Screening for Impaired Glucose Tolerance

Results from a population-based study in 21,057 individuals

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OBJECTIVE — To study the distribution of fasting plasma glucose and impaired glucose tolerance (IGT) in a large general population and explore their possible implications for large-scale screening. The study focuses especially on the relation to age, obesity, and heredity background of diabetes.

RESEARCH DESIGN AND METHODS — A total of 21,057 men and women aged 30–60 years were used for this cross-sectional study. Individuals with known diabetes and individuals with a fasting plasma glucose ≥7 mmol/l were excluded. A physical examination, including blood sampling and an oral glucose tolerance test, was conducted.

RESULTS — The relative risk for IGT increased more than fourfold among obese subjects compared with normal-weight subjects, yet only 25% of IGT subjects were obese. Similarly, IGT subjects more frequently reported having first-degree relatives with diabetes than did subjects with normal glucose tolerance. Nonetheless, >70% of IGT subjects reported no heredity background of diabetes. Subjects with IGT showed higher mean values of BMI, blood pressure, and triglycerides. Only 13% of the men and 19% of the women having impaired fasting glucose (IFG) fulfilled the criteria of IGT.

CONCLUSIONS — The present study shows that a high-risk screening strategy for IGT targeted solely toward subjects with obesity and/or heredity background of diabetes will fail to detect the majority of subjects with IGT in the general population. The new concept of IFG may not replace the concept of IGT as a risk marker for worsening to diabetes.

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Impaired glucose tolerance (IGT) was defined in 1979 and replaced terms such as borderline diabetes, pre-diabetes, latent diabetes, and chemical diabetes (1,2). IGT is determined after an overnight fast by performing an oral glucose tolerance test (OGTT) measuring the glucose level 2 h after ingestion of a 75-g oral glucose load (3). An individual is classified as having IGT if the fasting plasma glucose is less than required for the diagnosis of diabetes and the 2-h plasma glucose during an OGTT is intermediate between the normal and the diabetic range. The purpose of the IGT classification was to define subjects at increased risk of developing cardiovascular disease and/or type 2 diabetes. Earlier studies have reported a twofold increase in cardiovascular disease in men and an even larger increase in women in a group of subjects with IGT when compared with control subjects with normal glucose tolerance (4,5). This finding might be attributable to the clustering of cardiovascular risk factors found in the insulin resistance syndrome (6,7).

Insulin resistance seems to be an essential part of the development of IGT (8,9) and recently the importance of a disturbed insulin secretion (especially of the first phase) has been emphasized (10,11). It is generally accepted that IGT may represent an intermediate stage in the natural history of type 2 diabetes (12,13), and a yearly deterioration to diabetes of 1.5–4% in IGT subjects over a 10-year period has been found in many populations (14). At follow-up after 2 years in the Hoorn Study, 28.5% of the IGT subjects had worsened to diabetes. In this study, high fasting proinsulin levels, an indication of a β-cell dysfunction, seemed to predict the worsening to diabetes (15).

For several years, it has been debated if it is feasible to prevent type 2 diabetes by using a high-risk strategy consisting of a screening procedure for IGT and a subsequent long-term intervention program (13,16,17). Recently, the criterion for diagnosis of diabetes was changed with a lowering of the fasting plasma glucose threshold from 7.8 to 7.0 mmol/l (18,19). This new definition of diabetes was used in the analyses of the present article.

The aims of the present cross-sectional study were *1*) to describe the distribution of IGT in a large study population with special reference to differences in age, body weight, and hereditary background of diabetes; *2*) to estimate the agreement between impaired fasting glucose (IFG) and IGT; and *3*) to evaluate the cardiovascular risk factor pattern in subjects with IGT compared with subjects with normal glucose tolerance.

RESEARCH DESIGN AND METHODS

Study population

Since 1985, in the province of Västerbotten in the north of Sweden, there has been an ongoing community intervention program on cardiovascular disease and diabetes—the Västerbotten Intervention Program (VIP). As a part of this program, all men and

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

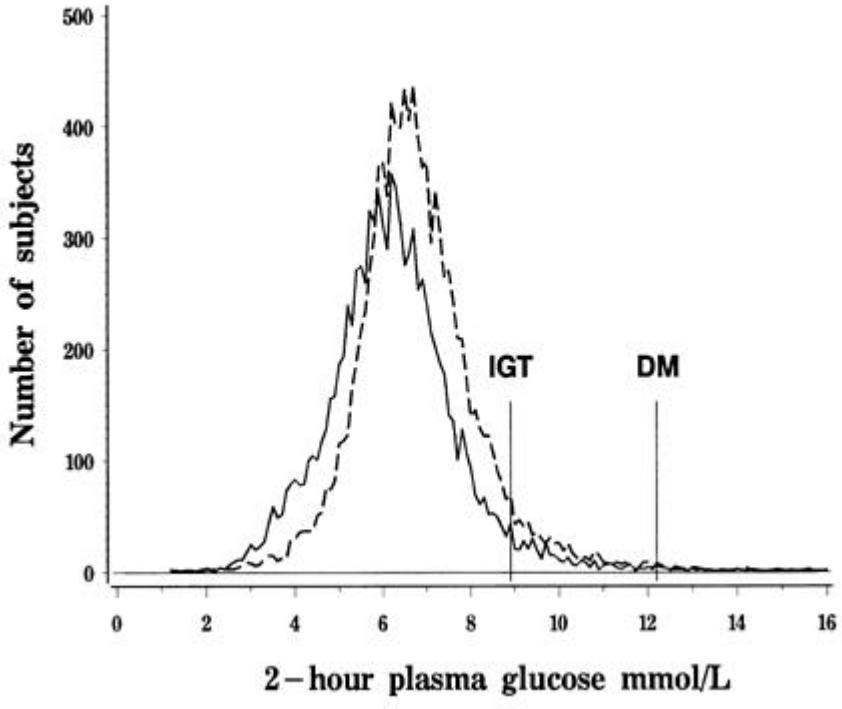

Figure 1—*The distribution of plasma glucose concentrations 2 h after a 75-g glucose challenge in men (——) and women (– – –) in the VIP, 1992–97* (n = *21,057). DM, diabetes.*

women were invited to a health survey at the age of 30, 40, 50, and 60 years. From 1992, the requested minimum fasting period before blood sampling was changed from 4 to 8 h. In practice, this implied an overnight fast. The participation rate during various years in the VIP has varied between 55 and 60% of the eligible persons invited. To explore potential socioeconomic differences between participants and nonparticipants in the study, a record linkage was made between all invited to the 1992 and 1993 health surveys (participants and nonparticipants) and the 1990 Population and Housing Census in Sweden. No obvious social differences (employment, education, and total income) were found when participants were compared with non-participants (20).

Inclusion criteria for the present study population were a completed health survey within the VIP, preceded by >8 h of fast and without missing values in the main variables of the study such as fasting and stimulated (2-h) plasma glucose and BMI. Participants with known diabetes (*n* = 458) and participants with a fasting plasma glucose ≥7.0 mmol/l (*n* = 384) were excluded. During the period from January 1992 to June 1997, 21,057 subjects (9,863 men and 11,194 women) fulfilled these criteria and formed the basis of the present study. Of these, 53 men and 72 women had a 2-h plasma glucose during an OGTT in the diabetic range.

Methods

A total of 48 examination teams were used in the sampling procedure. Only four teams conducted <100 health surveys. All participants in the study received a questionnaire on lifestyle, including smoking habits, diet, and level of physical activity. At the health survey, blood pressure was measured after a 5-min rest. Body weight was measured in light indoor clothing and recorded to the nearest kilogram. Height was measured to the nearest centimeter without shoes. BMI was calculated as weight (kilograms) divided by height (meters) squared. Smokers were defined as those reporting daily smoking. Ex-smokers or "occasional" smokers were classified as nonsmokers. On all participants a simplified OGTT was performed according to the World Health Organization (WHO) standard, using a 75-g anhydric glucose load and measuring plasma glucose after 2 h (3). All stimulated (2-h) glucose concentrations were measured on capillary plasma using Reflotron benchtop analyzers (Boehringer Mannheim, Mannheim, Germany) (21). Since 2-h glucose measurements in capillary plasma yield higher values (on average 1.1 mmol/l higher) than in venous plasma, IGT has, in agreement with WHO standards (3), been defined as a 2-h plasma glucose of ≥8.9 and <12.2 mmol/l. A 2-h plasma glucose of ≥12.2 mmol/l was considered as the diabetic range. Total cholesterol and triglyceride concentrations were measured in a similar manner at the time of the health survey on fresh fasting plasma using Reflotron benchtop analyzers (21), whereas plasma for HDL cholesterol was sent to a nearby hospital for analysis. HDL cholesterol was measured after precipitation of the other lipoproteins with sodium phosphowolframate/magnesium chloride. Sampling for plasma triglyceride and HDL cholesterol concentrations was optional

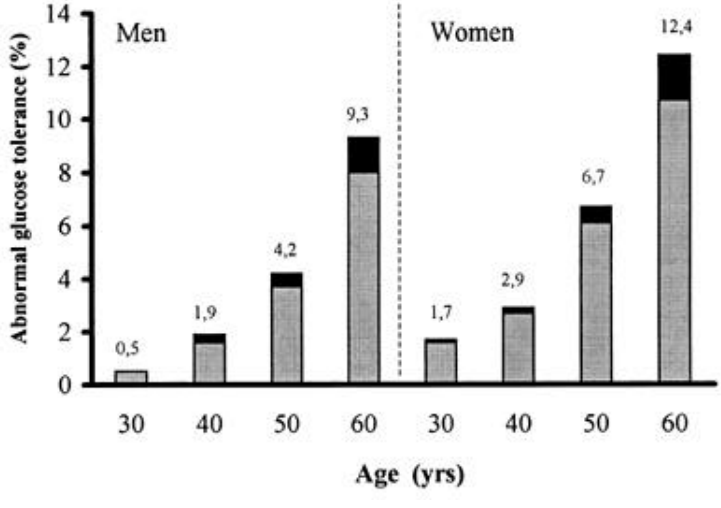

Figure 2—*The distribution of abnormal glucose tolerance in men and women in different age-groups in the VIP, 1992–97* (n = *21,057). IGT (■) and 2-h plasma glucose values in the diabetic range (■) are shown.*

Table 1—*Cardiovascular risk factors, proportions of smoking, and hereditary background of diabetes for subjects with normal glucose tolerance and IGT*

	Men		Women	
	Normal	IGT	Normal	IGT
n	9,459	351	10,511	611
BMI (kg/m²)	25.7 ± 0.04	27.4 ± 0.18*	24.9 ± 0.04	26.9 ± 0.17*
Body weight (kg)	81.6 ± 0.12	85.8 ± 0.64*	67.4 ± 0.11	72.0 ± 0.47*
Systolic blood pressure (mmHg)	128.3 ± 0.16	136.6 ± 0.81*	124.1 ± 0.15	132.6 ± 0.63*
Diastolic blood pressure (mmHg)	80.2 ± 0.10	84.6 ± 0.53*	76.9 ± 0.09	80.8 ± 0.39*
Fasting plasma glucose (mmol/l)	5.37 ± 0.01	5.74 ± 0.03*	5.28 ± 0.01	5.60 ± 0.02*
2-h plasma glucose (mmol/l)	6.07 ± 0.01	9.87 ± 0.07*	6.57 ± 0.01	9.87 ± 0.04*
Total cholesterol (mmol/l)	5.82 ± 0.01	5.75 ± 0.07	5.69 ± 0.01	5.74 ± 0.05
Triglycerides (mmol/l)	1.54 (1.10–1.97)	1.84 (1.34–2.47)*	1.35 (1.02–1.64)	1.57 (1.15–2.14)*
HDL cholesterol (mmol/l)	1.20 ± 0.01	1.12 ± 0.04*	1.44 ± 0.01	1.25 ± 0.03*
Daily smoking (%)	17.7	15.4	22.0	18.2†
First-degree relative with diabetes (%)	14.6	24.5*	14.6	28.3*

Data are *n*, age-adjusted means ± SEM, geometric means (interquartile range), or %. *n* for triglycerides: 6,032 men, 7,462 women; *n* for HDL cholesterol: 2,719 men, 2,780 women. Hypothesis testing was performed with Student's *t* test for differences in means and with χ^2 test for differences in proportions. *$P < 0.001$ vs. normal; †$P < 0.05$ vs. normal.

and conducted in 65 and 26% of the subjects, respectively.

The study was approved by the Research Ethics Committee at Umeå University and the data handling procedures by the National Computer Data Inspection Board.

Statistical analysis

The Statistical Analysis System (SAS) version 6.12 (SAS Institute, Cary, NC) was used. The triglyceride concentration had a skewed distribution and an approximate normal distribution was achieved after logarithmic transformation, which was used in all statistical analyses. Adjustment for age was performed by using analysis of covariance.

RESULTS — Figure 1 illustrates the unimodal distribution of 2-h plasma glucose in the study population. The proportion of IGT was significantly higher in women (5.5%) than in men (3.6%). In both men and women abnormal glucose tolerance (IGT and undiagnosed diabetes) increased with age (Fig. 2). The prevalence of abnormal glucose tolerance was 0.5% in 30-year-old men, reaching 9.3% at the age of 60. The corresponding results for women were 1.7 and 12.4%. In addition, 0.5% of the men and 0.6% of the women had a capillary 2-h plasma glucose level in the diabetic range (≥12.2 mmol/l).

The mean age of men (53.4 years) and women (52.3 years) with IGT was significantly higher than the mean age of men (45.8 years) and women (45.9 years) with normal glucose tolerance ($P < 0.001$). In both men and women, age-adjusted means of BMI, body weight, blood pressure, fasting plasma glucose, 2-h plasma glucose, and plasma triglyceride concentration were higher and HDL cholesterol lower in subjects with IGT compared with subjects with normal glucose tolerance. There was no difference in total plasma cholesterol concentration. Subjects with IGT more often reported having first-degree relatives with diabetes ($P < 0.001$) (Table 1).

In Fig. 3, BMI was divided in seven subgroups from underweight (<20 kg/m²) to severe obesity (≥35 kg/m²). The relative frequency of IGT among obese subjects (BMI ≥30 kg/m²) was four times that of subjects with normal body weight (BMI 20–24.9 kg/m²) (10.8 vs. 2.7%). Overweight subjects (BMI 25–29.9 kg/m²) had a frequency of IGT twice that of subjects with normal weight (5.4 vs. 2.7%). However, comparing absolute numbers of individuals with IGT in the different body weight classes, as indicated by the bars in Fig. 3, did show that the majority of subjects with IGT were found among those with a modestly increased body weight (45%) or with a normal body weight (28%). Only 25% of the subjects with IGT were classified as obese.

In Table 2 the prevalence of IGT or undiagnosed diabetes (2-h plasma glucose in the diabetic range) was calculated for different combinations of age, BMI, and hereditary background of diabetes, i.e., answering "yes" on the question concerning diabetes among first-degree relatives. In addition, numbers-needed-to-screen in order to detect one individual with abnormal glucose tolerance (the sum of IGT and undiagnosed diabetes) was calculated. In stratified subgroup analyses comparing individuals of the same sex, age, and body weight, an association was found between hereditary background of diabetes and a higher proportion of IGT in 60-year-old men of normal weight ($P < 0.05$) and in 40- and 60-year-old women with overweight ($P < 0.05$). Nonetheless, 168/222 (75.6%) men and 257/361 (71.2%) women with IGT reported no hereditary background of diabetes. Numbers-needed-to-screen to find

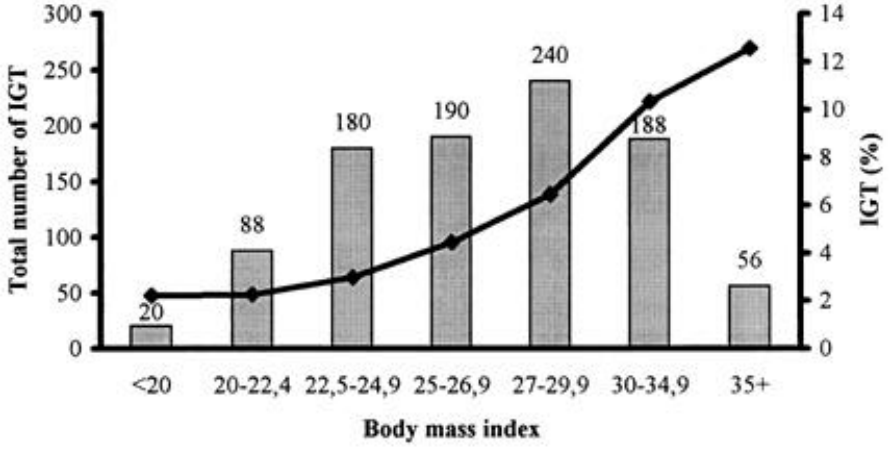

Figure 3—*The age-adjusted prevalence of IGT (curve) and the total numbers of subjects with IGT (bars) in relation to body weight in the VIP* (n = *21,057*).

Table 2—*Prevalence in the population of IGT and undiagnosed diabetes in relation to age, BMI, and hereditary background of diabetes*

Type of exposure	*n*	Prevalence		Number-needed-to-screen
		IGT	Diabetes	
Men 40 years of age				
BMI <27, no hereditary background	1,769	1.1 (20)	0.2 (4)	77
BMI <27, with hereditary background	268	1.9 (5)	0 (0)	53
BMI ≥27, no hereditary background	661	2.0 (13)	0.2 (1)	46
BMI ≥27, with hereditary background	180	4.4 (8)	1.7 (3)	16
Men 60 years of age				
BMI <27, no hereditary background	1,199	4.6 (55)	0.8 (9)	19
BMI <27, with hereditary background	221	8.6 (19)	0.9 (2)	11
BMI ≥27, no hereditary background	642	12.5 (80)	2.0 (13)	7
BMI ≥27, with hereditary background	158	13.9 (22)	3.2 (5)	6
Women 40 years of age				
BMI <27, no hereditary background	2,218	2.0 (44)	0.1 (2)	48
BMI <27, with hereditary background	448	2.9 (13)	0 (0)	35
BMI ≥27, no hereditary background	494	3.9 (19)	0.4 (2)	23
BMI ≥27, with hereditary background	146	8.2 (12)	0.7 (1)	11
Women 60 years of age				
BMI <27, no hereditary background	1,274	8.6 (110)	0.6 (8)	11
BMI <27, with hereditary background	344	9.6 (33)	2.3 (8)	8
BMI ≥27, no hereditary background	686	12.2 (84)	2.0 (14)	7
BMI ≥27, with hereditary background	250	18.4 (46)	5.2 (13)	4

Data are *n* or % (*n*). All subjects with diabetes and all with fasting plasma glucose ≥7.0 mmol/l were excluded. Number-needed-to-screen is the number needed to determine one case of abnormal glucose tolerance (the sum of IGT and undiagnosed diabetes).

one person with abnormal glucose tolerance in 40-year-old men and women were three to six times higher than in 60-year-old subjects of comparable weight and hereditary background of diabetes (Table 2).

A high degree of discrepancy was found when the newly introduced concept of impaired fasting glucose (IFG), i.e., a fasting plasma glucose ≥6.1 and <7.0 mmol/l, was compared with IGT. Using IFG as a means to detect IGT showed a low sensitivity and a high specificity. With a prevalence of IGT in the present study population of ~5% the positive predictive value was low. In men, only 13% of the IFG subjects showed a 2-h plasma glucose in the range of IGT. The corresponding figure in women was 19% (Table 3).

CONCLUSIONS — The VIP may at present be the largest population-based survey using an OGTT to classify participants in different glucose tolerance categories (20). The new diagnostic criteria of diabetes were applied in the present study (18,19) and all subjects with a fasting plasma glucose of ≥7.0 mmol/l were excluded. A prevalence of IGT in the 30- to 60-year-old population of 3.6% for men and of 5.5% for women was found. The present study confirms the results of earlier studies of a significantly more atherothrombotic risk factor profile (BMI, blood pressure, and triglycerides) in the group of IGT compared to the normal group (22,23). It was optional to measure triglyceride and HDL cholesterol concentrations. The choice whether to include these variables was made at the start of the study by the different examination teams (health care centers). This option may have compromised the representativeness of the cohort with respect to these variables—however, probably much less so than if every participant separately were to make that decision.

Although the relative risk of having IGT increased by increasing body weight and by reporting hereditary background of diabetes, the study clearly demonstrated that the majority of the IGT subjects were nonobese and had no hereditary background of diabetes. This result must seriously call into question programs for primary prevention of type 2 diabetes in which the screening procedure for IGT subjects is targeted solely toward obesity and hereditary background of diabetes. At least this is true if we assume that IGT is the predominant risk variable for worsening to diabetes, overriding both body weight and heredity. On the other hand, if the screening were to target only 60-year-old overweight people, it ought to be effective from a cost-benefit point of view, even if the chosen subgroup represents only a small portion of IGT in the population. Simultaneously, we must acknowledge the imprecision that exists in using the OGTT with low within-subject reproducibility for repeated OGTTs (24). It should also be noted that this study was performed in a population with a relatively low prevalence of obesity (25). Obviously, if the prevalence of obesity is higher, a higher absolute number of individuals with abnormal glucose tolerance will be detected among obese people. However, even if the prevalence of obesity were twice as high as in the Swedish population, the majority of people with IGT would still be nonobese.

Using the two-step model for diabetes proposed by Saad (26), the diabetic process can be divided into a first step, which includes the transition from normal to IGT, and a second step, which is the worsening from IGT to type 2 diabetes. In six prospective studies the worsening from IGT to diabetes varied from 3.6 to 8.7% per year

Table 3—*Comparison between IFG and IGT*

OGTT	Fasting glucose	
	Normal	IFG
Men (*n* = 9,810)		
Normal	8,652 (88.2)	807 (8.2)
IGT	234 (2.4)	117 (1.2)
Women (*n* = 11,122)		
Normal	9,896 (89.0)	615 (5.5)
IGT	468 (4.2)	143 (1.3)

Data are *n* (%). For IFG to predict IGT for men (women): sensitivity 0.33 (0.23), specificity 0.92 (0.94), and positive predictive value 0.13 (0.19).

(27). In the combined analysis of all six studies, but not in all of the separate studies, BMI was associated with increased diabetes incidence independently of fasting and postload glucose levels. However, family history of diabetes was not associated with worsening of IGT to diabetes.

The positive predictive value of IFG for IGT was low, suggesting that we cannot apply our present experience of the relationship between IGT and type 2 diabetes on individuals having IFG. At present, no method seems to be able to replace the OGTT when working with a high-risk strategy in the primary prevention of diabetes (17,28,29). The usefulness of IFG must be determined in future long-term prospective studies.

In summary, the majority of the IGT subjects in the present population-based study were nonobese and reported no first-degree relatives with diabetes. IFG may not be used instead of IGT when screening for high-risk individuals in the primary prevention of type 2 diabetes.

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