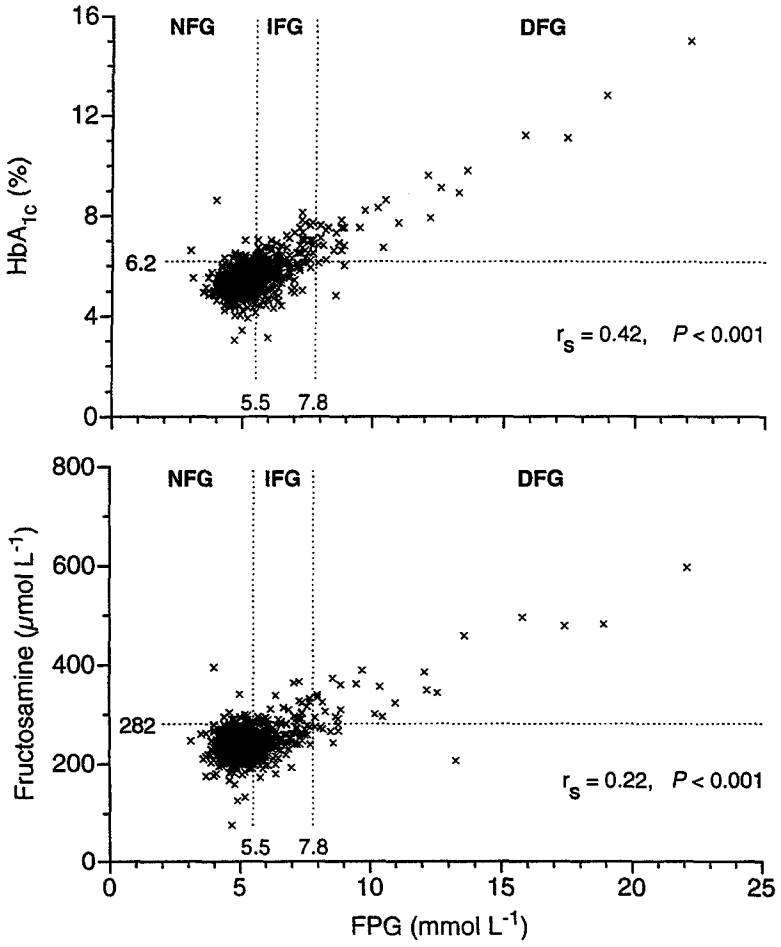

Fig 2. Correlation of HbA_{1c} and fructosamine with initial FPG (n = 1,472). The normal reference range upper 95th percentile for HbA_{1c} and fructosamine is 6.2% and 282 μmol · L^{-1}, respectively.[14]

Table 2. Characteristics of Subjects Entering the FHS Categorized by WHO Criteria on a 2-Hour 75-Gram OGTT

Characteristic	All	NGT	IGT	DM	*P*
No. of subjects	227 (100%)	82 (37%)	83 (37%)	58 (26%)	
Male gender (%)	41	48	35	40	NS
Age (yr)	50 ± 9	47 ± 9	51 ± 9	51 ± 9	<.01
Ethnic group (%)					
Caucasian	91	39	38	23	
Afro-Caribbean	2	25	50	25	.01
Asian	7	12	25	63	
BMI ($kg \cdot m^{-2}$)	29.1 ± 4.7	28.4 ± 4.3	29.4 ± 5.2	29.9 ± 4.5	NS
Waist to hip ratio	0.86 ± 0.09	0.86 ± 0.01*	0.87 ± 0.01*	0.90 ± 0.01*	<.001
Birthweight (kg) (n = 131)	3.2 ± 0.7	3.3 ± 0.1*	3.3 ± 0.1*	2.9 ± 0.1*	<.05
FPG ($mmol \cdot L^{-1}$)†	6.0 (5.8-6.4)‖	5.8 ± 0.1*	6.0 ± 0.1*	6.7 ± 0.1*	<.001
HbA_{1c} (%)	5.8 ± 0.6	5.6 ± 0.5	5.7 ± 0.5	6.1 ± 0.7	<.001
Fructosamine ($\mu mol \cdot L^{-1}$)	225 ± 24	217 ± 2*	225 ± 2*	240 ± 3*	<.001
Fasting plasma insulin ($mU \cdot L^{-1}$)†	10.0 (6.0-16.8)	9.3 (5.7-15.1)‡	9.7 (5.7-16.8)‡	11.8 (7.3-19.1)‡	<.01
Fasting triglyceride ($mmol \cdot L^{-1}$)	1.2 (0.7-2.2)	1.1 (1.1-1.2)§	1.3 (1.2-1.4)§	1.6 (1.4-1.7)§	<.01
Total cholesterol ($mmol \cdot L^{-1}$)	5.0 ± 1.0	5.0 ± 0.9	4.9 ± 0.9	5.0 ± 1.2	NS
HDL cholesterol ($mmol \cdot L^{-1}$)	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.2	NS
LDL cholesterol ($mmol \cdot L^{-1}$)	3.2 ± 0.8	3.2 ± 0.8	3.2 ± 0.8	3.2 ± 0.9	NS
Systolic BP (mm Hg)	124 ± 17	123 ± 14	124 ± 19	126 ± 18	NS
Diastolic BP (mm Hg)	78 ± 11	78 ± 11	77 ± 11	78 ± 10	NS
Hypertensive (%)	23	26	20	25	NS

NOTE. Data are the mean ± SD except as follows: *adjusted mean ± SEM with gender as covariate; †mean of −10 minutes, −5 minutes, and 0 minutes OGTT samples; ‡geometric mean (±SD interval); §adjusted geometric mean (±SE interval) with gender as covariate; and ‖median (interquartile range). Clinical measurements and biochemical samples were taken at the same time as the OGTT. Hypertensive indicates BP ≥150/90 mm Hg or taking antihypertensive medication. Data for OGTT classification groups are adjusted for gender and ethnic group when significant. *P* values are for a trend test across groups (NS = $P > .05$).

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein.

between subjects with NGT, IGT, or DM, whereas a significantly greater proportion (63%) of the 17 Asian subjects were found to have previously undiagnosed NIDDM ($P = .01$). There was a nonsignificant trend for a greater mean BMI in subjects with glucose intolerance or diabetes. With gender as a covariate, the mean waist to hip ratio showed a significantly increasing trend ($P < .001$) and birth weight (remembered by 131 subjects) showed a significantly decreasing trend ($P < .05$) with worsening glucose tolerance. Mean FPG, HbA_{1c}, and fructosamine and geometric mean plasma insulin and triglyceride levels tended to be significantly greater with worsening glucose tolerance.

A total of 148 of 1,127 women tested had a history of gestational diabetes. The proportion of these subjects with IFG was similar to that of the group as a whole, as was the OGTT glycemic categorization.

DISCUSSION

The objective of this study was to identify, by a simple two-stage procedure, subjects potentially at risk of developing NIDDM for enrollment in a randomized diabetes prevention trial (FHS). Earlier identification and treatment of subjects with IFG may be advantageous, because by the time diabetes has developed, half of the subjects have evidence of diabetes-related tissue damage.[1] Improved glycemic control has been shown by the Diabetes Control and Complications Trial in insulin-dependent diabetes to reduce microvascular complications.[15] The UKPDS, which is due to report in 1998, may determine in NIDDM whether improved glycemic control can reduce the incidence of macrovascular and microvascular complications.[16] It has been suggested that there is a FPG threshold[10] of 7.8 $mmol \cdot L^{-1}$ and a glycated hemoglobin threshold of 8.1% for microvascular complications.[17] On the other hand, epidemiological studies of the general population indicate that once subjects have glucose tolerance above the 95th percentile of the normal range, they are at increased risk for cardiovascular disease.[2,3,18] It is uncertain whether identification and early treatment of subjects at increased risk for NIDDM will be helpful in preventing progression to diabetes or reducing the risk of cardiovascular disease.

Screening for diabetes does not as yet fulfill the appropriate criteria for a therapeutic intervention program. This may be reflected by the fact that only 11% of the subjects studied here were referred by their general practitioner for glycemic testing. That 67% of the cohort were self-referred in response to heightened public awareness demonstrated a general concern for long-term health; 77% of the subjects identified as having IFG were willing to join a randomized intervention study.

Sequential FPG measurement offers a simple and inexpensive community-based process for identifying subjects with IFG who might not otherwise be detected. Subjects at increased risk of diabetes who have NFG values will need to be retested at appropriate intervals, as it is likely that their glucose tolerance will worsen with time due to progressive β-cell dysfunction.[16,19,20] A single FPG measurement has been said to have poor sensitivity and specificity with a low positive predictive value for IGT.[8,21] This study shows that two-stage FPG measurements identified two consecutive increased but not diabetic FPG levels in 19% of 1,580 subjects thought to be at increased risk of diabetes, and that this approach is acceptable to otherwise

healthy subjects. A subsequent OGTT in 223 of these subjects showed that 63% had IGT or DM on the basis of WHO criteria,[10] and of those with NGT, 73% continued to have elevated FPG or HbA_{1c}.

In this targeted population, initial HbA_{1c} and fructosamine correlated significantly with FPG with reasonable discrimination for subjects who had DFG (88% and 75% of whom had elevated HbA_{1c} and fructosamine, respectively). Neither test was successful in identifying subjects with IFG, the corresponding proportions being 15% and 8%, respectively. The lower number of subjects with elevated fructosamine (2%) as compared with HbA_{1c} (17%) at the time of the OGTT may reflect short-term changes they have made in diet and/or life-style after being told of their IFG on two consecutive occasions.

Two consecutive FPG estimations in potentially at-risk subjects were simple to organize, and there appeared to be excellent cooperation from the subjects in fasting beforehand. Recruitment was facilitated by media advertising and the organization of dedicated weekend days for glucose testing, with the provision of a simple breakfast as an incentive. Nineteen percent of those who came forward had IFG and 7% were shown to have DFG or NIDDM according to WHO OGTT criteria.[10] This finding is similar to that of the Second National Health and Nutrition Survey, in which having a diabetic parent conferred a higher risk of DM or IGT, which increased significantly in the presence of another risk factor (eg, obesity).[22] Only 29% of the subjects who came forward were male, compared with 41% of those subsequently shown to have IFG on two occasions. This is in accordance with other recent observations that NIDDM in this age group is more prevalent in men.[1,23] As might be expected, subjects with IFG on two occasions, who had OGTT-defined IGT or DM, were significantly older. Diabetic subjects also had a higher waist to hip ratio than those with NGT or IGT. The trend for an increasing fasting plasma insulin with worsening glucose tolerance probably reflects insulin resistance associated with increasing central adiposity. The concomitant higher plasma triglyceride may reflect a metabolic disturbance secondary to hyperglycemia or the associated insulin resistance. In addition, the high levels of circulating triglyceride and insulin may contribute to the IGT-associated increased risk of cardiovascular disease.

The observation by Philipps et al[24] that low birthweight is associated with IGT in later life is supported by this study, which shows that (after gender correction) there was a significant trend of low birthweight with worsening glucose tolerance. While this would be in accordance with the hypothesis that deficient fetal and neonatal nutrition may contribute to glucose intolerance later in life, the association is weak and might be explained by the thrifty-gene hypothesis favoring survival of babies of low birthweight.[25]

Asian subjects in this study were more likely to have undiagnosed diabetes, which reflects the known higher prevalence of this condition in Asian immigrants in the United Kingdom.[26]

In summary, 227 subjects with IFG on two occasions have been entered into a randomized controlled trial to determine whether therapy with (1) reinforced healthy-living, dietary, and exercise advice compared with basic advice[11] and (2), in a factorial design, a sulfonylurea (gliclazide) compared with placebo[12] will prevent or delay the progression to NIDDM.

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REFERENCES

1. UK Prospective Diabetes Study Group: UK Prospective Diabetes Study VIII: Study design, progress and performance. Diabetologia 34:877-890, 1991

2. Jarrett RI, Keen H, McCartney P: The Whitehall Study: Ten year follow-up report on men with impaired glucose tolerance with reference to worsening to diabetes and predictors of death. Diabet Med 1:279-283, 1984

3. Eschwège E, Richard JL, Thibult N, et al: Coronary heart disease mortality in relation with diabetes, blood glucose and plasma insulin levels. The Paris Prospective Study, ten years later. Horm Metab Res Suppl 15:41-46, 1985

4. Pan W-H, Cedres LB, Liu K, et al: Relationship of clinical diabetes and symptomatic hyperglycemia to risk of coronary heart disease mortality in men and women. Am J Epidemiol 123:504-516, 1986

5. Perry IJ, Wannamethee G, Whincup PH, et al: Asymptomatic hyperglycaemia and major ischaemic heart disease events in Britain. J Epidemiol Community Health 48:538-542, 1994

6. McPhillips JB, Barrett-Connor E, Wingard DL: Cardiovascular disease risk factors prior to the diagnosis of impaired glucose tolerance and non–insulin-dependent diabetes mellitus in a community of older adults. Am J Epidemiol 131:443-453, 1990

7. McDonald GW, Fisher GF, Burnham C: Reproducibility of the oral glucose tolerance test. Diabetes 14:473-480, 1965

8. Riccardi G, Vaccaro O, Rivelles A, et al: Reproducibility of the new diagnostic criteria for impaired glucose tolerance. Am J Epidemiol 212:422-429, 1985

9. Holman RR, Turner RC: The basal plasma glucose: A simple relevant index of diabetes. Clin Endocrinol (Oxf) 14:279-286, 1981

10. World Health Organization: Diabetes mellitus. World Health Organ Tech Rep Ser 727, 1985

11. Fasting Hyperglycaemia Study Group: The Fasting Hyperglycaemia Study: II. Randomized controlled trial of reinforced healthy living advice in subjects with increased but not diabetic fasting plasma glucose. Metabolism 46:50-55, 1997 (suppl 1)

12. Fasting Hyperglycaemia Study Group: The Fasting Hyperglycaemia Study: III. Randomized controlled trial of sulfonylurea therapy in subjects with increased but not diabetic fasting plasma glucose. Metabolism 46:56-60, 1997 (suppl 1)

13. UK Prospective Diabetes Study Group: UK Prospective Diabetes Study XI: Biochemical risk factors in type 2 diabetic patients at diagnosis compared with age-matched normal subjects. Diabet Med 11:534-544, 1994

14. SAS Institute: Statistical Analysis System (ed 6). Cary, NC, SAS Institute, 1990

15. Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications of insulin-dependent diabetes mellitus. N Engl J Med 329:977-986, 1993

16. UK Prospective Diabetes Study Group: UK Prospective Diabetes Study XVI: Overview of six years' therapy of type 2 diabetes—A progressive disease. Diabetes 44:1249-1258, 1995

17. Krolewski AS, Laffel LM, Krolewski M, et al: Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. N Engl J Med 332:1251-1255, 1995

18. Alberti KGMM: The clinical implications of impaired glucose tolerance. Diabet Med 13:927-937, 1996

19. Kadowaki T, Miyake Y, Hagura R, et al: Risk factors for worsening to diabetes in subjects with impaired glucose tolerance. Diabetologia 26:44-49, 1984

20. Cook JT, Page RC, Levy JC, et al: Hyperglycaemic progression in subjects with impaired glucose tolerance: Association with decline in beta cell function. Diabet Med 10:321-326, 1993

21. Harris MI: Impaired glucose tolerance in the US population. Diabetes Care 12:464-474, 1993

22. Harris MI, Hadden WC, Knowler WC, et al: Prevalence of diabetes and impaired glucose tolerance and plasma glucose levels in US population aged 20-74. Diabetes 36:523-534, 1987

23. Welborn TA, Glatthaar C, Whittall D, et al: An estimate of diabetes prevalence from a national population sample: A male excess. Med J Aust 150:78-81, 1989

24. Philipps K, Barker DJ, Hales CN, et al: Fetal growth and impaired glucose tolerance in men and women. Diabetologia 36:225-228, 1993

25. McCance DR, Pettit DJ, Hanson RL, et al: Birth weight and non–insulin dependent diabetes: Thrifty genotype, thrifty phenotype, or surviving small baby genotype? Br Med J 308:942-945, 1994

26. Samanta A, Burden AC, Fent B: Comparative prevalence of non–insulin dependent diabetes mellitus in Asian and white Caucasian adults. Diabetes Res Clin Pract 4:1-6, 1987