Fasting Glucose, Obesity, and Metabolic Syndrome as Predictors of Type 2 Diabetes: The Cooper Center Longitudinal Study

Laura F. DeFina, MD,* Gloria Lena Vega, PhD,† David Leonard, PhD,† and Scott M. Grundy, MD, PhD†

Background: To determine risk for type 2 diabetes in subjects with fasting glucose levels in the ranges of normoglycemia, mild hyperglycemia, and intermediate hyperglycemia and to assess the effect of obesity and metabolic syndrome on this risk.

Subjects and Methods: Incidence of type 2 diabetes mellitus was evaluated in 28,209 relatively healthy subjects participating in the Cooper Center Longitudinal Study. They were included in the study if they had more than 1 fasting plasma glucose measurement, anthropometry, and other parameters of interest. Three subgroups were identified: normoglycemic (<5.6 mmol/L), mild hyperglycemia (5.6–6.0 mmol/L), and intermediate hyperglycemia (6.1–7.0 mmol/L). Diabetes incidence was calculated in categories of sex, age, obesity, and metabolic syndrome status. Incident diabetes was assessed at the earliest clinic visit at which the individual exhibited a blood glucose level of more than 7.0 mmol/L or reported a diagnosis of diabetes.

Results: Thirty-one percent of men and 15.9% of women had mild hyperglycemia and 11.9% of men and 3.6% of women had intermediate hyperglycemia. Yearly conversion rates to diabetes were low in individuals with normoglycemia and mild hyperglycemia but were strikingly higher in those with intermediate hyperglycemia. In subjects with intermediate hyperglycemia, presence of obesity and/or metabolic syndrome doubled conversion rates to diabetes.

Conclusions: This study showed a marked difference in outcomes in subjects with mild and intermediate hyperglycemia. Moreover, obesity and metabolic syndrome were associated with strikingly elevated risk for diabetes in subjects with intermediate hyperglycemia. Thus intermediate hyperglycemia plus obesity/metabolic syndrome seemingly justifies intensive clinical intervention for prevention of both diabetes and cardiovascular disease.

Key Words: fasting blood glucose, obesity, metabolic syndrome, diabetes risk predictors

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The Diabetes Prevention Program (DPP) reported that the onset of type 2 diabetes can be delayed either by intensive lifestyle intervention or with glucose-lowering drugs.¹ These observations, among others,^{2–4} have engendered interest in the prevention of diabetes in individuals at risk. The major risk factors for diabetes are impaired fasting glucose (IFG) and impaired glucose tolerance (IGT).⁵ Other risk factors for diabetes are obesity, family history, and metabolic syndrome. For clinical

prevention of type 2 diabetes, with either intensive lifestyle intervention or with drugs (eg, metformin), patient selection becomes a critical issue. For example, a recent American Diabetes Association (ADA) consensus statement recommended that lifestyle changes be advocated for any person with either IFG or IGT,⁶ but before drug therapy is used, an individual should be found to have both IFG and IGT. Oral glucose tolerance testing (OGTT) is required to detect IGT. There are advantages and disadvantages to requiring OGTT before clinical intervention. Among the latter are extra costs, inconvenience, and variability in results. Consideration therefore might be given to alternate approaches to identifying individuals with IFG who are at higher risk for conversion to diabetes and who would benefit from intensive lifestyle intervention. To examine factors affecting conversion of IFG to diabetes, we analyzed follow-up data in the Cooper Center Longitudinal Study (CCLS). Two questions were addressed: (a) at what levels of fasting glucose in persons with IFG should intensive lifestyle intervention be considered? and (b) what additional factors short of OGTT can be used to guide the decision for clinical intervention?

MATERIALS AND METHODS

The CCLS includes data on more than 100,000 patients seen at the Cooper Clinic from 1970 to 2010. Subjects participating in CCLS had a thorough medical history and physical examination, anthropometry, extensive laboratories, and cardiovascular fitness testing. Patients signed an informed consent and approved use of their data for research. Data collection and informed consent are reviewed and approved by The Cooper Institute Institutional Review Board annually. Privacy precautions were preserved through The Cooper Institute policies and procedures. All data were deidentified before analysis.

Study Population

The current study consisted of 28,209 patients, 78.4% of them men, and ages 18 to 98 years. Data were evaluated for all available clinic visits between 1971 and 2009 for each individual seen at least twice and for whom each visit had complete data for age, body mass index, and fasting blood glucose. Patients with fasting blood glucose levels of less than 3.9 mmol/L and more than 7.0 mmol/L were excluded from this analysis. The cohort consists of persons who are predominantly non-Hispanic white (>95%), college-educated, employed or formerly employed in professional occupations, middle to upper income, have access to health care, and are generally self-referred to the clinic, although approximately 30% are referred by their employer for executive preventive care examinations. Follow-up intervals ranged from annually to 39 years apart based on physician's recommendation, patient's preference, or corporate policy. At the time of these analyses, medication data were not available in the database other than current use of insulin or not.

*From The Cooper Institute, Dallas TX; and †University of Texas Southwestern Medical Center, Dallas TX.

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Reprints: Laura F. DeFina, MD, The Cooper Institute, 12330 Preston Rd,

Dallas TX 75230. E-mail: ldefina@cooperinst.org.

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Anthropometric Measurements

The Cooper Clinic evaluation consists of anthropometric information including height, weight, and waist girth. Height and weight were measured in light clothing and without shoes using a standard clinical scale and stadiometer. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist girth was measured at the level of the umbilicus with a plastic anthropometric tape.

Clinical Measurements

The comprehensive medical history and physical examination included vital signs and laboratory tests. Seated resting blood pressure was obtained with a mercury sphygmomanometer using the American Heart Association protocol. Fasting venous blood was drawn after a 12-hour fast and was assayed for blood glucose, high-density lipoprotein, low-density lipoprotein, triglycerides, and routine clinical chemistries using automated techniques at the Cooper Clinic laboratory following the standards of the US Centers for Disease Control and Prevention Lipid Standardization Program. Four levels of fasting glucose were identified: normoglycemia (3.9–5.5 mmol/L), mild hyperglycemia (5.6–6.0 mmol/L), intermediate hyperglycemia (6.1–7.0 mmol/L), and type 2 diabetes (>7.0 mmol/L). The term *intermediate hyperglycemia* as recommended by the World Health Organization and International Diabetes Federation⁵ includes both IFG and IGT. However, in the current paper, it will refer exclusively to IFG with a fasting glucose of 6.1–7.0 mmol/L. A diagnosis of metabolic syndrome was based on recent consensus criteria,⁷ which requires 3 or more of the following risk factors: waist circumference greater than 102 cm in men and greater than 88 cm in women or, in the absence of waist circumference, BMI of 29 kg/m² or greater in men and BMI of 26 kg/m² or greater in women; triglyceride level of 150 mg/dL or greater or treatment with drugs for elevated triglycerides; HDL cholesterol of less than 40 mg/dL in men and less than 50 mg/dL in women or treatment with drugs for decreased HDL-C; blood pressure of 130/85 mm Hg or higher or on drug treatment for hypertension; and fasting glucose of more than 5.6 mmol/L.

Statistical Analysis

For each individual with initial glucose in the range of 3.9 to 7.0 mmol/L, time to incident diabetes was calculated as the difference in examination year between the initial clinic visit and the earliest clinic visit at which the individual exhibited a blood glucose level greater than 7.0 mmol/L or reported a diagnosis of diabetes. The time to incident diabetes was therefore interval censored. Subgroup-specific incidence rates were estimated by fitting exponential survival models to those subgroups, treating the time to incident diabetes as right censored and continuous. The error in assuming that event times are right-censored and continuous if in fact they are interval censored is negligible if the incidence rates are small, as they are in the present analysis. Exponential survival models also provided significance tests of subgroup factors. In each model, fasting glucose was entered as a main effect along with one other subgrouping effect and the corresponding interaction effect. Incidence models were fit to sex-specific subsamples and to the entire sample. Regression rates were estimated in a similar manner, calculating the time to achieve glucose for each individual initially in the range of 5.6 to 7.0 mmol/L.

Data are summarized as means $\pm$ SD. Demographic and clinical variables assessed at the initial clinic visit were tested for sex-specific trends using the Jonckheere-Terpstra nonparametric trend test and for sex differences using the Wilcoxon rank sum test. For comparisons of glucose categories within sexes, independent samples *t* test were performed. SAS/STAT software (Cary NC), version 9.1, was used for all analyses.

RESULTS

Baseline characteristics at the first examination for men and women with normoglycemia, mild hyperglycemia, and intermediate hyperglycemia are shown in Table 1. Fifty-seven percent of the men and 80.6% of the women were normoglycemic; 30.6% and 15.9% of men and women, respectively, had mild hyperglycemia, and 11.9% of men and 3.6% of women had intermediate hyperglycemia. There were 1138 incident cases of diabetes in the men and 130 in the women during a

TABLE 1. Demographic and Clinical Characteristics Assessed at Initial Clinic Visit, Cooper Center Longitudinal Study

	Men			Women		
Glycemia status	Normal	Mild	Intermediate	Normal	Mild	Intermediate
Fasting blood glucose range, mmol/L	3.89–5.50	5.55–6.06	6.11–6.94	3.89–5.50	5.55–6.06	6.11–6.94
Number of subjects (% of sex)	12,709 (57.5)	6771 (30.6)	2635 (11.9)	4909 (80.6)	967 (15.9)	218 (3.6)
Characteristic*	Mean (SE)			Mean (SE)		
Age, yrs	43.3 (0.1)	45.3 (0.1)	47 (0.2)	44.6 (0.1)	47.8 (0.3)	50.8 (0.7)
BMI, kg/m ²	26 (0.0)	26.7 (0.0)	27.4 (0.1)	22.9 (0.1)	24.1 (0.1)	25.7 (0.4)
BMI $\geq$ 30 kg/m ² , %	10.6	14.5	21.0	5.3	9.5	19.7
Hypertension, %	11.8	16.0	21.3	9.2	12.	19.7
Smoker, %	14.7	14.9	15.9	7.3	6.9	8.7
Blood glucose, mmol/L	5.07 (0.00)	5.71 (0.00)	6.29 (0.00)	4.92 (0.00)	5.68 (0.01)	6.30 (0.02)
Triglycerides, mmol/L	1.36 (0.01)	1.57 (0.01)	1.82 (0.03)	.99 (0.01)	1.15 (0.03)	1.36 (0.05)
HDL cholesterol, mmol/L	1.22 (0.00)	1.20 (0.00)	1.18 (0.01)	1.68 (0.01)	1.63 (0.01)	1.62 (0.04)
non-HDL cholesterol, mmol/L	3.98 (0.01)	4.21 (0.01)	4.37 (0.03)	3.38 (0.01)	3.66 (0.03)	3.90 (0.08)
Metabolic syndrome, %	9.3	39.0	52.9	3.5	19.5	40.4
Systolic blood pressure, mm Hg	120.1 (0.1)	122.7 (0.2)	126.4 (0.3)	112.4 (0.2)	116.4 (0.5)	122.2 (1.2)
Diastolic blood pressure, mm Hg	80.4 (0.1)	82.1 (0.1)	83.7 (0.2)	75.8 (0.1)	77.7 (0.3)	79.8 (0.7)

*Trends in differences between sexes: all significant, $P < 0.001$; within sex: all significant, $P < 0.001$ except Smoker, %; $P = 0.19$ (men) and $P = 0.99$ (women).

FIGURE 1. Annualized conversion to diabetes for all men and all women grouped by glycemic status (normoglycemia [white], mild hyperglycemia [gray], and intermediate hyperglycemia [black]). Numbers inside the bars represent the number of individuals.

follow-up ranging from 1 year to 39 years, with a mean (SD) of 7.1 (6.8) years.

For both men and women, by trend analysis, higher glucose levels were associated with a greater rate of conversion to diabetes ($P < 0.001$). Annualized conversion rates for normoglycemic subjects were less than 0.5% (Fig. 1). For men with mild hyperglycemia, 0.8% converted to diabetes per year; for women, the rate was 0.6% per year. For men with intermediate hyperglycemia, progression was 2.5% per year; whereas in women, it was 2.3% per year.

For all men, age was not associated with rates of conversion to diabetes ($P = 0.104$ by trend analysis). However, in both categories of hyperglycemia, older men were more likely to develop diabetes than younger men of the matched categories (Fig. 2). For all women, age was positively associated with risk for diabetes ($P < 0.005$). This can be explained by the greater risk in the large number of normoglycemic women; in mild and

FIGURE 2. Annualized conversion to diabetes for men and women younger than 55 years and 55 years or older. White bars indicate normoglycemia, gray bars indicate mild hyperglycemia, and black bars indicate intermediate hyperglycemia. Asterisk indicates that older persons had significantly greater rates of conversion to diabetes compared to rates in younger people in the same glycemic category.

FIGURE 3. Annualized conversion to diabetes for men and women with body mass index less than 30 kg/m² and 30 kg/m² or more. White bars indicate normoglycemia, gray bars indicate mild hyperglycemia, and black bars indicate intermediate hyperglycemia. Asterisk indicates that obese persons had significantly greater rates of conversion to diabetes compared to rates in nonobese people in the same glycemic category.

intermediate hyperglycemia groups, there were no differences when older and younger women were compared (Fig. 2).

In all men, increasing BMI was associated with greater risk for diabetes ($P < 0.001$). Likewise, in both categories of hyperglycemia, elevated BMI was associated with greater rates of conversion to diabetes (Fig. 3). For all women, BMI was unrelated to risk for diabetes. However, there was a trend toward a higher conversion rates in women with intermediate hyperglycemia ($P = 0.054$). (Fig. 3). Note that the number of obese women with intermediate hyperglycemia was relatively small.

For all men, the presence of metabolic syndrome raised the risk for conversion to diabetes ($P < 0.001$). Furthermore, metabolic syndrome increased conversion to diabetes for each category of glycemia (Fig. 4). For all women, metabolic syndrome

FIGURE 4. Annualized conversion to diabetes for men and women with and without metabolic syndrome. White bars indicate normoglycemia, gray bars indicate mild hyperglycemia, and black bars indicate intermediate hyperglycemia. Asterisk indicates that persons with metabolic syndrome (+MetS) had significantly greater rates of conversion to diabetes compared to rates in people without metabolic syndrome (-MetS) in the same glycemic category.

did not increase conversion to diabetes. However, in women with intermediate hyperglycemia, metabolic syndrome was accompanied by greater conversion to diabetes (Fig. 4).

Finally, Figure 5 shows the regression to normoglycemia from mild hyperglycemia and intermediate hyperglycemia by sex. The graph shows that mild hyperglycemia was twice as likely to regress to normal as in those with intermediate hyperglycemia.

DISCUSSION

The DPP demonstrated that intensive intervention with lifestyle changes or with metformin therapy in patients who have the combination of IGT and IFG will reduce the rate of conversion to type 2 diabetes.¹ This led an ADA consensus panel to state that individuals with IFG should undergo OGTT to identify coexisting IGT as a guide to clinical intervention.⁶ Although the panel noted that any person with either IFG or IGT should be encouraged to adopt healthy life habits, no mention was made of the benefits of initiating intensive lifestyle intervention such as that used in the DPP. The latter is not without considerable cost and cannot be undertaken lightly. At the least, it will require involvement of a team of professionals backing up a physician's prescription if there is to be any hope for successful prevention. For example, in DPP, once the trial ended and professional lifestyle intervention was discontinued, the weight loss achieved during the trial was mitigated.⁸

If IFG is to be used as a guide to clinical prevention of diabetes, consideration must be given as to what constitutes a definition of IFG. The World Health Organization/International Diabetes Federation maintains that the fasting level should be in the range of 6.1 to 7.0 mmol/L (110–125 mg/dL).⁵ This range contrasts to the ADA's recommended 5.6 to 7.0 mmol/L (100–125 mg/dL).⁹ The rationale for the ADA's definition was to eliminate the need for OGTT to identify IGT. It was believed that the fasting range of 5.6 to 7.0 mmol/L would identify most subjects with IGT. This rationale, however, does not hold. Many more people have fasting levels of 5.6 to 7.0 mmol/L than have IGT.⁵ This led the ADA's consensus panel to recommend testing for IGT to determine who is a higher-risk candidate for clinical prevention of diabetes.⁶ In this study, we addressed the question

of whether there is an alternative to OGTT for identifying persons with IFG at high enough risk to institute clinical prevention of diabetes through intensive lifestyle therapy.

The current study showed a striking difference in risk for diabetes in those with intermediate hyperglycemia compared to mild hyperglycemia (Fig. 1). Other investigators have reported similar findings.^{10–12} Moreover, as also previously reported,^{10,13} there were more than twice as many subjects with mild hyperglycemia as with intermediate hyperglycemia. Although the relative risk for diabetes in persons with mild hyperglycemia is higher than in those with normoglycemia, the absolute rate of conversion to diabetes of the former is relatively low. Moreover, a sizable portion of those initially having mild hyperglycemia reverted to normoglycemia on subsequent testing. Although people with mild hyperglycemia, or even normoglycemia,¹⁴ can be advised to adopt lifestyle changes, there is less justification for intensive clinical intervention to reduce risk for diabetes. Instead, attention can be given to those with intermediate hyperglycemia who are at higher risk. We can therefore ask whether there are subgroups of the latter subjects who should receive intensive preventive therapy.

The current study included several risk factors that alter the rate of conversion to diabetes in subjects with intermediate hyperglycemia. As shown in Figure 2, men older than 55 had a greater risk for developing diabetes in mild and intermediate hyperglycemic categories compared to those younger than 55. In women as a group, age was a factor in predicting diabetes; but this trend was not reflected in mild and intermediate hyperglycemic categories. Obese men as a group had higher conversion to diabetes compared to nonobese men as did those in mild and intermediate hyperglycemic categories. An effect of obesity in women was less evident. Moreover, in both men and women with intermediate hyperglycemia, the metabolic syndrome was a particularly strong predictor compared to those without metabolic syndrome (Fig. 4).

In the CCLS, absolute rates of conversion of mild hyperglycemia and intermediate hyperglycemia tended to be lower than reported for other populations.^{10–12} This likely can be explained by a younger average age and less obesity than in other studies. Nonetheless, the differences in relative risk based on the risk factors studied are quite evident; these same risk factors, moreover, have been shown by others to affect conversion of intermediate hyperglycemia to diabetes.^{12,15}

The ADA consensus conference pointed out that adding IGT to IFG doubles the risk for diabetes compared to IFG alone.⁶ Besides identifying some IFG patients at usually high risk for diabetes, OGTT may discover additional patients with type 2 diabetes. Furthermore, some people with IFG may have IGT without obesity or metabolic syndrome. It is possible that adding IGT to IFG reflects more risk than, for example, IFG plus metabolic syndrome, although our study does not address this question. If this is confirmed, then a more conservative recommendation of requiring IFG + IGT before starting metformin therapy may be prudent.

On the other hand, the combination of intermediate-level IFG + metabolic syndrome or obesity seems sufficient to justify intensive lifestyle intervention based on our findings. This approach has the advantage of attacking both diabetes and cardiovascular risk.⁷ The extent to which intensive lifestyle intervention will delay onset of diabetes has not been determined. However, if a clinical decision is made to withhold OGTT selection of IFG subjects with intermediate hyperglycemia for intensive preventive measures when they are obese or have the metabolic syndrome seems reasonable. The investment of precious clinical resources for those with mild hyperglycemia or

FIGURE 5. Annualized regression to normoglycemia for men and women with mild hyperglycemia (gray bars) and intermediate hyperglycemia (black bars).

for persons with intermediate hyperglycemia but without these added risk factors seems more difficult to justify.

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