*Short communication***The relative risks of hyperglycaemia, obesity and dyslipidaemia in the relatives of patients with Type II diabetes mellitus****J.T.E. Shaw^{1,2}, D.M. Purdie³, H.A.W. Neil⁴, J.C. Levy², R.C. Turner²**¹ Department of Diabetes and Endocrinology, Princess Alexandra Hospital, Brisbane, Australia² Diabetes Research Laboratories, Radcliffe Infirmary, Oxford, UK³ Department of Social and Preventive Medicine, University of Queensland, Brisbane, Australia⁴ Division of Public Health and Primary Care, University of Oxford, UK

Summary Type II (non-insulin-dependent) diabetes mellitus has a substantial genetic component; however, its molecular basis remains largely unknown. The mode of inheritance is likely to be polygenic, with penetrance influenced by environmental factors. Although the familial aggregation of Type II diabetes is acknowledged, there is little data concerning the prevalence of diabetes in the relatives of subjects with diabetes in comparison with the general population, and our objective was to address this question in the defined geographic region of Oxfordshire, England. We studied 139 first degree relatives of 90 probands with Type II diabetes who attended routine diabetes clinics in Oxfordshire and documented the fasting plasma glucose, triglyceride and HDL-cholesterol concentrations and BMI of these subjects. The probands were selected without regard to family history of diabetes. The control population data were derived from two large-scale Oxford community studies which documented the prevalences of known and newly diagnosed diabetes. The prevalences of newly diagnosed and known diabetes were calculated for each group. The mean BMI, and concentrations of fasting glucose, triglyceride and HDL-cholesterol were compared and prevalence ratios for obesity (defined as BMI > 30 kg/m²), hyperglycaemia (defined as fasting plasma glucose ≥ 6.1 mmol/l), and dyslipidaemia (defined as triglyceride > 2.0 mmol/l,

HDL < 1.0 mmol/l) were calculated. There was a fourfold higher prevalence of hyperglycaemia in the first degree relatives of subjects with Type II diabetes compared with the control population: the prevalence ratio after adjustment for age, sex and BMI was 4.32 (95 % confidence interval 2.29–8.17). The relatives had a considerably higher fasting plasma glucose concentration than the control population (5.18 ± 0.67 mmol/l (mean $\pm$ 1 SD) vs 4.76 ± 1.59 mmol/l, $p = 0.0001$), and this difference remained statistically significant after adjustment for age, sex and obesity. The relatives were significantly more obese, had higher fasting plasma insulin concentrations and had lower HDL-cholesterol concentrations. In conclusion, there is a strong familial aggregation of hyperglycaemia and obesity in the relatives of subjects with Type II diabetes and these subjects have higher fasting plasma insulin concentrations and lower HDL-cholesterol than the general population. These data indicate the particular relevance of screening the first degree relatives of subjects with Type II diabetes, as intervention strategies which aim to improve the metabolic profile are indicated for a large proportion of these subjects. [Diabetologia (1999) 42: 24–27]

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Type II (non-insulin-dependent) diabetes mellitus has a substantial genetic component as indicated by the high concordance in monozygotic twins [1, 2]. Although there has been considerable progress in identifying the genes responsible for maturity onset diabetes of the young, there has been relatively little progress in identifying the genes responsible for the

more common late onset forms of Type II diabetes which do not have a simple Mendelian genetic basis and in which penetrance is influenced by environmental factors [3]. The familial clustering of Type II diabetes is acknowledged, however, there is little data regarding the relative risk of diabetes in the relatives of subjects with Type II diabetes when compared with the general population. This paper documents the prevalences of metabolic abnormality and obesity in the relatives of subjects with Type II diabetes and compares these prevalences with those found in the general population.

Subjects and methods

The protocol was approved by the Central Oxford Research and Ethics Committee and informed consent was obtained from all subjects. We ascertained 90 Caucasian probands with Type II diabetes and at least one living first degree relative without regard to family history of diabetes from subjects attending the United Kingdom Prospective Diabetes Study Clinics in Oxfordshire, England. The probands were diagnosed with Type II diabetes on the basis of age at onset after 35 years, no history of ketosis, and treatment for a minimum of 3 months with diet or oral hypoglycaemic agents. The probands were of mean age 62 ± 14 years (± 1 SD) and were of mean BMI 29 ± 5 kg/m². We studied the 139 first degree relatives of these subjects: 83 were the offspring and 56 were siblings of subjects with Type II diabetes. The control population data were derived from two large-scale community studies done in the same geographic region (Oxfordshire) which documented the frequencies of known and newly diagnosed patients with diabetes [4, 5]. The Oxford Community Diabetes Study documented the age-specific prevalence of known patients with diabetes for a population sample of 40079 adult subjects in the Oxford region [4]. The distributions of plasma glucose, cholesterol and triglyceride concentrations were documented in a screening study of an Oxford population sample of 4201 subjects aged 25–60 years without known diabetes [5]. The relatives and the control subjects were of similar age: 42 ± 8 years (mean $\pm$ SD) and 43 ± 9 years respectively, and there was no difference in socio-economic class between the two groups.

BMI was calculated as weight (kg) divided by height (metres) squared. Blood samples were drawn from all subjects after a 12-h overnight fasting for plasma glucose estimation. Plasma glucose was measured with a glucose oxidase method. Plasma triglyceride and HDL-cholesterol concentrations were measured for the 4201 subjects in the control population [5] and for 91 of the first degree relatives of subjects with Type II diabetes. Plasma triglyceride was measured with an enzymatic colorimetric method (Boehringer Mannheim, Mannheim, Germany) using the Cobas FARA analyser (Roche Diagnostics, Basel, Switzerland); coefficient of variation (CV) less than 3%. The plasma HDL-cholesterol was measured after precipitation with sodium heparin and manganese chloride; CV 4–8%. Insulin concentrations were measured in all the first degree relatives and in a random subset of 1338 subjects from the control population sample. Plasma insulin was measured in duplicate by radio-immunoassay with a charcoal absorption step to separate bound from free insulin, using Novo Human MC Insulin (Novo Research Laboratories, Bagsvaerd, Denmark) as standard, Wellcome RD 10 (Wellcome Research Laboratories, Beckenham, Kent, UK) guinea-pig anti-porcine insulin

antiserum and ¹²⁵I-labelled insulin (Amersham International, Amersham, UK) as tracer. Between-assay CV for duplicates was 10% at 7.7 mU/l and 9% at 29.9 mU/l. Intra-assay CV was less than 10% in the range encountered in this study. Cross-reactivity with intact proinsulin was approximately 100% and with split proinsulins approximately 50%. All samples were measured in one laboratory using the same analytical methods.

Mean values of BMI, fasting plasma glucose, fasting plasma insulin, HDL-cholesterol and triglyceride concentrations were obtained and those for the relatives and for the control population were compared using the Students *t*-test. Linear regression analysis was carried out to compare the means adjusting for age, sex and BMI. Prevalence ratios were calculated for fasting plasma glucose equal or greater than 6.1 mmol/l, BMI greater than 30 kg/m², HDL-cholesterol less than 1.0 mmol/l and triglyceride level greater than 2.0 mmol/l. Although it is somewhat arbitrary to dichotomise continuous variables, these criteria were selected before analysis and are used clinically in the assessment of cardiovascular risk. The glucose criterion corresponds with the threshold for “impaired fasting glucose” (IFG) as defined by the American Diabetes Association [6]. Both crude and adjusted prevalence ratios were calculated, the latter taking into account age, sex and BMI. The intercorrelations between the variables were assessed using Pearson correlation coefficients. All analyses were done using the SAS statistical package.

Results

The prevalence of known and newly diagnosed diabetes at different ages in the control population and in the first degree relatives of subjects with Type II diabetes are shown in Table 1. Overall, there was a four-fold higher rate of diabetes in the first-degree relatives compared with the control population.

Mean levels of BMI, fasting plasma glucose, fasting plasma insulin, triglyceride and HDL-cholesterol for the relatives and for the control population were calculated. The relatives were considerably more obese than the control population, with mean BMI 27.7 ± 5.9 kg/m² (± 1 SD) compared with 25.4 ± 11.0 kg/m² for the control population ($p = 0.0004$). The mean fasting plasma glucose for the relatives was 5.29 ± 0.94 mmol/l compared with 4.76 ± 1.59 mmol/l for the control population ($p < 0.0001$), and the difference remained significant after adjustment for age, gender and BMI ($p = 0.0002$). After exclusion of the subjects with known diabetes, the mean fasting plasma glucose for the relatives was 5.18 ± 0.67 mmol/l, and the difference between the two groups remained significant ($p = 0.0001$). The mean fasting plasma insulin for the relatives was 9.0 ± 5.4 mU/l compared with 3.3 ± 1.4 mU/l for the control population ($p = 0.0001$) and the difference remained significant after adjustment for age, sex and BMI ($p = 0.0001$). There was only a small difference in triglyceride levels between the two groups. The mean HDL-cholesterol for the relatives was

Table 1. Age-specific prevalence of newly diagnosed hyperglycaemia (fasting plasma glucose ≥ 6.1 mmol/l) and known diabetes per 1000 subjects

Age years	Sample <i>n</i>	Prevalence of newly diagnosed hyperglycaemia	Prevalence of known diabetes ^b	Prevalence of newly diagnosed hyperglycaemia and known diabetes
Control population				
20–29	250	4.0	3.8	7.8
30–39	1204	14.1	6.3	20.4
40–49	1665	23.4	7.1	30.5
50–59	958	39.7	15.8	55.5
Total	4077 ^a	23.3	10.8	34.1
The first degree relatives of subjects with Type II diabetes				
20–29	5	200	0	200
30–39	47	63.8	42.6	106.4
40–49	64	109.4	62.5	171.9
50–59	23	173.9	0.0	173.9
Total	139	107.9	43.2	151.1

^a 23 had a missing DOB^b Population data (ref 4)

1.21 $\pm$ 0.31 mmol/l, compared with 1.50 $\pm$ 0.39 mmol/l for the control population ($p = 0.0001$), and again this difference remained statistically significant after adjustment for age, sex and BMI ($p = 0.0001$).

The prevalence ratio for hyperglycaemia (fasting plasma glucose ≥ 6.1 mmol/l) in the relatives compared with the control population was 4.94 (95 % confidence interval 3.00–8.14). After adjustment for age, sex and BMI, the prevalence ratio was 4.32 (95 % confidence interval 2.29–8.17). When the siblings and offspring of diabetic subjects were considered separately, the prevalence ratios for hyperglycaemia were similar in each group, for the siblings 4.69 (95 % confidence interval 1.71–12.84), and for the offspring 4.12 (95 % confidence interval 1.89–8.98). There was a significantly higher prevalence of obesity (defined as BMI > 30 kg/m²) amongst the relatives compared with the control population, with an adjusted prevalence ratio of 2.79 (95 % confidence interval 1.83–4.26). The prevalence ratio for HDL less than 1.0 mmol/l in the relatives compared with the control population, adjusted for age, sex and BMI, was 4.68 (95 % confidence interval 3.02–7.25).

The intercorrelations between BMI, age, fasting plasma glucose, fasting plasma insulin, triglyceride and HDL-cholesterol were analysed. In the first degree relatives all the variables were correlated apart from HDL-cholesterol, which was correlated with fasting plasma insulin and triglyceride but not with the other variables. In the control population all the variables were intercorrelated.

Discussion

The current data indicate that the relatives of subjects with Type II diabetes have a higher than fourfold risk

of hyperglycaemia. These subjects also have higher BMI and fasting plasma insulin concentration and lower HDL-cholesterol concentrations than the general population.

The probands were recruited without regard to family history of Type II diabetes and thus ascertainment bias should not be a concern in these data. The increased prevalence of Type II diabetes in the relatives of affected subjects is likely to reflect genetic predisposition to hyperglycaemia with additional effects from shared environment and lifestyle. Type II diabetes is recognised to arise from a combination of insulin resistance and impaired beta-cell function [7]. Obesity is a major factor in the development of diabetes because it is a determinant of insulin resistance. Separate genetic determinants for insulin resistance, beta-cell function and energy balance are likely to contribute to Type II diabetes, quite apart from environmental influences. After adjustment for obesity, age and sex, the prevalence ratio for hyperglycaemia in the first degree relatives remained statistically significant, indicating that the familial clustering of Type II diabetes does not simply reflect familial determinants for obesity.

As insulin concentrations were assessed using a non-specific radioimmunoassay, it is possible that fasting plasma insulin concentrations could have been overestimated in the relatives if they had an increased proinsulin to insulin ratio. Proinsulin concentrations are near normal in newly diagnosed subjects with Type II diabetes who have mild hyperglycaemia [8] and tend to normal as fasting plasma glucose approaches the normal range [9]. As the relatives in the present study had a mean fasting plasma glucose of 5.29 mmol/l, it is unlikely that a raised proinsulin to insulin ratio would have contributed an important bias to the assessment of fasting plasma insulin.

The term impaired fasting glucose refers to a metabolic stage intermediate between normal glucose homeostasis and diabetes. The expert committee of the American Diabetes Association chose 6.1 mmol/l as the upper limit of normoglycaemia [6]. Although it is recognised that this choice is somewhat arbitrary, it is near the level above which acute phase insulin secretion is lost in response to intravenous injection of glucose [10] and is associated with a progressively greater risk of developing micro- and macrovascular complications [11–15]. Impaired fasting glucose is recognised as a major risk factor for the development of Type II diabetes and cardiovascular disease [11]. Impaired fasting glucose and Type II diabetes are associated with the insulin resistance syndrome (also known as syndrome X, Reaven's syndrome or the metabolic syndrome) which consists of insulin resistance, compensatory hyperinsulinaemia to maintain glucose homeostasis, obesity (especially visceral obesity), dyslipidaemia of the high triglyceride or low-HDL cholesterol type or both, and hypertension [16]. The intercorrelations identified in our data between BMI, fasting plasma glucose, fasting plasma insulin, triglyceride and HDL-cholesterol are consistent with the hypothesis that insulin resistance is a major aetiological factor underlying these associations. Insulin resistance is directly involved in the pathogenesis of Type II diabetes and the insulin resistance syndrome contains many features that increase cardiovascular risk. The clustering of cardiovascular risk factors in the relatives of subjects with Type II diabetes is likely to reflect shared genetic determinants for insulin resistance, with additional contributions from shared environment and lifestyle.

Screening programs have been advocated in a bid to detect individuals with metabolic abnormalities at an early stage in order to institute measures to prevent the development of Type II diabetes and cardiovascular disease. Dietary modification, exercise and weight loss are usually advised for such individuals; however, the success of these programmes in maintaining sustained weight loss and metabolic improvement in the longer term are poor. Thiazolidinedione therapy may be a suitable modality for the prevention of Type II diabetes [17]. Preliminary studies indicate that the treatment of obese subjects with impaired glucose tolerance with these agents leads to improvement in insulin sensitivity, glucose tolerance and lipid profile [18]. It is logical to speculate that treatment of insulin resistance in the prediabetic state might prevent or delay the ultimate development of Type II diabetes and this hypothesis will be tested in a large-scale National Institutes of Health-sponsored, multi-centre study. These initiatives focus attention on the cost-effectiveness of screening for metabolic abnormalities in the general population. Type II diabetes is a common familial condition, and our data indicate that the relatives of diabetic subjects share an inherit-

ed or environmental predisposition or both to a clustering of metabolic risk factors. The familial aggregation of hyperglycaemia, obesity and dyslipidaemia that we have documented indicates the particular relevance of metabolic screening in the first degree relatives of subjects with Type II diabetes.

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