Risk of Diabetes in the New Diagnostic Category of Impaired Fasting Glucose

A prospective analysis

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OBJECTIVE — To prospectively evaluate progression to diabetes in individuals with impaired glucose regulation as defined according to fasting glucose alone or an oral glucose tolerance test (OGTT) (i.e., both fasting and postload glucose) to compare the ability of these two screening methods to identify people at high risk of developing diabetes.

RESEARCH DESIGN AND METHODS — A working population of 1,245 nondiabetic telephone company employees aged 40–59 years was studied by OGTT in 1980. Participants were classified according to baseline fasting glucose only (as encouraged by the American Diabetes Association [ADA]) or OGTT (as recommended by the 1998 World Health Organization [WHO] consultation). Progression to diabetes was evaluated 11.5 years later according to the 1997 ADA criteria of a fasting plasma glucose level ≥7.0 mmol/l.

RESULTS — With the use of the OGTT, baseline prevalence of impaired glucose regulation was substantially higher than that with fasting glucose alone (7.2 vs. 3.2%); the two groups only overlap for 40.9% of the cases because a fairly large number of people with postload hyperglycemia (59.1%) have normal fasting glucose. Progression to diabetes in participants with normal fasting glucose and postload hyperglycemia is significantly more frequent than that of people with normoglycemia (32.5 vs. 7.2%; $P < 0.001$) and not significantly different from that of people with both fasting and postload hyperglycemia (i.e., 44.0%). However, the former are not identified as being at unusually high risk of diabetes unless an OGTT is performed. When the use of fasting glucose alone or OGTT was validated as a marker of progression to diabetes, sensitivity was substantially higher for the OGTT (33.3 vs. 9.0%) without major differences in specificity (92.6 vs. 97.0%).

CONCLUSIONS — These data (the only data so far available in Caucasians) support the viewpoint that for the identification of people at high risk of diabetes, the use of the OGTT should be maintained.

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In 1997, an expert committee of the American Diabetes Association (ADA) revised the classification and diagnostic criteria for diabetes promulgated by the National Diabetes Data Group in 1979 and by the World Health Organization (WHO) in 1980–1985 (1–3). The ADA expert committee encourages the use of fasting glucose rather than the oral glucose tolerance test (OGTT) for the diagnosis of diabetes and other categories of glucose regulation in clinical and epidemiological studies (4). Furthermore, the threshold for the diagnosis of diabetes has been lowered to a fasting plasma glucose level of 7.0 mmol/l (126 mg/dl), and the new diagnostic category of impaired fasting glucose (IFG), defined as fasting plasma glucose level of 6.1–6.9 mmol/l (110–125 mg/dl) and indicated together with the previous impaired glucose tolerance (IGT) as an intermediate stage between normal glucose regulation and diabetes, has been introduced. However, while evidence is given that a fasting glucose level of 7.0 mmol/l performs as well as a postload glucose level of ≥11.0 mmol/l (200 mg/dl) in the prediction of retinopathy, no validation is provided for the use of fasting glucose as compared with postload glucose to identify individuals at high risk of developing diabetes.

A provisional report of a WHO consultation on the diagnosis and classification of diabetes has been recently published (5). In this statement, in agreement with the ADA proposal, the threshold of 7.0 mmol/l for the diagnosis of diabetes is maintained and so is the category of IFG; however, at variance with the ADA guidelines, the OGTT is recommended as a screening procedure whenever possible, and the condition of IFG is included together with IGT in the broader category of impaired glucose regulation.

The clinical significance of the new category of IFG is little known, therefore extrapolating to this group the knowledge we have accumulated on IGT may not be correct because the two categories do not seem to extensively overlap and may well differ in terms of risk of developing overt diseases (6–11). In particular, the risk of progression to diabetes for individuals classified as having IFG is to date totally unexplored in Caucasians. This is a relevant piece of information needed to fully evaluate the prognostic value of IFG, which is particularly relevant now that the burden of diabetes is rapidly increasing and possibilities for the prevention of type 2 diabetes in high-risk individuals are being explored with increasing intensity.

Against this background, we focus on glucose metabolism abnormalities to evaluate the risk of progression to diabetes in people with impaired glucose regulation,

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Abbreviations: ADA, American Diabetes Association; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; WHO, World Health Organization.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline clinical characteristics of participants examined or not examined at follow-up*

	Examined	Not examined
n	560	581
Age (years)	44.1 ± 4.0*	47.8 ± 5.2
BMI (kg/m²)	26.9 ± 4.4	26.9 ± 4.2
Fasting glucose (mg/dl)	76.1 ± 14.7	75.1 ± 17.2
Postload glucose (mg/dl)	80.6 ± 30.1	78.5 ± 30.4
Sex (% male)	76.7†	53.3

*$P < 0.05$; †$P < 0.0001$ examined vs. not examined.

defined according to fasting and/or postload glucose.

RESEARCH DESIGN AND METHODS

— From 1979 to 1980, 1,285 telephone company employees (827 men [64%] and 458 women [36%]) in the age range of 40–59 years were screened in the province of Naples for major cardiovascular risk factors. Height and weight were recorded, and BMI was calculated. The screening protocol included, among others, an OGTT performed in the morning in the fasting state with a 75-g glucose load (1). Glucose was measured by the glucose oxidase method on venous whole blood (12) immediately deproteinized with perchloric acid; measurements were made before and 120 min after load. Excluded from this procedure were people who reported taking medication for diabetes (*n* = 29) or who had a previous diagnosis of diabetes made by a doctor (*n* = 11), thus leaving 1,245 participants with previously unknown diabetes. Participants were classified retrospectively on the basis of fasting glucose alone or on the basis of the OGTT (i.e., both fasting and postload glucose measurements). The following cutoff points were used: for fasting glucose, ≥6.1 mmol/l (110 mg/dl) equals diabetes, 5.6–6.0 mmol/l (100–109 mg/dl) equals IFG, <5.6 mmol/l (100 mg/dl) equals normoglycemia; for postload glucose, ≥10.0 mmol/l (180 mg/dl) equals diabetes, 6.7–9.9 mmol/l (120–179 mg/dl) equals IGT, <6.7 mmol/l (120 mg/dl) equals normoglycemia. A complete data set was available for 1,141 nondiabetic participants of whom 560 (49.0%) (430 men and 130 women) were reexamined in 1990–1991, i.e., 11.5 years apart. The main reason for loss of follow-up was the difficulty in tracing people who had in the meantime retired from work. This particularly affected the response rate in women because in those years, women retired at a younger age (5 years earlier) as compared with men. As a result, male gender was significantly more prevalent, and age was significantly lower among responders; however, this applied equally to the two groups with abnormal fasting glucose or abnormal OGTT (48.8 vs. 48.4 years and 53 vs. 50% males, respectively, for those not examined). Other characteristics of participants examined and not examined at follow-up are given in Table 1; no significant differences were observed with respect to BMI and fasting and postload glucose.

The second examination included measurement of fasting glucose on venous plasma and assessment of use of medications for diabetes. Progression to diabetes was defined as a fasting plasma glucose level ≥7.0 mmol/l, according to the 1997 ADA criteria or use of hypoglycemic drugs at the second examination.

Statistical analysis

Statistical analysis was performed by SPSS (13). Data are given as means and SDs or percentages. Differences between continuous variables were tested by an unpaired *t* test. Differences between proportions were tested by χ^2 analysis. Odds ratios, 95% CIs, sensitivity, and specificity were calculated according to standard methods.

RESULTS

— When solely using fasting glucose measurement in 1,141 participants, 36 (3.2%) had IFG (fasting glucose level of 5.6–6.0 mmol/l), while when using the OGTT, 86 participants (7.2%) were diagnosed with impaired glucose regulation (fasting glucose level of 5.6–6.0 mmol/l and/or postload glucose level of 6.7–9.9 mmol/l). The two groups with IFG or with impaired glucose regulation only overlap for 41.2% of the cases, because 58.2% of those with impaired glucose regulation had postload hyperglycemia but fasting glucose levels well within the normal range (Fig. 1*C*), and they are therefore identified as being at high risk of developing diabetes only if an OGTT is performed (i.e., postload glucose is measured). The progression to diabetes in 11.5 years, defined on the basis of a fasting plasma glucose level ≥7.0 mmol, according to the 1997 ADA criteria or treatment at the second examination, was observed in a similar proportion of those with impaired glucose regulation identified on the basis of fasting glucose or OGTT (25 vs. 30% respectively; NS) (Table 2). Only five people were taking hypoglycemic drugs: 3, 1, and 1 in the group with baseline normoglycemia, impaired fasting glucose, or impaired OGTT, respectively. These individuals also had a fasting glucose level >7.0 mmol/l.

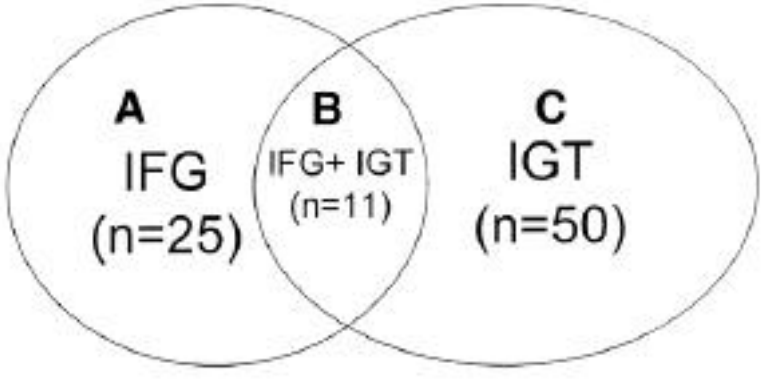

Figure 1—*Distribution of fasting and postload hyperglycemia in people with impaired glucose regulation at baseline (A + B) (n = 36) are identified on the basis of abnormal fasting glucose alone, as recommended by the 1997 ADA criteria. B + C (n = 61) are identified on the basis of abnormal postload glucose, as recommended by 1980–1985 WHO criteria. A + B + C (n = 86) are those with impaired glucose regulation, as identified by the 1998 WHO provisional report on the basis of abnormal fasting or postload glucose.*

Table 2—*Progression to diabetes by baseline fasting glucose alone or OGTT at 11.5 years of follow-up*

	Baseline measurements		
Fasting glucose	*n*	Progressed to diabetes [*n* (%)]	Odds ratio (95% CI)
Normal	540	49 (9.1)	1
Impaired	20	5 (25.0)	3.9 (1.01–10.4)
OGTT			
Normal	500	36 (7.2)	1
Impaired	60	18 (30.0)	5.5 (2.4–11.0)

OGTT was performed with fasting and/or postload glucose.

The diagnosis of impaired glucose regulation performed with the use of fasting glucose alone or with the OGTT were comparatively evaluated as markers of progression to diabetes; sensitivity was substantially higher with the use of the OGTT than with the use of solely fasting glucose (33.3 vs. 9.3%, respectively), without major differences in specificity (92.6 vs. 97.0%, respectively).

The two groups with impaired glucose regulation reported in Table 2 are not mutually exclusive; therefore, further analysis was performed using both fasting and postload glucose measurements to classify the participants (Table 3). Four groups were thus obtained: *1*) individuals with normoglycemia according to both fasting and postload glucose measurements, *2*) those with impaired glucose regulation according to both fasting and postload glucose measurements, *3*) those with normal fasting glucose and postload hyperglycemia (isolated postload hyperglycemia), and *4*) those with impaired fasting glucose and postload normoglycemia (isolated fasting hyperglycemia). Not unexpectedly, progression to diabetes was higher in all three groups with impaired glucose regulation at baseline with either criterion, as compared with individuals with baseline fasting and postload normoglycemia. Interestingly, in the group with postload hyperglycemia but normal fasting glucose, the rate of progression to diabetes was 32.5% in 11.5 years, which is not significantly different from that observed in people with both fasting and postload hyperglycemia (44.4%). Nonetheless, the former were not identified as being at high risk of diabetes unless an OGTT was performed and postload glucose was measured (Table 2).

CONCLUSIONS — Results of this study indicate that baseline with the use of the OGTT, the prevalence of abnormalities of glucose regulation is substantially higher than that with the sole use of fasting glucose measurement (7.1 vs. 3.1). Furthermore, only a minority of those with impaired fasting glucose have impaired postload glucose and vice versa (Fig. 1).

Clearly, the two tests diagnose different groups of people with impaired glucose regulation; furthermore, there are data indicating that reclassification occurs to a different extent depending on the age and BMI structure of the study population (11,14–16). Given this discordance, it is of the utmost importance to evaluate whether for clinical and epidemiological purposes it is reasonable to rely on fasting glucose alone as a marker of future progression to diabetes, thus discouraging the use of the OGTT. Results of this study are relevant inasmuch as they provide prospective data not available before. To our knowledge, this is in fact the first report in Caucasians on the risk of progression to diabetes in the new high-risk class of IFG identified by 1997 ADA and 1998 WHO diagnostic criteria (4,5). These data clearly indicate that impaired glucose regulation, defined either according to fasting glucose or with the use of the OGTT (i.e., both fasting and postload glucose measurement) is associated with a high risk of progression to diabetes. However, with the use of fasting glucose alone, a fairly large group of people at high risk of developing diabetes is not identified because their fasting glucose is well within the normoglycemic range, i.e., these people are diagnosed as having impaired glucose regulation only if an OGTT is performed because they show isolated postload hyperglycemia.

Therefore, it is our view that notwithstanding the inconveniences caused by the execution of the OGTT and the relatively low reproducibility of this test (17,18), it remains debatable whether it is appropriate to rely on fasting glucose alone for the identification of people at high risk of developing diabetes.

In fact, glucose metabolism abnormalities (either IFG or IGT) do not represent clinical entities per se, but represent high-risk conditions; therefore, the choice of the screening test has clear implications for prevention and is an issue of major practical importance at a time when lifestyle changes as well as the use of drugs are being tested with increasing intensity as means for primary prevention of type 2 diabetes in high-risk people (19–24). On the basis of the results of this study and assuming that diabetes could effectively be prevented, the use of fasting glucose alone as a screening test identifies only a small proportion of people in whom appropriate treatment might delay or hamper the development of diabetes. In addition, by measuring postload glucose, sensitivity increases substantially, thus extending a potentially beneficial treatment to a much larger group of people without loss in specificity. When screening, the advantage of using a quicker and less expensive test such as fasting glucose must be weighed against the disadvantage of missing too many potentially preventable cases; on the other hand, because treatment is usually costly and not always devoid of untoward effects (on either physical or psychological well-being), it is of utmost importance to keep unnecessary treatment to a minimum. The use of the OGTT, as recommended by WHO, seems to meet these

Table 3—*Progression to diabetes by baseline glycemic status defined according to fasting and postload glucose at 11.5 years of follow-up*

Baseline glucose				
Fasting	Postload	*n*	Progressed to diabetes [*n* (%)]	Odds ratio (95% CI)
Normal	Normal	500	36 (7.2)	1
Impaired	Impaired	9	4 (44.4)	10.3 (2.2–46.8)
Normal	Impaired	40	13 (32.5)	6.2 (2.7–13.8)
Impaired	Normal	11	1 (9.1)	1.2 (0.3–10.2)

requirements better than the sole use of fasting glucose, as encouraged by the 1997 ADA criteria.

Limitations of this study mainly arise from the low reexamination rate; this is a crucial problem when assessing prevalence and incidence of diseases, which is not among the aims of this work. The rate of progression to diabetes in our study is lower than expected: those lost to follow-up were also more likely to have diabetes. As far as progression to diabetes is concerned, those lost to follow-up were older and more frequently women; however, this applied equally to the two groups with abnormal fasting glucose or abnormal OGTT, while no differences in other predictors of diabetes, such as BMI and fasting or postload glucose, were observed between those examined or not examined at follow-up. The OGTT was not performed at the second examination and diabetes was diagnosed on the basis of a fasting glucose level ≥7.0 mmol, according the 1997 ADA criteria; however, results based on fasting glucose are in our opinion still relevant because this is the currently recommended definition for clinical diagnosis of diabetes. Small numbers prevent performing separate analyses according to sex, age, or BMI strata, thus leaving unexplored whether results can be extrapolated to other populations with different sex and age composition. Notwithstanding these limitations given the lack of information on this important topic and the considerable length of time required to perform ad hoc studies, our findings represent an important piece of information from which better insight can be gained on the most appropriate strategy for the identification of people at high risk of developing diabetes.

In conclusion, the results of this study, the only population-based study so far available in Caucasians, support the WHO viewpoint that the OGTT should be maintained if screening for individuals at high risk of developing diabetes is required.

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