Postprandial Glucose Improves the Risk Prediction of Cardiovascular Death Beyond the Metabolic Syndrome in the Nondiabetic Population

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OBJECTIVE — With increasing evidence about the cardiovascular risk associated with postprandial nonfasting glucose and lipid dysmetabolism, it remains uncertain whether the postprandial glucose concentration increases the ability of metabolic syndrome to predict cardiovascular events.

RESEARCH DESIGN AND METHODS — This was an observational study of 15,145 individuals aged 33–75 years without diabetes or cardiovascular diseases. Postprandial glucose was obtained 2 h after a lunch meal. Metabolic syndrome was diagnosed using the criteria of the U.S. National Cholesterol Education Program Adult Treatment Panel III. Cardiovascular and all-cause deaths were primary outcomes.

RESULTS — During a median follow-up of 6.7 years, 410 individuals died, including 82 deaths from cardiovascular causes. In a Cox model adjusting for metabolic syndrome status as well as age, sex, smoking, systolic blood pressure, LDL, and HDL cholesterol levels, elevated 2-h postprandial glucose increased the risk of cardiovascular and all-cause death (per millimole per liter increase, hazard ratio 1.26 [95% CI 1.11–1.42] and 1.10 [1.04–1.16], respectively), with significant trends across the postprandial glucose quintiles. Including 2-h postprandial glucose into a metabolic syndrome–included multivariate risk prediction model conferred a discernible improvement in the model in discriminating between those who died of cardiovascular causes and who did not (integrated discrimination improvement 0.4, P = 0.005; net reclassification improvement 13.4%, P = 0.03), however, the improvement was only marginal for all-cause death.

CONCLUSIONS — Given the risk prediction based on metabolic syndrome and established cardiovascular risk factors, 2-h postprandial glucose improves the predictive ability to identify nondiabetic individuals at increased risk of cardiovascular death.

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Proposed in 1988 by Reaven (1), the construct that impaired glucose regulation and insulin resistance to glucose stimulation frequently coexist with elevated blood pressure and dyslipidemia has been evolving into several diagnostic criteria of metabolic syndrome (2–4), a well-established risk for development of cardiovascular events and type 2 diabetes. Of those, the definitions recommended by the U.S. National Cholesterol Education Program Adult Treatment Panel III (ATP III) (2) and the International Diabetes Federation (IDF) (3) are the most widely used, partly because only fasting glucose and lipid concentrations are required. It has been increasingly recognized that postprandial glucose might be a better risk predictor for cardiovascular events than fasting glucose in nondiabetic and diabetic populations alike (5). A study using confirmatory factor analysis indicated that postprandial glucose appeared to be more correlated with metabolic syndrome than fasting glucose (6). However, concerns have not been fully addressed for whether elevated postprandial glucose would increase the risk of adverse outcomes of metabolic syndrome diagnosed according to the ATP III or IDF criteria.

Although postprandial glucose is traditionally obtained using an oral glucose tolerance test (OGTT), accumulating evidence shows that postprandial glucose after a mixed meal might be more likely to reflect physiological responses to a glucose challenge in daily life than an OGTT (7,8). Therefore, the aim of this study was to examine the relationship of postmeal postprandial glucose with cardiovascular and all-cause deaths in nondiabetic individuals.

RESEARCH DESIGN AND METHODS — A prospective observational cohort enrolled 17,299 self-referred individuals aged 30–75 years, who attended health examinations at the National Taiwan University Hospital between January 1995 and December 2002. At baseline, structured questionnaires were used to collect family history, current smoking status, and medical histories. We excluded individuals with diabetes or with a medical history of myocardial infarction, coronary heart disease, stroke, carotid artery stenosis, or peripheral artery disease at baseline. Diabetes was defined if one of following existed: current use of antidiabetic agents, diet modifications because of diabetes, fasting glucose ≥7.0 mmol/l (126 mg/dl), or 2-h postprandial glucose ≥11.1 mmol/l (200 mmol/l). To our knowledge, this study used confirmatory factor analysis to confirm the relationship of postprandial glucose with cardiovascular and all-cause deaths in nondiabetic individuals.
mg/dl). Also excluded were those who had incomplete baseline data, missing fasting glucose or 2-h postprandial glucose data, severely impaired renal function (serum creatinine levels ≥330 μmol/l [6 mg/dl]), or comorbidity with cancer. Accordingly, we included a total of 6,024 women and 9,121 men for the analysis. The study protocol was approved by the hospital’s institutional review board.

Laboratory measurements

Venous blood samples were collected from each participant after at least a 12-h overnight fast, and 2-h postprandial glucose was obtained 2 h after a standard 650-kcal lunch meal, which was composed of 110 g carbohydrates, 27–30 g protein, and 8–10 g fat. Total cholesterol levels were measured using the CHOD-PAP method (Boehringer Mannheim, Mannheim, Germany), and HDL cholesterol was measured after precipitation of apolipoprotein B–containing lipoproteins, with phosphotungstic acid and magnesium ions (Boehringer Mannheim). Triglyceride concentrations were measured by the GPO-DAOS method (Wako Pure Chemicals, Tokyo, Japan). LDL cholesterol concentrations were calculated using the Friedewald formula. Plasma fasting glucose and 2-h postprandial glucose concentrations were measured using a Hitachi 7450 automated analyzer (Hitachi, Tokyo, Japan). A1C was measured using a DCA 2000 analyzer (Bayer Diagnostics, Elkhart, IN).

Definition of metabolic syndrome and postprandial hyperglycemia

Of the criteria available for diagnosis of metabolic syndrome, the two recommended by the IDF and ATP III, respectively, do not require postprandial glucose as a clinical measurement of insulin resistance. Because a previous study has proved substantial agreement between the ATP III and IDF criteria (9), we did not assess the effects of the IDF criteria on the results of this study.

Metabolic syndrome was defined using the modified ATP III definition (9). Individuals with three or more of the following five criteria are regarded as having metabolic syndrome: 1) BMI of ≥27 kg/m² for an Asian population (10); 2) systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg; 3) fasting plasma glucose ≥6.1 mmol/l (100 mg/dl); 4) triglyceride level ≥1.69 mmol/l (150 mg/dl); and 5) HDL cholesterol level <1.29 mmol/l (50 mg/dl) for women or <1.04 mmol/l (40 mg/dl) for men. Individuals with a 2-h postprandial glucose of ≥7.8 mmol/l (140 mg/dl) were defined as having postprandial hyperglycemia, because those with normal glucose regulation rarely have a plasma glucose level of ≥7.8 mmol/l (140 mg/dl) or higher (11).

Ascertainment of the causes of death

Mortality and causes of death were ascertained according to a national register database, which was provided by the National Health Administration, and was updated at the end of 2007, by linking identification numbers of individuals to the database. Cardiovascular death was defined as deaths from cardiovascular causes if the registered death codes ranged from 390 to 459, based on ICD-9.

Statistical analysis

Data are summarized as means ± SD for continuous variables and as percentages for categorical variables. Baseline characteristics are represented by quintiles of 2-h postprandial glucose and postprandial hyperglycemia, because those with normal glucose
model 2, those in model 1 plus systolic blood pressure (quintile groups), HDL cholesterol (quintile groups), and LDL cholesterol (quintile groups); and model 3, metabolic syndrome (presence/absence) was added into model 2. P values for linear trend were calculated with the median from each quintile group.

To further evaluate the improvement in predictive ability of metabolic syndrome for cardiovascular and all-cause death after 2-h postprandial glucose was added to multivariate Cox models, we compared the measures of discrimination and calibration between the models with and without 2-h postprandial glucose. Three methods were used to assess the extent to which 2-h postprandial glucose increased the discriminative performance of risk prediction. The first was to compare the differences of the area under the receiver operating characteristic curves (AUROC) between risk prediction models with and without 2-h postprandial glucose. Receiver operating characteristic curves were constructed by plotting sensitivity versus 1 − specificity obtained using multivariate logistic regression, and AUROCs were compared using a nonparametric test (12).

Because AUROC values may not be sensitive enough to express the improvement of discrimination performance, we also used two other methods: net reclassification improvement (NRI) and integrated discrimination improvement (IDI) as described by Pencina et al. (13). Based on the prior predictive risk, individuals were classified into four risk categories of 0–1%, 1–3%, 3–6%, and ≥6% derived from a probability distribution of 5-year risk for cardiovascular death (14) and then were reclassified according to the predictive risks in regression models including 2-h postprandial glucose. The NRI was the difference between the percentage of reclassifying those with events into higher risk categories and those without events into lower risk categories (indicating improvement in the discrimination performance) and the percentage of reclassifying those with events into lower risk categories and those without events into higher risk categories (indicating failure to improve the discrimination performance). The overall reclassification improvement was statistically examined by an asymptotic test (13). Similarly, individuals were grouped into four categories of 0–10%, 10–25%, 25–35%, and ≥35%, which were defined on the assumption that cardiovascular death was accountable for ~15% of all-cause death according to the 2006 mortality statistics from the World Health Organization. Because the clinical consensus on risk cutoffs for cardiovascular and all-cause death has not been established, the IDI was applied to estimate the discrimination improvement in average sensitivity and any potential increase in average 1 − specificity and was examined using an asymptotic test (13).

Model calibration was assessed with the Hosmer-Lemeshow goodness-of-fit $X^2$ statistic, a measure of discrepancy describing how well the predicted probabilities fit observed outcomes. A model with a smaller Hosmer-Lemeshow statistic is better calibrated, whereas a model with a statistic of >20 is regarded as having a lack of calibration (15).

The metabolic syndrome by a postprandial hyperglycemia interaction term was used in a multivariate Cox model to explore the effect modification of metabolic syndrome with postprandial hyperglycemia on risk of cardiovascular and all-cause death, and multivariate-adjusted relative risks of primary outcomes were plotted by stratification.

All statistical tests were two-tailed with a type I error of 0.05, and $P < 0.05$ was regarded as statistically significant. All of the statistical analyses were performed with SAS (version 9.1; SAS Institute, Cary, NC) and Stata (version 10; StataCorp, College Station, TX).

**RESULTS**

**Baseline characteristics**

As summarized in Table 1, with increasing quintiles of 2-h postprandial glucose, individuals were more likely to have a higher prevalence of ATP III metabolic syndrome, higher total cholesterol, triglycerides, LDL cholesterol, fasting glucose, and A1C, but lower HDL cholesterol.

**Postprandial blood glucose as a predictor for cardiovascular and all-cause death independently of metabolic syndrome**

Of the 15,145 nondiabetic participants, 410 died during a median follow-up of 6.7 years (interquartile range 3.3 years), including 82 deaths from cardiovascular causes. As outlined in Table 2, after adjustment for sex, age, smoking status, systolic blood pressure, and LDL and HDL cholesterol in a Cox model, elevated 2-h postprandial glucose was associated with increased risks of cardiovascular and all-cause death (hazard ratios 1.10 (1.04–1.16), $P = 0.0002$; 1.11 (1.05–1.18), $P = 0.0002$; and 1.12 (1.03–1.21), $P = 0.0004$).
ratio 1.26 [95% CI 1.11–1.43] for cardiovascular death; 1.10 [1.03–1.16] for all-cause death). Furthermore, additional adjustment for the presence or absence of metabolic syndrome maintained the independent association between 2-h postprandial glucose and risks of cardiovascular and all-cause death. Moreover, the trends toward heightened risks of primary outcomes were also found to be significant across the increasing quintiles of 2-h postprandial glucose. Compared with the absence of postprandial hyperglycemia (Fig. 1), the presence of postprandial hyperglycemia raised the relative risk of 2.22 (95% CI 1.40–3.52) for cardiovascular death and of 1.56 (1.25–1.94) for all-cause death. There was no evidence of substantial heterogeneity in relative risks of primary outcomes associated with postprandial hyperglycemia between subgroups with or without metabolic syndrome.

**Comparison in discrimination and calibration between metabolic syndrome–included multivariate prediction models before and after adding 2-h postprandial glucose**

Table 3 and supplementary Tables A1 and A2 (available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc08-2337/DC1) present a summary of the statistics for the evaluation of the model discrimination performance and calibration. Although AUC values marginally increased after 2-h postprandial glucose was incorporated in the metabolic syndrome–included multivariate-adjusted models (Table 3), we observed significant improvements using the NRI and IDI methods. Using the predicted risk obtained from the metabolic syndrome–included prediction model incorporating 2-h postprandial glucose (supplementary Table A1), we found that, of 82 cardiovascular deaths, 17 individuals with events were reclassified into higher risk categories, whereas 6 were classified into lower risk categories; accordingly, the reclassification improvement was 13.4% (17/82 × 100%). However, in 14,901 individuals who did not die of cardiovascular disease (supplementary Table A2), 558 were designated as lower risk and 567 as higher risk, thereby indicating 0.0% (558/14,901 × 100%) in reclassification improvement. Therefore, the NRI was 13.4% (95% CI 2.2–24.5, P = 0.02), suggesting that the risk prediction for cardiovascular death improved after 2-h postprandial glucose was added into the model. Although the clinical implication of the absolute value of IDI awaits further clarification, the improvement in discrimination performance in the prediction model for cardiovascular death after addition of 2-h postprandial glucose.

**Table 3—Improvement in discrimination performance and calibration for risk prediction of cardiovascular death and all-cause death in the multivariate-adjusted model after including 2-h postprandial glucose**

|                | AUC          | IDI (%) | NRI (%) | Calibration, χ²* |
|----------------|--------------|---------|---------|-----------------|
| **Cardiovascular death** |              |         |         |                 |
| Established risk factors + MetS† | 0.81 (0.77–0.85) | Referent | Referent | 10.6            |
| Established risk factors + MetS + 2-h PG† | 0.82 (0.79–0.86) | 0.4 (0.1–0.7)§ | 13.4 (2.2–24.5)‡ | 6.3             |
| **All-cause death** |              |         |         |                 |
| Established risk factors + MetS† | 0.77 (0.75–0.80) | Referent | Referent | 11.0            |
| Established risk factors + MetS + 2-h PG† | 0.78 (0.75–0.80) | 0.2 (0.0–0.3)‡ | 3.6 (1.2–6.0)§ | 8.1             |

Data are values (95% CI). *Values were obtained using the Hosmer-Lemeshow test. †Established risk factors included age, sex, smoking status, systolic blood pressure, HDL cholesterol, and LDL cholesterol for adjustment. ‡P < 0.05; §P < 0.01. MetS, metabolic syndrome; PG, postprandial glucose.

Figure 1—Association of postprandial hyperglycemia with the risk of cardiovascular and all-cause death according to the presence or absence of metabolic syndrome. Postprandial hyperglycemia was defined as 2-h postprandial glucose ≥7.8 mmol/l (140 mg/dl). Relative risk was adjusted for age-groups (35–44, 45–54, 55–64, 65–74, and ≥75 years), sex, smoking status (yes/no), systolic blood pressure (quintile groups), HDL cholesterol (quintile groups), and LDL cholesterol (quintile groups) in a Cox proportional hazards analysis. The dashed vertical lines represent the corresponding overall point estimates, and the solid horizontal lines represent the 95% CI. Pinteraction was obtained by the interaction test between metabolic syndrome and postprandial hyperglycemia.
glucose was also demonstrated by the estimate of IDI of 0.4% (95% CI 0.1–0.7, \( P = 0.005 \)), which might, however, be more pertinent than NRI when a consensus on clinical risk categories has not be established. Likewise, for all-cause death, NRI was 3.6% (95% CI 1.2–6.0, \( P = 0.003 \)) (supplementary Table A2), and IDI was 0.2% (0.0–0.3, \( P = 0.03 \)), indicating that the addition of 2-h postprandial glucose into prediction models would marginally improve discriminative ability of the models.

Assessed by the use of the Hosmer-Lemeshow test, the models with 2-h postprandial glucose had smaller a \( \chi^2 \) statistic than those without 2-h postprandial glucose, for predicting both cardiovascular death and all-cause death (Table 3). Moreover, all models with and without 2-h postprandial glucose represented adequate calibration.

CONCLUSIONS — In this study we investigated the independent and incremental utility of 2-h postprandial glucose in risk prediction for cardiovascular and all-cause death in the nondiabetic population. Our data demonstrated that increased 2-h postprandial glucose was an independent risk predictor of cardiovascular and all-cause death and that the addition of 2-h postprandial glucose into risk prediction, which includes metabolic syndrome status and established cardiovascular risk factors, could improve the predictive ability of the risk for cardiovascular death.

Postprandial hyperglycemia differs from fasting hyperglycemia in pathophysiology and the risk of adverse outcomes. Postprandial hyperglycemia results mainly from a moderate to severe decrease in muscle insulin sensitivity and late-phase insulin secretory response to oral glucose; whereas fasting hyperglycemia results mainly from a defect in hepatic insulin sensitivity and first-phase insulin response (16). Our findings concur with those of a meta-analysis of 38 prospective studies, which demonstrated that nondiabetic postprandial hyperglycemia significantly raises the likelihood of cardiovascular events or death and that the relationship remains after cardiovascular risk factors have been adjusted for (17). The underlying pathobiological changes linking elevated postprandial glucose and cardiovascular diseases consist mainly of elevated oxidative stress and endothelial dysfunction, leading to atherothrombotic propensities of elevated postprandial glucose, such as oxidation of LDL cholesterol, vasocostriction, and thrombogenicity (18). Moreover, interventions targeting elevated postprandial glucose are of clinical significance for optimizing comprehensive glycemic control in individuals with diabetes and with impaired glucose regulation to lower the risk of adverse outcomes (19).

It has been shown that the mixed-meal test is well correlated with the OGTT in measures of insulin sensitivity and is more likely to have a stronger pancreatic \( \beta \)-cell response to an equal amount of carbohydrate than the OGTT (7), perhaps suggesting that a mixed-meal test could be more suitable for evaluating the reserve of insulin secretion. Evidence has emerged about the association between postmeal glucose concentrations and the cardiovascular risk. In women with normal glucose regulation, those with elevated postmeal postprandial glucose tend to have increased carotid intima medial thickness (20). In a recent study assessing the relationship between postmeal glucose and incident cardiovascular complications, it was reported that elevated postmeal glucose, but not fasting glucose, predisposes patients with type 2 diabetes to increased cardiovascular risk (21). There is also growing interest in the increased risk of cardiovascular events in relation to postprandial lipid concentrations, which were obtained after normal food intake (22,23).

Some limitations and weakness in this study need careful concern. First, BMI, rather than waist circumference, was used as the obesity criterion of metabolic syndrome in this study. However, findings from previous studies have confirmed that, in this setting, using either BMI or waist circumference leads to no difference in predicting cardiovascular events (24). Second, the NRI method is affected by the risk categories used, and no consensus had existed on clinically significant risk categories of cardiovascular death when our analysis was conducted. Nonetheless, the improvement in reclassification for cardiovascular death was corroborated by the use of IDI, a method with no fixed cutoffs for risk categorization (13). Third, caution should be taken in generalizing our results to a community-based population because this study cohort was based on participants undergoing health check-ups at a university hospital. Fourth, compared with the survey in the general population including individuals with diabetes, the incidence of cardiovascular death seemed to be low in our study, partly because only individuals without diabetes were included. Thus, one should be cautious when the relative risks with wide CIs are considered.

Despite these concerns, our findings provide evidence that elevated postprandial glucose independently posed heightened risks of cardiovascular and all-cause death and that the inclusion of postprandial glucose into risk prediction for cardiovascular death increases the risk predictive ability. Future trials to examine the difference in the risk of adverse outcomes between definitions of metabolic syndrome using fasting or postprandial nonfasting glucose and lipid criteria may be of clinical interest.

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