All Pre-Diabetes Is Not the Same: Metabolic and Vascular Risks of Impaired Fasting Glucose at 100 Versus 110 mg/dl

The Screening for Impaired Glucose Tolerance Study 1 (SIGT 1)

LAWRENCE S. PHILLIPS, MD[1]
WILLIAM S. WEINTRAUB, MD[2]
DAVID C. ZIEMER, MD[1]
PAUL KOLM, PHD[2]
JOVONNE K. FOSTER, MS[2]
VIOLA VACCARINO, MD, PHD[2]
MARY K. RHEE, MD, MS[1]
RAHIM K. BUDHWANI, MPH[1]
JANE M. CAUDLE, MLN[1]

The dramatic increase in incidence of diabetes (1) has prompted efforts to identify individuals who have milder glucose intolerance, because early management with lifestyle change and/or medication can delay progression to diabetes with its attendant morbidity, mortality, and cost (2). It has long been recognized that impaired glucose tolerance (IGT) is a diabetes precursor, but recognition of IGT requires oral glucose tolerance tests (OGTTs), which many health care providers are reluctant to order (3). As a more convenient alternative, the American Diabetes Association has emphasized screening by measurement of fasting plasma glucose (FPG) and lowered the cutoff for abnormal FPG progressively from 140 to 125 to 110 mg/dl. However, compared with IGT, an impaired fasting glucose (IFG) cutoff of 110 mg/dl provided good specificity but reduced sensitivity for detecting risk of developing diabetes (4–6).

To obtain increased sensitivity, the American Diabetes Association recently lowered the cutoff for IFG from 110 to 100 mg/dl (7), and application of this cutoff has increased the number of Americans thought to have "pre-diabetes" to 41 million (8). Although such individuals are considered candidates for management aimed at decreasing their risk of progressing to diabetes (9), the metabolic and cardiovascular risks of individuals with very modest abnormalities in FPG are not well understood. In this study, we compared measures of risk in individuals with fasting glucose 100–109 mg/dl (IFG100) with those with fasting glucose 110–125 mg/dl (IFG110).

RESEARCH DESIGN AND METHODS

— The study was approved by the Emory University Institutional Review Board and involved 550 adult volunteer subjects who were not known to have diabetes and were in general good health (had not needed to miss work during the previous week). As part of the Screening for Impaired Glucose Tolerance (SIGT) study, standard 75-g OGTTs were performed in the morning after an overnight fast, and fasting blood and urine samples were obtained for measurement of biomarkers. Normal glucose tolerance (NGT) was characterized by fasting glucose <100 mg/dl and 2-h glucose <140 mg/dl, IGT by 2-h glucose 140–199 mg/dl, diabetes by 2-h glucose ≥200 mg/dl, and IFG as described above; 13 subjects with fasting glucose >125 mg/dl were excluded from analysis because they could not be included in the IFG categories. Plasma glucose and other biomarkers were measured in the Clinical Laboratory at Grady Memorial Hospital using the Beckman LX-20 (Beckman, Brea, CA). Biomarkers were expressed relative to the upper quintile (high) of values of the 368 subjects with NGT. The "metabolic syndrome" was examined as defined by both International Diabetes Federation (10) and National Cholesterol Education Program (NCEP) (11) criteria. Statistical analyses were conducted using S-Plus, version 6 (Insightful, Seattle, WA), and Stata, version 7 (Stata, College Station, TX).

RESULTS

— Clinical demographics were similar in 95 subjects with IFG100 compared with 41 subjects with IFG110, respectively: age 50 vs. 51 years, BMI 32.2 vs. 33.8 kg/m^2, female 44 vs. 46%, and black 36 vs. 41% (all P = NS). Relative to NGT, IFG100 and IFG110 were associated with ("conferred") significant (Fig. 1) but comparable risk of the metabolic syndrome by International Diabetes Federation criteria (odds ratio ([OR] 7.10 [95% CI 4.39–11.46] vs. 10.33 [4.87–21.88]), but IFG110 conferred greater risk by NCEP criteria (5.86 [3.66–9.37] for IFG100 vs. 17.25 [7.58–39.14] for IFG110; P = 0.025). There were also only minor differences in risk for elevated C-reactive protein (1.27 [0.76–2.12] vs. 1.54 [0.77–3.09]) and alanine aminotransferase (4.03 [2.55–6.38] vs. 2.87 [1.52–5.41]). However, only IFG110 increased the risk for high urine albumin-to-creatinine ratio (0.59 [0.32–1.08] for IFG100 vs. 2.05 [1.05–4.02] for IFG 110) and LDL cholesterol >130 mg/dl (0.99 [0.61–1.58] vs. 2.42 [1.28–4.56]) (both P < 0.03 for IFG100 vs. IFG110).

In contrast, there was a more dramatic difference in risk of postchallenge

From the [1]Division of Endocrinology and Metabolism, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia; and the [2]Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia.

Address correspondence and reprint requests to Lawrence S. Phillips, MD, General Clinical Research Center, Emory University Hospital, Room GG-23, 1364 Clifton Rd., Atlanta, GA 30322. E-mail: medlsp@emory.edu.

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W.S.W. and P.K. are currently affiliated with Christiana Hospital, Newark, Delaware.

Abbreviations: FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NCEP, National Cholesterol Education Program; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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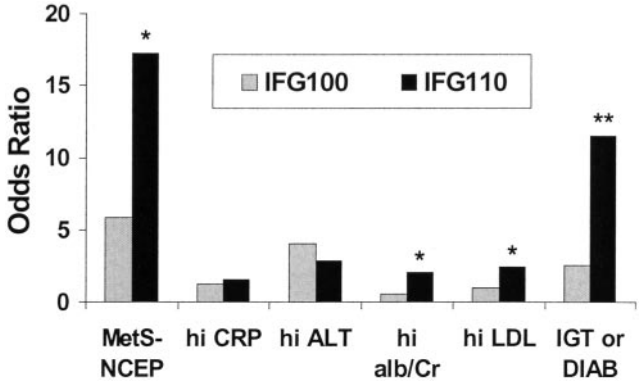

Figure 1—*ORs for metabolic and/or cardiovascular risk abnormalities associated with IFG100 (FPG 100–109 mg/dl) and IFG110 (FPG 110–125 mg/dl). Biomarker levels expressed relative to the upper quintile of values in individuals with NGT (high C-reactive protein [hi CRP], high alanine aminotransferase [hi ALT], high urine albumin-to-creatinine ratio [hi alb/Cr]), or the prevalence in individuals with NGT (metabolic syndrome by NCEP criteria [MetS-NCEP], LDL cholesterol >130 mg/dl [hi LDL], IGT, or diabetes [DIAB]). *$P < 0.05$, **$P < 0.005$.*

glucose intolerance (IGT or diabetes). The risk conferred by IFG100 was 2.53 (1.55–4.13), while the risk for IFG110 was 11.54 (5.78–23.02) ($P = 0.0004$). In multivariable analyses adjusting for age, race, sex, and BMI, the risk of glucose intolerance was OR 3.22 (95% CI 1.84–5.66) for IFG100 vs. 13.14 (6.12–28.23) for IFG110 ($P = 0.001$).

CONCLUSIONS — The present studies demonstrate that although pre-diabetes, characterized as IFG100 and IFG110, identifies individuals with similar demographics, IFG110 carries increased risk of the metabolic syndrome by NCEP criteria, LDL cholesterol >130 mg/dl, and high urine albumin-to-creatinine ratio, and IFG110 is much more likely to confer risk of postchallenge hyperglycemia. It has previously been reported that individuals with progressive elevation in FPG are more likely to have IGT or diabetes (9). However, we are not aware of previous comparisons of the risks in individuals added by inclusion under "newer" criteria (IFG100) versus the risks conferred by the "older" criteria (IFG110).

Recognition of pre-diabetes is important to identify individuals who have risks that can be modified to improve outcomes. The Baltimore Longitudinal Study of Aging has shown that mortality is increased in men by levels of FPG >110 mg/dl and/or 2-h OGTT glucose levels >140 mg/dl, even after adjustment for the presence of other risk factors (12), and mortality was also independently increased by the presence of postchallenge hyperglycemia in men in the Whitehall Study (13) and in both men and women in the DECODE (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) study (14). Although it is not yet established in randomized controlled trials that mortality and/or cardiovascular events can be decreased in individuals with such mild hyperglycemia by interventions other than treatment with acarbose (15), the hypothesis is being tested in ongoing studies with rosiglitazone, nateglinide, ramipril, and valsartan. Moreover, several different studies have shown that lifestyle change and/or medication can reduce progression from IGT to diabetes (2,16–18), and such interventions appear to be cost-effective (19). Such considerations indicate that identification of pre-diabetes should be a national priority.

The present study demonstrates that it is particularly important to follow recognition of IFG110 with additional diagnostic and therapeutic strategies. Since IGT and diabetes are associated with increased mortality (above), detection of IFG110 should also prompt consideration of further evaluation by OGTT.

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References

1. Wild S, Roglic G, Green A, Sicree R, King H: Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 27:1047–1053, 2004
2. Knowler WC, Hamman RF, Edelstein SL, Barrett-Connor E, Ehrmann DA, Walker EA, Fowler SE, Nathan DM, Kahn SE: Prevention of type 2 diabetes with troglitazone in the diabetes prevention program. *Diabetes* 54:1150–1156, 2005
3. Davidson MB: Counterpoint: the oral glucose tolerance test is superfluous (Editorial). *Diabetes Care* 25:1883–1885, 2002
4. Vaccaro O, Ruffa G, Imperatore G, Iovino V, Rivellese AA, Riccardi G: Risk of diabetes in the new diagnostic category of impaired fasting glucose: a prospective analysis. *Diabetes Care* 22:1490–1493, 1999
5. Shaw JE, Zimmet PZ, de Courten M, Dowse GK, Chitson P, Gareeboo H, Hemraj F, Fareed D, Tuomilehto J, Alberti KG: Impaired fasting glucose or impaired glucose tolerance: what best predicts future diabetes in Mauritius? *Diabetes Care* 22:399–402, 1999
6. Unwin N, Shaw J, Zimmet P, Alberti KGMM: Impaired glucose tolerance and impaired fasting glycaemia: the current status on definition and intervention. *Diabet Med* 19:708–723, 2002
7. Genuth S, Alberti KG, Bennett P, Buse J, Defronzo R, Kahn R, Kitzmiller J, Knowler WC, Lebovitz H, Lernmark A, Nathan D, Palmer J, Rizza R, Saudek C, Shaw J, Steffes M, Stern M, Tuomilehto J, Zimmet P, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 26:3160–3167, 2003
8. CDC Diabetes Program: National diabetes fact sheet: national estimates on diabetes [article online], 2003. *CDC Diabetes Pubs* Available from www.cdc.gov/diabetes/pubs/factsheet.htm
9. Genuth S: Lowering the criterion for impaired fasting glucose is in order (Commentary). *Diabetes Care* 26:3331–3332, 2003
10. Alberti KG, Zimmet P, Shaw J: The metabolic syndrome–a new worldwide definition. *Lancet* 366:1059–1062, 2005
11. Metabolic syndrome [article online], 2006. Available from http://americanheart.org/presenter.jhtml?identifier=4756. Accessed 15 January 2006
12. Sorkin JD, Muller DC, Fleg JL, Andres R: The relation of fasting and 2-h postchallenge plasma glucose concentrations to mortality: data from the Baltimore Longitudinal Study of Aging with a critical review of the literature. *Diabetes Care* 28:2626–2632, 2005
13. Brunner EJ, Shipley MJ, Witte DR, Fuller JH, Marmot MG: Relation between blood glucose and coronary mortality over 33 years in the Whitehall Study. *Diabetes Care* 29:26–31, 2006

14. The DECODE Study Group, the European Diabetes Epidemiology Group: Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria: Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe. *Lancet* 354: 617–621, 1999
15. Chiasson J-L, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M: Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 290:486–494, 2003
16. Laaksonen DE, Lindstrom J, Lakka TA, Eriksson JG, Niskanen L, Wikstrom K, Aunola S, Keinanen-Kiukaanniemi S, Laakso M, Valle TT, Ilanne-Parikka P, Louheranta A, Hamalainen H, Rastas M, Salminen V, Cepaitis Z, Hakumaki M, Kaikkonen H, Harkonen P, Sundvall J, Tuomilehto J, Uusitupa M: Physical activity in the prevention of type 2 diabetes: the Finnish diabetes prevention study. *Diabetes* 54:158–165, 2005
17. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, Cao HB, Liu PA, Jiang XG, Jiang YY, Wang JP, Zheng H, Zhang H, Bennett PH, Howard BV: Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and Diabetes Study. *Diabetes Care* 20:537–544, 1997
18. Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Tan S, Berkowitz K, Hodis HN, Azen SP: Preservation of pancreatic β-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* 51: 2796–2803, 2002
19. Herman WH, Hoerger TJ, Brandle M, Hicks K, Sorensen S, Zhang P, Hamman RF, Ackermann RT, Engelgau MM, Ratner RE: The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. *Ann Intern Med* 142: 323–332, 2005