Glycemic Status and Development of Kidney Disease

The Framingham Heart Study

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OBJECTIVE — Diabetes is a major risk factor for the development of kidney disease and is the leading cause of end-stage renal disease in the U.S. Whether pre-diabetes is associated with the development of kidney disease is unclear.

RESEARCH DESIGN AND METHODS — Subjects free of chronic kidney disease (CKD) were drawn from the Framingham Heart Study offspring cohort (1991–1995), given an oral glucose tolerance test, and followed for an average of 7 years for development of CKD (glomerular filtration rate [GFR] of <59 ml/min per 1.73 m^2 in women and <64 ml/min per 1.73 m^2 in men). Multivariable logistic regression models, adjusted for cardiovascular disease risk factors including age, sex, hypertension, smoking, BMI, total and HDL cholesterol levels, and prevalent myocardial infarction or congestive heart failure, were used to estimate the odds of patients developing kidney disease among glycemic categories.

RESULTS — Of 2,398 subjects (53% women; mean age 54 years), 63% were normoglycemic, 29% had impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), 3.4% were newly diabetic, and 4.6% had known diabetes. By glycemic category, mean GFR at follow-up was 87, 85, 82, and 78 ml/min per 1.73 m^2, respectively. The fully adjusted odds of developing CKD were 0.98 (95% CI 0.67–1.45), 1.71 (95% CI 0.83–3.55), and 1.93 (95% CI 1.06–3.49) among those with IFG or IGT, newly diagnosed diabetes, or known diabetes, respectively, compared with those who were normoglycemic at baseline. Among participants without diabetes, metabolic syndrome was not associated with kidney disease at follow-up (odds ratio 1.46, $P = 0.06$).

CONCLUSIONS — Cardiovascular disease risk factors explain much of the relationship between prediabetes and the development of chronic kidney disease. Clinical trials are warranted to determine whether vascular risk factor modification can slow the decline of kidney function among those with pre-diabetes.

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Diabetes is the leading cause of end-stage renal disease (1-9). The age-adjusted incidence of end-stage renal disease among subjects with diabetes is 199.8 per 100,000 person-years compared with 13.7 per 100,000 person years among their nondiabetic counterparts (10).

Whether impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) are associated with the prospective development of chronic kidney disease (CKD) has not been fully elucidated. Data from cross-sectional studies show that alterations in glucose metabolism and hyperinsulinemia are associated with impaired kidney function (11–13). However, the association of clinically relevant glycemic disease categories as defined by the American Diabetes Association (14,15) with CKD has not been established. The finding that declines in kidney function are present early on among subjects with glucose intolerance could help direct therapeutic interventions to prevent the progression of kidney disease.

Thus, we sought to examine the development of CKD in adults with prediabetes, metabolic syndrome, and diabetes in the general population, using the Framingham Heart Study to conduct this longitudinal study.

RESEARCH DESIGN AND METHODS

— The Framingham Heart Study began in 1948 with the enrollment of 5,209 men and women, 28–62 years of age, with subjects undergoing examinations every 2 years (16,17). In 1971, 5,124 men and women were enrolled into the Framingham Offspring Study, which included the children or spouses of the children of the original cohort. Offspring subjects underwent examinations approximately every 4 years; the design and methodology have been previously described (18,19). The current sample comprised subjects from the Framingham Offspring Study who attended a baseline examination in 1991–1995 (examination 5) and returned for a follow-up examination in 1998–2001 (examination 7). Although 5,124 participants enrolled in the Framingham Offspring Study, 462 died before the start of examination cycle 5, and 863 living members did not attend, resulting in 3,799 attendees. Among those, 618 did not have creatinine measured, 230 had existing kidney disease (glomerular filtration rates [GFRs] of <59 ml/min per 1.73 m^2 in women and <64 ml/min per 1.73 m^2 in men), 61 did not have glucose or glucose tolerance data, and 27 were missing other covariates; another 94 died before exam-

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Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; HOMA-IR, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; K/DOQI, National Kidney Foundation Kidney Disease Outcome Quality Initiative; NGT, normal glucose tolerance; NHANES, National Health and Nutrition Examination Survey.

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

ination, 7, 262 did not attend examination 7, and 109 did not have creatinine measured at examination 7, with a net total of 2,398 participants eligible for analysis in the present study. Subjects with GFRs of ≥59 ml/min per 1.73 m^2 in women and ≥64 ml/min per 1.73 m^2 in men who attended an examination in 1991–1995 (baseline) were followed for a mean of 7.0 years (range 4.3–10.6 years) for incident kidney disease in relation to glycemic status at baseline. Average follow-up time did not differ by glycemic status at baseline.

Exposure measures

A 75-g oral glucose tolerance test was administered at baseline and classified participants as having normal glucose tolerance (NGT) (fasting plasma glucose [FPG] < 100 mg/dl [5.5 mmol/l] and 2-h glucose < 140 [7.8 mmol/l]), IFG or IGT (FPG 100–125 [5.5–6.9 mmol/l] or 2-h glucose 140–199 [7.8–11.0 mmol/l]), previously undiagnosed diabetes (FPG ≥126 [7.0 mmol/l] or 2-h glucose ≥200 [11.1 mmol/l] without prior known diabetes), or known diabetes (diabetes treatment or FPG ≥126 [7.0 mmol/l] at the baseline and at a prior examination) (14,15).

Assessment of insulin resistance

Fasting insulin levels were measured in EDTA plasma as total immunoreactive insulin (Coat-A-Count Insulin; Diagnostic Products, Los Angeles, CA). Among participants with NGT, insulin resistance was assessed from fasting insulin and glucose levels and the homeostasis model assessment of insulin resistance (HOMA-IR): HOMA-IR = fasting glucose (millimoles per liter) × fasting insulin (microunits per milliliter)/22.5 (20).

Metabolic syndrome

Metabolic syndrome was defined according to Adult Treatment Panel III criteria (21). Criteria for IFG were modified according to new American Diabetes Association guidelines (FPG 100–125 mg/dl) (15). Participants with diabetes were excluded from these analyses.

Outcome measures

Kidney function was estimated by GFR, which was calculated using the simplified Modification of Diet in Renal Disease Study equation (22,23) defined as GFR = $186.3 \times (\text{serum creatinine})^{-1.154} \times \text{age}^{-0.203} \times (0.742\ [\text{for women}])$. The outcome variable of interest was based on National Kidney Foundation Kidney Disease Outcome Quality Initiative (K/DOQI) Working Group definition of kidney disease as a GFR <60 ml/min per 1.73 m^2 (23). This particular cutoff was chosen by the K/DOQI Working Group because of the increased prevalence of hypertension, anemia, derangements in calcium-phosphorus metabolism, reduction in serum albumin, and reductions in functional status that occur below this cutoff (23). The use of a cut point of GFR <60 ml/min per 1.73 m^2 classified 50% more women as having kidney disease than men, so we modified the K/DOQI definition and reclassified kidney disease as a GFR at or below the sex-specific 5th percentile (59 ml/min per 1.73 m^2 in women and 64 ml/min per 1.73 m^2 in men). Thus, participants were eligible for this study if they had a baseline GFR >59 ml/min per 1.73 m^2 (women) or >64 ml/min per 1.73 m^2 (men). Serum creatinine level was measured using the modified Jaffe method. Because the measure of creatinine can vary across different laboratories, creatinine was calibrated using a two-step process. First, National Health and Nutrition Examination Survey (NHANES) III creatinine values were calibrated to the Cleveland Clinic Laboratory, requiring a correction factor of 0.23 mg/dl (24). Then, mean creatinine values from Framingham, by sex-specific age-groups (20–39, 40–59, 60–69, and 70+), were aligned with the corresponding corrected NHANES III age- and sex-specific means. All GFRs >200 ml/min per 1.73 m^2 were assigned a value of 200.

Risk factors

Details about the methods of risk factor measurement and laboratory analysis have been described (25). Each examination included a cardiovascular disease assessment and blood testing. Subjects with systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg (average of two readings taken by the examining physician) or receiving medication for treatment of hypertension were defined as hypertensive. Fasting lipid measures included total and HDL cholesterol levels. Smoking status was defined as smoking one or more cigarette per day in the year preceding the examination. BMI was defined as weight in kilograms divided by the square of height in meters.

Statistical analysis

The primary outcome was the development of CKD at the follow-up examination. Logistic regression models (26) were used to examine the odds of developing CKD by glycemic category at baseline (NGT, IFG or IGT, newly diagnosed diabetes, or known diabetes). All analyses were determined a priori and conducted using SAS (27) on a SUN Sparc Ultra-2 (SUN Microsystems, Santa Clara, CA). Models were crude, age and sex adjusted, and fully adjusted. Covariates in the fully adjusted models included age, sex, baseline GFR, systolic blood pressure, hypertension treatment, cigarette smoking, BMI, total and HDL cholesterol levels, and prevalent myocardial infarction or congestive heart failure. Secondary analyses were performed excluding all subjects with diabetes and examining the effect of metabolic syndrome on the development of CKD. Metabolic syndrome analyses were adjusted for age, sex, baseline GFR, smoking, and prevalent myocardial infarction or congestive heart failure. Lastly, participants with NGT were stratified above and below the median of HOMA-IR to determine whether excess risk of developing kidney disease was detectable as a function of insulin resistance. $P < 0.05$ was the criterion for statistical significance.

RESULTS — Of 2,398 subjects (53% women; mean age 54 years) at baseline, nearly two-thirds were normoglycemic, slightly less than one-third had IFG or IGT, 3.4% had newly diagnosed diabetes, and 4.6% had known diabetes (Table 1). The change in GFR by glycemic status from baseline to follow-up was −6, −9, −24, and −24 ml/min per 1.73 m^2, respectively.

At follow-up, 7% of subjects had CKD. By glycemic category, the prevalence of CKD at follow-up increased by worsening baseline glycemia (P for trend < 0.001) (Fig. 1).

The odds of developing CKD by glycemic category were examined in crude, age, sex, and baseline GFR adjusted, and fully adjusted models (Table 2). In crude models, IFG or IGT conferred a 65% increased odds of developing CKD (odds ratio [OR] 1.65), new diabetes conferred a threefold odds increase (3.22), and known diabetes conferred nearly a fivefold odds increase (4.69). Adjustment for age, sex, and baseline GFR attenuated the increased odds among those with IFG or IGT. After further adjustment for multiple vascular disease risk factors, participants with known diabetes at baseline had a twofold odds of developing CKD (1.93).

Table 1—*Characteristics of study participants*

	NGT	IFG or IGT	New diabetes	Known diabetes
n	1,502	704	82	110
Age (years)	52 ± 9	56 ± 9	59 ± 9	60 ± 8
Sex (% female)	59	44	50	41
Baseline GFR (ml/min per 1.73 m^2)	93 ± 24	94 ± 27	106 ± 38	102 ± 35
Follow-up GFR (ml/min per 1.73 m^2)	87 ± 18	85 ± 18	82 ± 19	78 ± 25
Kidney disease at follow-up (%)	5	8	15	20
Systolic blood pressure (mmHg)	121 ± 17	131 ± 18	138 ± 21	140 ± 18
Hypertension treatment (%)	11	24	27	39
Hypertension (%)	22	44	56	62
Current smoking (%)	19	18	20	19
BMI (kg/m^2)	26.4 ± 4.5	28.9 ± 4.9	31.4 ± 6.2	30.3 ± 5.0
Total cholesterol (mg/dl)	202 ± 35	208 ± 37	213 ± 37	205 ± 41
HDL cholesterol (mg/dl)	52 ± 15	47 ± 14	42 ± 13	41 ± 12
Prevalent myocardial infarction or congestive heart failure (%)	2	5	4	12
Fasting glucose (mg/dl)	90 ± 6	105 ± 8	139 ± 44	178 ± 62
Fasting insulin (units)	7 ± 6	11 ± 9	20 ± 15	24 ± 29
HOMA-IR (units)	1.65 ± 1.45	2.98 ± 2.38	7.18 ± 5.55	11.15 ± 14.10

Data are means ± SD unless otherwise indicated. Unless specified, data represent characteristics obtained at the baseline examination (1991–1995).

After adjustment for vascular risk factors, the risk of CKD among those with newly diagnosed diabetes was no longer significant (1.71, $P = 0.15$).

Metabolic syndrome and kidney disease

In the nondiabetic sample ($n = 2,145$), 31% had the metabolic syndrome at baseline (mean age 56 years). In follow-up, 9% of participants ($n = 73$) with the metabolic syndrome developed CKD compared with 5% of participants ($n = 60$) without it. After multivariable adjustment (age, sex, and baseline GFR, smoking, and prevalent myocardial infarction or congestive heart failure), the metabolic syndrome was not a significant predictor of developing CKD (OR 1.46, $P = 0.06$).

Insulin resistance and kidney disease

After exclusion of all participants with IGT, IFG, and diabetes, the odds of developing CKD at follow-up was examined among participants above (≥1.286 units) or below the median of HOMA-IR. In follow-up, 6% ($n = 44$) of participants above the median of HOMA-IR developed CKD compared with 4% ($n = 29$) of participants below it. In models adjusted for age, sex, and baseline GFR, participants above the median of HOMA-IR had a nonsignificantly increased odds of developing CKD (OR 1.61, $P = 0.06$). This relationship was attenuated after multivariable adjustment (1.17, $P = 0.58$).

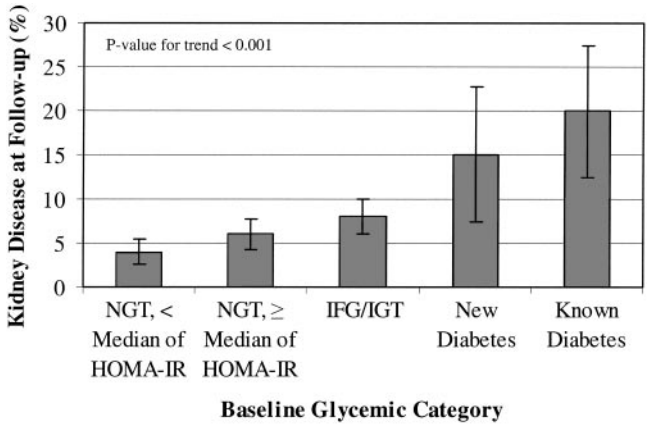

Figure 1—*Prevalence of kidney disease at follow-up by baseline glycemic status. Bars represent 95% CI.*

CONCLUSIONS — The risk of developing chronic kidney disease associated with pre-diabetes and newly diagnosed diabetes is largely accounted for by coexisting vascular disease risk factors. Similarly, vascular disease risk factors attenuated most of the relationship between insulin resistance and CKD. Gradation of risk for CKD appears to be linear across the spectrum of glycemic status, and known diabetes is a strong and independent risk factor for CKD.

Our findings suggest that concomitant vascular disease risk factors explain most of the increased odds of development of CKD seen among participants with IFG and newly diagnosed diabetes. Traditionally, diabetic nephropathy is thought to be a microvascular complication of diabetes, characterized by the classic Kimmelstiel-Wilson syndrome lesion. However, it has been shown that less than one-third of patients with diabetes and increased urinary albumin excretion actually demonstrate this classic lesion (28). Further evidence exists to suggest that classic diabetic lesions may not underlie kidney disease and diabetes in a substantial number of individuals. Among adults with diabetes, the prevalence of albuminuria is only 29% (29). In a recent cross-sectional survey using data from NHANES III, 33% of diabetic adults with a GFR <60 ml/min per 1.73m^2 (CKD stages 3–5) (23) did not have evidence of either albuminuria (microalbuminuria or macroalbuminuria) or retinopathy (30). Taken together, these data suggest that CKD in the setting of pre-diabetes might be thought of as an additional complication of macrovascular atherosclerosis.

These data add to the results of prior cross-sectional studies demonstrating that alterations of glucose metabolism and hyperinsulinemia are associated with impaired kidney function (11–13). Data from NHANES III demonstrated an increased odds of CKD by increasing HOMA-IR across the spectrum of nondiabetic participants. The most striking results come from those with HOMA-IR values in the upper quartile compared with those in the lower quartile (OR 2.65). Differences from our study include the inclusion of in-

Table 2—*Chance of developing kidney disease at follow-up by glucose tolerance category at baseline

	IFG or IGT	*P* value	New diabetes	*P* value	Known diabetes	*P* value
Unadjusted	1.65 (1.16–2.36)	0.006	3.22 (1.67–6.19)	<0.001	4.69 (2.79–7.90)	<0.001
Age, sex, and baseline GFR adjusted	1.25 (0.86–1.81)	0.25	2.38 (1.19–4.75)	0.01	3.03 (1.73–5.31)	<0.001
Fully adjusted†	0.98 (0.67–1.45)	0.94	1.71 (0.83–3.55)	0.15	1.93 (1.06–3.49)	0.03

Data are OR (95% CI). *Normal fasting glucose is the referent category. Patients with kidney disease at follow-up were distributed as follows: NGT ($n = 76$), IFG/IGT ($n = 57$), new diabetes ($n = 12$), and known diabetes ($n = 22$). †Includes adjustment for age, sex, baseline GFR, systolic blood pressure, hypertension treatment, cigarette smoking, BMI, total and HDL cholesterol levels, and prevalent myocardial infarction or congestive heart failure.

dividuals with IFG and the cross-sectional nature of the data. In another cross-sectional study of 321 individuals with untreated essential hypertension and hypertensive nephrosclerosis, increased plasma glucose and insulin resistance were observed when creatinine clearance was <50 ml/min per 1.73 m^2 (11). However, the patients in this study were untreated hypertensive patients with hypertensive nephrosclerosis, limiting the generalizability of these findings. Further, these authors did not adjust for concomitant vascular disease risk factors.

Our baseline cross-sectional data demonstrate increasing GFR values across the spectrum of hyperglycemia. The most likely explanation for our cross-sectional findings comes from physiologic studies of kidney function, which have demonstrated that GFR is elevated among individuals with IGT and newly diagnosed diabetes both at baseline and during at least 4 years of follow-up. These findings are consistent with hyperfiltration in the early stages of diabetes. In studies of the natural history of diabetic nephropathy among the Pima Indians, GFRs at baseline among those with NGT, IGT, and newly diagnosed diabetes were 123, 135, and 143 ml/min, respectively. At follow-up, GFR further increased by 14% in subjects with IGT and by 18% in those with newly diagnosed diabetes, whereas increases were not seen in those with diabetes of longer duration (31). Thus, this finding may explain why we did not see greater differences in mean GFR by baseline glycemic categories. Of note, in our data, declines in GFR were the greatest among those with new or known diabetes, whereas they were modest in those with NGT or IGT.

The strengths of our study include the use of a population-based sample not selected for diabetes, CKD, or vascular disease risk factors, rigorous ascertainment and documentation of exposures and outcomes, and longitudinal data with near-complete follow-up. Some limitations to our work exist. Our interval follow-up time of 7 years may have been insufficient to allow for the development of interim CKD among those with newly diagnosed diabetes and pre-diabetes. All participants were required to attend a baseline and follow-up examination. It is likely that those with the most severe disease died or developed serious comorbidities impeding their ability to return for the follow-up examination. Thus, we may have incurred a survival bias in which we underestimated the effects of hyperglycemia on the development of CKD. We did not have information on microalbuminuria, a known risk factor for the development of kidney disease in the setting of diabetes (31,32). The inclusion of microalbuminuria, had this information been available, may have affected our results. Specifically, participants considered free of CKD may actually have proteinuria and therefore would have been misclassified. This misclassification may have biased our results toward the null. Lastly, we had low power to detect differences in the development of CKD by glycemic category. To have 80% power, we needed ORs of 1.75 for IFG and IGT, an OR of 2.84 among those with newly diagnosed diabetes, and an OR of 2.34 among those with known diabetes. Similarly for metabolic syndrome, we needed an OR of 1.74 to detect differences in the development of CKD. Therefore, borderline *P* values may meet statistical significance in larger samples.

Cardiovascular disease risk factors explain much of the relationship between IFG and IGT and the development of CKD. Clinical trials are warranted to determine whether vascular risk factor modification can prevent the development of kidney disease among those with pre-diabetes.

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