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Worsening to Diabetes in Men with Impaired Glucose Tolerance ("Borderline Diabetes")

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Summary. Two hundred and four men with impaired glucose tolerance (borderline diabetes) discovered in a screening examination have been observed for five years and repeated tests of glucose tolerance performed. By pre-determined criteria 27 men 'worsened to diabetes' and this metabolic deterioration was not significantly influenced by treatment with carbohydrate restriction with or without a daily dose of 50 mg phenformin. Of the baseline variables measured prior to treatment allocation only the blood glucose values were significantly predictive of ultimate worsening to diabetes.

Key words: diabetes mellitus, impaired glucose tolerance, borderline diabetes.

The discovery of impaired glucose tolerance in the absence of symptoms attributable to diabetes mellitus poses problems both in interpretation and management. In many people glucose tolerance returns to normal spontaneously, while in some there is deterioration to gross hyperglycaemia with symptoms. In others the impairment of glucose tolerance changes little over many years. There is sparse information on factors which influence or predict the direction which the individual will take. In this communication we present the results of observations made over a five year period on a group of 204 men identified as 'borderline diabetics' following their participation in the Whitehall Survey [1], with an analysis of the relation between certain measurements made at baseline and subsequent 'worsening to diabetes'.

Subjects and Methods

All but eighteen of the subjects were recruited between 1968 and 1970 from the Whitehall Survey, a screening study of 20,000 male Civil Servants working in London [1]. The others were recruited during the pilot phase of the Survey, which was carried out using the same screening techniques, amongst Post Office employees.

Men with screening capillary blood sugar concentrations between 6.1–11.0 mmol/l (110 and 199 mg/dl) were recalled for a standard 50 g oral glucose tolerance test [2] performed *in the afternoon*, beginning at approximately 15.00 hours, after fasting from 08.00 hours (they were allowed a light breakfast). If the blood sugar was 11.1 mmol/l (200 mg/100 ml) or more at the Survey examination or during the glucose tolerance test the subject was referred directly to his general practitioner as a probable diabetic. Borderline diabetics were defined on the basis of the following criteria of impaired glucose tolerance:

(a) Survey blood sugar 6.1–11.0 mmol/l (110–199 mg/dl); and, at standard GTT,

(b) Peak blood sugar >10 mmol/l (180 mg/dl) *and* two hour blood sugar 6.7–11.0 mmol/l (120–199 mg/dl) and/or two values exceeding 10.0 mmol/l (180 mg/dl) and/or mean 2 hour blood sugar (Survey and G.T.T.) >6.7 mmol/l (120 mg/dl).

Trial Design (see also [2])

At the first visit subjects were allocated at random to one of four treatment groups:

(1) recommended 120 g/day carbohydrate diet + placebo capsule.

(2) recommended to 'limit sucrose (i. e. table sugar) intake' + placebo capsule.

(3) recommended 120 g/day carbohydrate diet + 50 mg. phenformin S. A. once daily.

(4) recommended to 'limit sucrose intake' and 50 mg phenformin S. A. once daily.

The restricted carbhydrate diet was carefully taught and reinforced with a specially prepared explanatory booklet. No recommendations or limitations were expressed about non-carbohydrate foods. The diet part of the trial was not 'blind' so that periodic reinforcement of dietary advice could be given. The drug trial was 'double-blind' and was planned to run for the first five years of the ten year study. Follow-up examinations were at approximately six month intervals.

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Table 1. Percentages worsening to diabetes in the presence and absence of certain baseline characteristics

Characteristic	Baseline characteristic present	Baseline characteristic absent
First degree family history of diabetes	16.0% n=25	14.7% n=156
ECG changes (code 1 or 2)[a]	8.0% n=25	16.0% n=156
History of arterial disease (angina, MI or claudication)	16.1% n=31	14.7% n=150
Current Smoking	16.9% n=77	13.5% n=104

[a] see [2]

Table 2. Comparison of baseline variables in those who did or did not worsen to diabetes (Mean, SD and number with available data in each group)

	Worsening to diabetes (n=27)	Not worsening to diabetes (n=154	T	P
2-hour blood glucose mg/dl	168.4 (27) ±22.0	146.1 (150) ±28.8	4.61	< 0.001
l-hour blood glucose mg/dl	231.8 (27) ±25.3	209.7 (151) ±32.0	4.00	< 0.001
Fasting blood glucose mg/dl	95.7 (27) ±18.4	84.4 (151) ±12.0	3.07	0.002
Body Mass Index	27.0 (26) ± 3.8	26.1 (149) ± 3.4	1.12	n. s.
$\log_{10}$ (Trigly ceride) mg/dl	2.1 (26) ±0.17	2.1 (152) ±0.21	1.05	n. s.
Heart Rate	80.3 (27) ±13.5	78.7 (154) ±16.7	0.49	n. s.
Cholesterol mg/dl	213.4 (26) ±55.0	219.0 (151) ±43.4	−0.49	n. s.
Age	55.8 (27) ±7.3	56.9 (154) ±7.0	−0.69	n. s.
Systolic blood pressure mmHg	138.1 (27) ±21.4	142.4 (154) ±26.9	−0.92	n. s.

All clinics were held in the afternoon. The blood glucose was usually measured two hours after a 50 g glucose load taken about 1¾ hours before the appointment time and after fasting from a light breakfast.

'Worsening to Diabetes'

Severe or sustained worsening of glucose tolerance was predetermined as a main reason for terminating participation in the trial, though observation was to be continued. The arbitrary criteria for determining this "worsening to diabetes" were:

(1) *two successive* two-hour post glucose blood sugars > 11.1 mmol/l (200 mg/dl).

(2) *three non-successive* two-hour blood sugars > 11.1 mmol/l (200 mg/dl).

(3) the development of unequivocal symptoms or signs of diabetes mellitus.

(4) a two-hour blood sugar > 11.1 mol/l (200 mg/dl) at a standard afternoon oral glucose tolerance test carried out at the 10th visit (i. e. 5 years), whether or not previous two-hour values were also elevated.

As these criteria were met, the subject was informed and promptly referred to his general practitioner with the recommendation that he be regarded as a diabetic and receive conventional clinical care.

At the first trial visit, venous blood was also taken, after the 8–10 hour fast, for measurement of cholesterol [3] and triglycerides [4]. Electrocardiography (limb leads only) was performed at the Survey using a Mingograph 31B and 'multipoint' electrodes and heart rate calculated from the record. All records for men in the trial were coded independently and in ignorance of the form of treatment by the same two observers using the Minnesota code [5].

Results

At the end of the five year follow-up period 27 of the 204 men had worsened to diabetes. Of these 2, 2, 7 and 16 fitted the criteria 1 to 4, respectively, detailed under 'Methods'.

Twenty three of the remaining patients could not be assessed because of default, death or non-availability. Of the remaining 154 patients who did not worsen to diabetes, only 20 did not have at least one two-hour blood glucose above 6.7 mmol/l (120 mg/dl) during follow-up.

Of the 16 men who qualified as worsening to diabetes at the 10th visit, five also came into categories 1 or 2, but nine had not previously had a two-hour blood sugar of 11.1 mmol/l (200 mg/dl) or above and two had only once previously shown this elevated level. The group is, therefore, heterogeneous in both the time taken too worsen to diabetes and in its method of definition.

The percentages in each of the four treatment groups worsening to diabetes were 13.3 (n = 45) of the placebo-sucrose restricted group, 18.4 (n = 49) in the phenformin-sucrose restricted group, 18.2 (n = 44) in the placebo – recommended diet group and 9.3 (n = 43) in the phenformin-recommended diet group. None of these was significantly different from any other. In the multiple logistic analysis (see below) treatment was not significantly predictive of worsening to diabetes. We therefore compared baseline data of the deteriorating and non deteriorating groups without regard to possible treatment effects. The percentage frequency of those worsening to diabetes in the presence and absence of certain baseline characteristics (family history of diabetes, evidence of arterial disease, smoking history) is shown in Table 1. Expectation of deterioration is not significantly influenced by their presence.

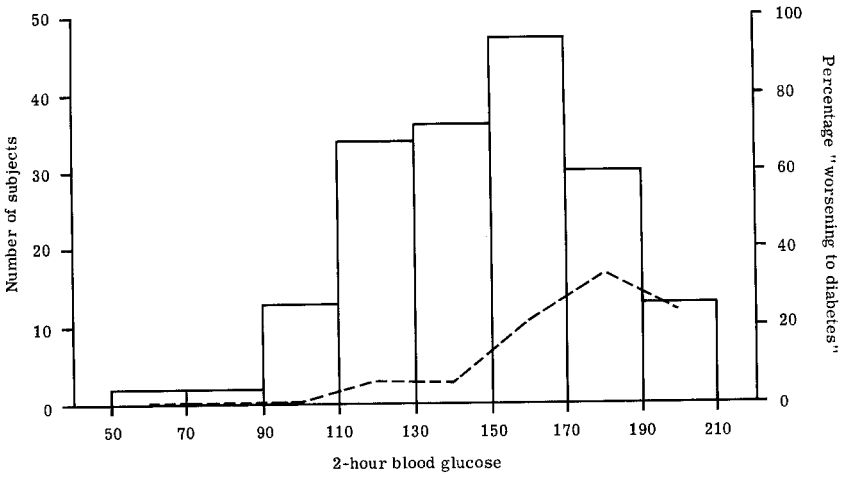

Fig. 1. Distribution of blood glucose levels (mg/dl) two hours after a 50 g oral glucose load at the baseline examination. The interrupted line shows the percentage in each blood glucose group 'worsening to diabetes'

In Table 2, other baseline variables are compared in the two groups. Blood glucose values from the afternoon glucose tolerance test performed prior to acceptance into the trial were used, rather than the single initial survey two-hour blood glucose, both in order to compare the predictive power of different time points and because the Survey conditions were necessarily less controlled. Values from the baseline GTT were significantly higher amongst those who worsened to diabetes; of these the concentration difference at two-hours had the largest t-value. Figure 1 shows the baseline two-hour blood glucose distribution together with the percentage worsening to diabetes in each category. The fall in rate of worsening to diabetes in the highest category does not represent a significant departure from a linear trend and is probably a chance fluctuation due to the small number with initial blood glucose levels above 10.5 mmol/l (190 mg/dl).

The relationship of baseline variables with worsening to diabetes within 5 years was examined further with a multiple logistic model to which the following 'predictors' were fitted: Age, Body Mass Index (BMI), Systolic Blood Pressure, Log_{10} Triglyceride concentration[1], Cholesterol concentration, Fasting Blood Glucose, 1-hour Blood Glucose, 2-hour Blood Glucose level, Heart Rate, together with 'dummy variables' for: Smoking, Carbohydrate Restriction, Phenformin Treatment (these latter factors not being continuous variables).

The baseline variables most powerfully predicting worsening to diabetes were the initial blood glucose values; none of the other variables approached conventional statistical significance. Despite the significant linear correlation between fasting and two-hour blood glucose ($r = 0.3$; $p < 0.001$), the inclusion of both fasting and 2-hour blood glucose accounted for more of the variance than an analysis with either variable on its own, suggesting that they have independent predictive power. Table 3 gives the calculated regression coefficients when the fasting and 2-hour blood glucose values (i) are accompanied by (ii) 1-hour blood glucose and (iii) BMI. The inclusion of other variables in the equation did not further improve predictive power. When considered in conjunction with the standard deviations of the blood glucose distributions the regression coefficients for fasting and two-hour blood glucose, though not identical, have approximately the same effect upon the logistic function. It would seem, therefore, that the two measures of glucose intolerance, although statistically and probably biologically related, are equally important in predicting subsequent worsening to diabetes.

Table 3. Multiple logistic model relating baseline variables to worsening to diabetes

n=177 Variable	Regression coefficient	S. E. of regression coefficient	T value
(i)			
Fasting blood glucose	0.0444	0.018	2.50[a]
Two-hour blood glucose	0.0256	0.010	2.69[a]
(ii) n=177 Variable			
Fasting blood glucose	0.036	0.019	1.97[a]
One-hour blood glucose	0.0088	0.008	1.10
Two-hour blood glucose	0.0227	0.010	2.32[a]
(iii) n=171 Variable			
Fasting blood glucose	0.0446	0.019	2.38[a]
Two-hour blood glucose	0.0242	0.010	2.47[a]
Body Mass Index	0.0649	0.070	0.93

[a] significant with $p < 0.05$

1 Logarithms were used to normalise the highly skewed distribution

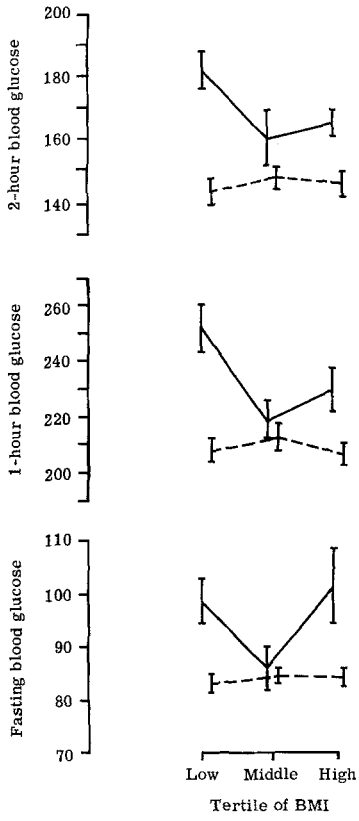

Fig. 2. Mean blood glucose levels (mg/dl) at three time points of the initial glucose tolerance test by tertile of body mass index (BMI). The solid line represents those who worsened to diabetes and the interrupted line those who dit not

The possible interaction of BMI with blood glucose in predicting worsening to diabetes was also examined by dividing the group into approximate tertiles of distribution of BMI; mean values of baseline blood glucose were calculated separately within each tertile for those who did or did not worsen to diabetes (Fig. 2). In the latter the mean blood glucose is similar in each BMI tertile. However, amongst, those who worsened to diabetes the mean two-hour and one-hour blood glucose is higher in the lowest tertile of body mass index than in the other two tertiles, the implication being that, when adiposity is least a greater elevation of initial blood sugar was required to predict worsening to diabetes.

Discussion

There have been several follow-up studies [6–13] on unselected populations screened for blood sugar though only three have published data on factors predicting metabolic deterioration. Each of these differs in the methods used and in the criteria adopted in defining worsening to diabetes. In the Oxford, Massachusetts Survey of 1946/47, subjects with post-prandial venous blood sugar levels of 7.8 mmol/l (140 mg/dl) or more or capillary blood sugar levels of 9.4 mmol/l (170 mg/dl) or more were subsequently tested at varying intervals over 17 years (6), during which three varieties of new diabetics were recognised: (A) receiving insulin treatment, (B) people with blood sugars persistently exceeding 11.1 mmol/l (200 mg/dl) post-prandially or 7.8 mmol/l (140 mg/dl) fasting, (C) as for B except that post-prandial levels were 9.4 mmol/l (170 mg/dl) and fasting levels 7.2 mmol/l (130 mg/dl). A control group with initial post-prandial blood sugar levels below 7.8 mmol/l (140 mg/dl) was also studied. The median period of follow-up was about 14 years. Compared with the control group, diabetes occurred 5 times more frequently in people with initial post-prandial blood sugars from 7.8 to 9.4 mmol/l (140–169 mg/dl) and 15 times more frequently in those with blood sugars of more than 9.4 mmol/l (169 m/dl). Diabetes also occurred very much more frequently in people 20% above ideal body weight (Metropolitan Life Insurance Co. standards) when their initial blood sugar levels exceeded 9.4 mmol/l (169 mg/dl), with a smaller excess when blood sugar levels were in the range 7.8 to 9.4 mmol/l (140–169 mg/dl). Overweight people with initially 'normal' blood sugars did not appear to be at increased risk, a finding which the present study supports. This suggests, perhaps, that adiposity is a diabetogenic factor only in those constituted in some special way, identifiable, at least in some, by lesser degrees of glucose intolerance. In the Birmingham Diabetes Survey [7] 50 g oral glucose tolerance tests were performed on 465 people with glycosuria and 343 people selected at random from the non-glycosuric population. Two follow-up reports have appeared, one at 5 years [8] and one at 10 years [9]. 'Florid diabetics' were defined as those with fasting blood sugar levels exceeding 7.2 mmol/l (130 mg/dl) and 'GTT diabetics' as those with fasting levels less than this, but with one hour levels above 10 mmol/l (180 mg/dl) and two-hour levels above 6.1 mmol/l (120 mg/dl). 45% of those with GTT diabetes progressed to florid diabetes in ten years – mostly during the first five years – and, in general, the higher the blood glucose levels in the original test, the more likely was a progression to florid diabetes. Four people who were not GTT diabetics initially became florid diabetics, but these all had minor abnormalities of glucose tolerance in their original test. The authors did not relate body weight to subsequent diabetes.

O'Sullivan and Mahan [10] studied 352 women identified as "chemical diabetics" by one of three criteria – (a) Mosenthal and Barry, (b) Fajans and

Conn, (c) U. S. Public Health Service (USPHS). They were followed for from 1–12 years. Clinical diabetes was diagnosed during follow-up if the fasting blood sugar exceeded 6.1 mmol/l (120 mg/dl), or the post-prandial blood sugar exceeded 10 mmol/l (180 mg/dl) or the post-glucose (100 g) blood sugar within three hours of ingestion exceeded 16.7 mmol/l (300 mg/dl). The USPHS criteria were the best predictors of worsening to diabetes and were the most stringent of the three, that is they required higher blood sugar levels. A family history of diabetes did not influence the frequency of worsening to diabetes. The group as a whole was overweight when diagnosed. The only comparison reported is between those below and above 150% (!) of ideal body weight. In those above there was a significant excess of diabetics in the Fajans and Conn and the USPHS diagnostic groups.

These three studies and our own have observed different population groups, selected in different ways and have used different criteria in defining worsening to diabetes. Nevertheless, one point seems to emerge – that the levels of blood sugar themselves best predict subsequent worsening to diabetes, however defined. The influence of obesity as a predictor is less clear. In our own study it did not contribute to prediction when blood sugar levels were taken into consideration, though there was some indication that the least obese only worsened to diabetes if they had rather greater degress of glucose intolerance at baseline. In the two American studies obesity appeared to contribute to prediction, though the statistical analysis was limited to cross-tabulation of grouped data. The American studies also appear to contain a substantial number of grossly obese subjects, who were rare in our group.

Despite the predictive value of impaired glucose tolerance, in each of the four studies a substantial proportion of people reverted to normal. O'Sullivan and Mahan stated that remission was more likely in those who lost 10 pounds or more, but did not present data or say whether this was a significant finding. We found a surprising similarity in behaviour of body weight change over the five year follow-up between those who did or did not worsen to diabetes (see Table 4). In a study of a selected population of first degree relatives of diabetics Köbberling et al. [14] were also unable to find any correlation between changes in weight and changes in glucose tolerance.

The Birmingham Diabetes Survey Working Party [9] suggested that the risk of worsening to diabetes rose sharply when the two-hour blood sugar exceeded 7.5 mmol/l (135 mg/dl). Figure 2 indicates a level of 140 mg/dl in our study above which the risk sharply increases. Given the different conditions of the two investigations, the results are remarkably alike.

Table 4

Mean weight change (±S. E.) between baseline and five years for those not worsening to diabetes (n=141)	−8.567 (±0.92) lbs.
Mean weight change (±S. E.) between baseline and five years for those worsening to diabetes (n=24)	−8.32 (±1.88) lbs.
Mean weight change (±S. E.) between baseline and visit at which worsening to diabetes was confirmed (n=24)	−7.167 (±1.74) lbs.

Our present and previous observations [15], supported by those discussed, sustain the view that the finding of lesser degrees of glucose intolerance do not justify the diagnosis of diabetes mellitus or even indicate a necessary eventual progression to diabetes. If a descriptive term is required to categorise someone with glucose intolerance, then we would suggest 'impaired glucoe tolerance' (IGT), avoiding the word diabetes with all its implications.

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