Insulin Resistance and Risk of Chronic Kidney Disease in Nondiabetic US Adults

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Abstract. This study examined the relationship of fasting serum glucose, insulin, C-peptide, glycosylated hemoglobin A (HbA1c), and Homeostasis Model Assessment (HOMA)-insulin resistance to risk of chronic kidney disease (CKD) among 6453 persons without diabetes (fasting glucose <126 mg/dl and not taking diabetes medication) who participated in the Third National Health and Nutrition Examination Survey and were aged 20 yr or older. CKD was defined as an estimated GFR <60 ml/min per 1.73 m^2. The prevalence of CKD was significantly and progressively higher with increasing levels of serum insulin, C-peptide, HbA1c, and HOMA-insulin resistance. After adjustment for potential confounding variables, the odds ratio of CKD for the highest compared with the lowest quartile was 4.03 (95% confidence interval [CI], 1.81 to 8.95; $P = 0.001$), 11.4 (95% CI, 4.07 to 32.1; $P < 0.001$), 2.67 (95% CI, 1.31 to 5.46; $P = 0.002$), and 2.65 (95% CI, 1.25 to 5.62; $P = 0.008$) for serum insulin, C-peptide, HbA1c levels, and HOMA-insulin resistance, respectively. For a one SD higher level of serum insulin (7.14 μU/ml), C-peptide (0.45 Δmol/ml), HbA1c (0.52%), and HOMA-insulin resistance (1.93), the odds ratio (95% CI) of CKD was 1.35 (1.16 to 1.57), 2.78 (2.25 to 3.42), 1.69 (1.28 to 2.23), and 1.30 (1.13 to 1.50), respectively. These findings combined with knowledge from previous studies suggest that the insulin resistance and concomitant hyperinsulinemia are presented in CKD patients without clinical diabetes. Further studies into the causality between insulin resistance and CKD are warranted.

Diabetic nephropathy remains the leading cause of end-stage renal disease (ESRD) in western populations (1) and accounts for over 40% of new cases of ESRD each year in the United States (2–4). The prevalence of diabetes has been increasing progressively in the US and other countries, and the number of adults with diabetes in the world is projected to increase to approximately 300 million in the year 2025 (5). As a consequence, diabetic ESRD is expected to become increasingly prevalent in the future (6). Patients with ESRD suffer from poor quality of life and shorter life expectancy compared with individuals of the same age in the general population (3,4). Those with diabetic ESRD have a much less favorable outcome than their counterparts with nondiabetic ESRD (4,7). Prevention of diabetes-related kidney disease is a key to decreasing the societal and personal burden of illness due to ESRD.

Insulin resistance and compensatory hyperinsulinemia have been associated with hypertension, hyperuricemia, increased levels of serum triglyceride, smaller denser LDL particles, circulating plasminogen activator inhibitor, and decreased levels of HDL (8,9). Furthermore, insulin resistance has been an underlying cause of type 2 diabetes and arteriosclerotic vascular disease (10–12). Several small clinical studies have noted insulin resistance in nondiabetic patients with mild renal dysfunction (13–15). However, there are sparse data on the relationship among insulin resistance, compensatory hyperinsulinemia, and the risk of chronic kidney disease (CKD) in nondiabetics.

We took advantage of the large representative sample of US adults who participated in the third National Health and Nutrition Examination Survey (NHANES III) to examine the relationship among glucose, C-peptide, insulin, HbA1c, and insulin resistance index and the risk of CKD.

Materials and Methods

Study Participants

NHANES III was conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention between 1988 and 1994. A detailed description of the study participants and methods has been published elsewhere (16). In brief, a stratified multistage probability design was employed to obtain a representative sample of the civilian non-institutionalized US general population (16). The study design included oversampling of those who were very young, elderly, non-Hispanic blacks, and Mexican-Americans to improve the precision of estimates in these groups. A sub-sample of 7832 NHANES III participants who were 20 yr and older were random selected to take part in morning visits at which fasting blood specimens were obtained. Persons without a fasting blood sample ($n = 485$), those with a missing glucose value ($n = 142$), and those with kidney failure according to National Kidney Foundation definition of

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an estimated GFR <15 ml/min per 1.73 m^2 ($n = 7$) were excluded from the current analysis. After the exclusions, we were able to utilize experience from 745 persons with and 6453 persons without diabetes for the main analyses.

Measurements

NHANES III data were collected by administration of a standardized questionnaire during a home interview followed by conduct of a detailed physical examination with collection of blood specimens at a mobile examination center or the participant's home. Information on a wide variety of sociodemographic, medical history, nutritional history, and family history questions, such as self-reported age, race/ethnicity, gender, years of education completed, history of smoking and hypertension, use of antihypertensive medication, alcohol consumption, and 24-h dietary recall, were obtained during the home interview (16).

BP was measured three times during the home interview and three times during the subsequent evaluation at the mobile examination center by trained observers using a standard protocol (16). BP for an individual participant was calculated as the average of all available systolic and diastolic readings. Hypertension was defined as the presence of a mean systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg and/or use of antihypertensive medication. Body weight and height were measured according to a standard protocol, and body mass index was calculated as an index for obesity.

For NHANES III participants who were assigned to a physical examination during a morning session, a blood sample was collected after an overnight fast of ≥8 h. Plasma glucose level was measured with a hexokinase enzymatic reference method (COBAS MIRA; Roche Diagnostics Corporation, Laboratory Systems, Indianapolis, IN), serum insulin level by means of a RIA (Pharmacia Diagnostics, Uppsala, Sweden), C-peptide level by use of a RIA (Bio-Rad Laboratories Inc, Hercules, Calif), and glycosylated hemoglobin concentration by means of ion-exchange HPLC with a glycosylated hemoglobin analyzer system (DIAMAT; Bio-Rad Laboratories Inc, Hercules, CA) at the University of Missouri, Columbia (16,17). Serum total cholesterol was measured enzymatically using a commercially available reagent mixture (Cholesterol/HP; Boehringer Mannheim Diagnostics, Indianapolis, IN) at the Johns Hopkins University Lipid Research Clinic, Baltimore, MD, and creatinine was analyzed by the modified kinetic Jaffe reaction method using a Hitachi 737 analyzer (Boehringer Mannheim Corporation, Indianapolis, IN) (16,17).

Diabetes was defined as a fasting plasma glucose ≥126 mg/dl and/or the current use of diabetes medication (18). A Homeostasis Model Assessment (HOMA) was used to evaluate insulin resistance (19). Assuming that normal subjects aged <35 yr with normal weight have an insulin resistance of 1, the values for a patient can be calculated from the fasting concentrations of insulin and glucose using the following formula: fasting serum insulin (μU/ml) × fasting plasma glucose (mmol/L)/22.5 (19).

GFR was calculated using the abbreviated equation developed by the Modification of Diet in Renal Disease (MDR) study (20). Estimated GFR = 186.3 × (sCr) − 1.154 × age − 0.203 × (0.742 if female) × (1.21 if black). Serum creatinine level was calibrated for measurement variance between NHANES III and MDRD clinical laboratories (21). Chronic kidney disease was defined as GFR <60 ml/min per 1.73 m^2 (6).

Statistical Analyses

Mean values of continuous variables and percentages of categorical variables were calculated by diabetes status. The statistical significance of differences in these characteristics across diabetes status was examined by means of the Z test (continuous variables) and the Wald Π^2 test (categorical variables) in multivariate regression models after adjustment for age, gender, and race/ethnicity.

The prevalence of CKD was determined by quartile of fasting glucose, insulin, C-peptide, HbA1c, and HOMA-insulin resistance among participants without diabetes. Age, gender, and race- and multivariate-adjusted logistic regression analysis was used to determine the odds ratio of CKD associated with diabetes mellitus and quartile of fasting glucose, insulin, C-peptide, HbA1c, and HOMA-insulin resistance among persons without diabetes. Next, the age-, gender-, race-, and multivariate-adjusted odds ratios of CKD associated with a one SD higher fasting glucose (10.91 mg/dl), insulin (7.14 μU/ml), C-peptide (0.45 Δmol/ml), HbA1c (0.52%), and HOMA-insulin resistance (1.93) were determined. In addition to age, gender, and race, multivariate models included systolic BP, body mass index, total cholesterol, education, physical activity, cigarette smoking, NSAID usage in the past month, and alcohol consumption.

The bivariate relationship on continuous variables was explored by plotting fasting glucose, insulin, C-peptide, HbA1c, and HOMA-insulin resistance *versus* estimated GFR, which does not impose any statistical modeling assumptions on the associations. Age-adjusted quantile regression models were also used to assess the relationship of glucose, insulin, C-peptide, HbA1c, and HOMA-insulin resistance *versus* estimated GFR. These models included fifth order polynomials for age, glucose, insulin, C-peptide, HbA1c, and HOMA-insulin resistance. Univariate and multivariate linear regression models were used to assess the association between fasting glucose, insulin, C-peptide, HbA1c, and HOMA-insulin resistance and estimated GFR. Regression coefficients were reported as the difference in estimated GFR (ml/min per 1.73 m^2) associated with a one SD increment in fasting glucose, insulin, C-peptide, HbA1c, and HOMA-insulin resistance. All statistical analyses were performed using Stata software that included functions for the analysis of complex survey data (22).

Results

General characteristics of the study participants are presented by diabetic status in Table 1. On average, nondiabetic participants were about 17 yr younger than diabetic participants. The percentages of males, non-Hispanic Blacks, and Mexican-Americans were higher, whereas the percentages of persons with a high school education, currently smoking cigarettes, and consuming alcohol were lower in those with *versus* those without diabetes. Mean systolic BP and body mass index values were significantly higher among persons with diabetes compared with their counterparts without diabetes. Diabetic participants had higher mean levels of plasma glucose, serum insulin, serum C-peptide, HbA1c, and HOMA-insulin resistance compared with nondiabetic participants. Diabetic participants also had a higher prevalence of elevated serum creatinine and CKD compared with their counterparts without diabetes. The percentage of persons with an elevated serum creatinine and CKD was significantly higher in diabetic participants compared with nondiabetic participants. After adjustment for age, race-ethnicity, gender, systolic BP, body mass index, total cholesterol, education, physical activity, cigarette smoking, NSAID usage during the preceding month, and alcohol consumption, the odds ratio of CKD associated with diabetes was 1.82 (95% CI, 1.18 to 2.81, $P = 0.007$).

Table 1. Characteristics of the 7198 study participants by diabetic status

Variables[a]	Diabetes (n = 745)	No Diabetes (n = 6453)	P[b]
Age, yr	60.3 (0.8)	43.5 (0.5)	<0.001
Male, %	52.7 (3.1)	47.1 (0.9)	0.007
Non-Hispanic Black, %	14.5 (1.6)	10.1 (0.6)	<0.001
Mexican-American, %	6.6 (0.7)	5.1 (0.5)	<0.001
≥ High School education, %	60.3 (3.0)	77.4 (1.2)	<0.001
Currently smoking, %	20.3 (2.4)	28.1 (1.0)	0.02
Alcohol consumption, %	32.4 (3.4)	56.1 (1.6)	0.001
Physically inactive, %	28.8 (2.2)	21.0 (1.1)	0.43
Serum cholesterol, mg/dl	221.6 (2.7)	203.0 (1.0)	0.14
Hypercholesterolemia, %	68.8 (2.4)	50.2 (1.3)	0.38
Systolic BP, mmHg	135.1 (1.0)	120.7 (0.4)	0.001
Hypertension, %	56.9 (2.8)	20.8 (0.9)	<0.001
Body mass index, kg/m^2	30.7 (0.3)	26.3 (0.1)	<0.001
Overweight, %	83.4 (1.9)	53.0 (1.2)	<0.001
NSAID use in previous month, %	70.3 (2.8)	78.1 (0.8)	0.28
Plasma glucose, mg/dl	186.7 (3.5)	95.1 (0.2)	<0.001
Serum insulin, μU/ml	25.7 (1.2)	10.0 (0.2)	<0.001
HOMA-insulin resistance[c]	12.2 (0.8)	2.4 (0.1)	<0.001
Serum C-peptide, ρmol/ml	1.19 (0.03)	0.68 (0.01)	<0.001
HbA1c, %	7.66 (0.10)	5.20 (0.02)	<0.001
Serum creatinine, mg/dl	1.14 (0.03)	1.06 (0.005)	0.29
Elevated creatinine,[d] %	7.1 (0.9)	3.1 (0.4)	0.02
Estimated GFR, ml/min/1.73m^2	101.1 (1.3)	112.8 (0.9)	0.08
Chronic kidney disease,[e] %	9.4 (1.3)	1.9 (0.2)	<0.001

[a] Mean or percentage (SE).
[b] Age, race-ethnicity, and gender adjusted.
[c] Insulin resistance estimated by Homeostasis Model Assessment.
[d] ≥1.6 mg/dl for males; ≥1.3 mg/dl for females.
[e] Estimated GFR <60 ml/min per 1.73m^2.

Table 2 shows the proportion of participants with CKD by quartile of glucose, insulin, C-peptide, HbA1c, and HOMA-insulin resistance among 6453 participants without diabetes. There was a significant positive relationship among higher serum glucose, insulin, C-peptide, HbA1c, and HOMA-insulin resistance and higher prevalence of CKD.

After adjustment for age, gender, and race-ethnicity, plasma glucose was no longer significantly associated with the odds of CKD (Table 3). In contrast, after adjustment for age, gender, and race-ethnicity, as well as adjustment for other established risk factors for CKD, a positive, significant, and dose-response relationship was noted among quartile of serum insulin, C-peptide, HbA1c, and HOMA-insulin resistance and the odds of CKD (Table 3). For serum insulin, C-peptide, HbA1c, and HOMA-insulin resistance, the multivariate-adjusted odds ratios of CKD for nondiabetic participants with the highest compared with the lowest quartile were 4.03 (95% CI, 1.81 to 8.95; $P = 0.001$), 11.4 (95% CI, 4.07 to 32.1; $P < 0.001$), 2.67 (95% CI, 1.31 to 5.46; $P = 0.002$), and 2.65 (95% CI, 1.25 to 5.62; $P = 0.008$), respectively (Table 3).

Age-, gender-, race/ethnicity-, and multivariate-adjusted odds ratios of CKD associated with a one SD higher level of glucose, insulin, C-peptide, HbA1c, and HOMA-insulin resistance among nondiabetic participants are presented in Table 4. Plasma glucose was not significantly associated with the odds of CKD, whereas serum insulin, C-peptide, HbA1c, and HOMA-insulin resistance were all positively and significantly associated with a higher odds of CKD.

The shapes of the association between fasting insulin, C-peptide, HbA1c, and HOMA-insulin resistance *versus* estimated GFR as a continuous variable among nondiabetic participants are displayed without any parametric assumptions in Figure 1. There was an inverse association between these variables and estimated GFR, which was noticeable even across normal values of renal function. The slope of estimated GFR on C-peptide was much steeper than that on serum insulin. In linear regression analyses, fasting insulin, C-peptide, HbA1c, and HOMA-insulin resistance were inversely and significantly associated with estimated GFR (Table 5). After adjustment for potential confounding variables, a 7.14 μU/ml higher level of insulin was associated with a 1.51 ml/min per 1.73 m^2 lower estimated GFR, a 0.45 Δmol/ml higher level of C-peptide was associated with a 4.27 ml/min per 1.73 m^2 lower estimated GFR, a 0.52% higher level of HbA1c was associated

Table 2. Prevalence of chronic kidney disease (GFR <60 ml/min per 1.73 m^2) according to quartiles of glucose, insulin, C-peptide, HbA1c, and HOMA-insulin resistance among 6453 persons without diabetes

	No. of Cases / Participants	% (SE)	*P*
Plasma glucose, mg/dl			
<88.9	20 / 1615	0.7 (0.2)	
88.9 to 95.1	38 / 1613	1.2 (0.3)	
95.2 to 101.9	54 / 1633	2.2 (0.5)	<0.001
≥102.0	73/1592	3.9 (0.6)	
Serum insulin, μU/ml			
<6.61	30 / 1604	0.8 (0.2)	
6.62 to 9.08	49 / 1601	1.8 (0.4)	
9.09 to 12.88	49 / 1599	2.2 (0.5)	<0.001
≥12.89	56 / 1597	3.6 (0.7)	
Serum C-peptide, ρmol/ml			
<0.403	11 / 1609	0.3 (0.1)	
0.404 to 0.636	18 / 1602	0.6 (0.2)	
0.637 to 0.937	46 / 1606	1.6 (0.3)	<0.001
≥0.938	108 / 1601	5.8 (0.8)	
HbA1c, %			
<5.0	21 / 1913	0.5 (0.1)	
5.1 to 5.3	30 / 1614	1.2 (0.3)	
5.4 to 5.6	43 / 1434	2.2 (0.4)	<0.001
≥5.7	91 / 1470	6.3 (0.9)	
HOMA-insulin resistance			
<1.493	31 / 1600	0.9 (0.2)	
1.493 to 2.147	44 / 1599	1.4 (0.3)	
2.148 to 3.153	47 / 1599	2.0 (0.4)	<0.001
≥3.154	62 / 1599	4.1 (0.8)	

with a 2.86 ml/min per 1.73 m^2 lower estimated GFR, and a 1.93 unit higher level of HOMA-insulin resistance was associated with a 1.71 ml/min per 1.73 m^2 lower estimated GFR.

Discussion

The present study identified a strong, positive, significant, and dose-response relationship among insulin resistance, insulin level, and risk of CKD among nondiabetic participants. This relationship was independent of age, gender, race, and other potential risk factors for CKD, such as BP, obesity, total cholesterol, education, physical activity, cigarette smoking, NSAID use, and alcohol consumption. These findings are noteworthy because they are based on a large, representative sample of the US general population. In addition, careful measures of study exposure and outcome variables allowed for precise estimation of the association. Numerous potentially confounding covariates were measured and adjustment for their effects on risk of CKD was taken into account in the present study.

Certain limitations should be considered in the interpretation of our findings. First, the cross-sectional study design used in NHANES III hinders the ability to draw inferences regarding causality among insulin resistance, hyperinsulinemia, and CKD. For instance, our findings do not allow one to determine whether insulin resistance and concomitant hyperinsulinemia contribute to the initiation or progression of CKD, whether impaired renal function contributes to the development of insulin resistance, or whether insulin resistance is merely a marker for other causes of CKD. Prospective cohort studies or mechanistic clinical studies may provide a better context for answering these questions.

Second, although the liver is the major site for insulin degradation, the kidney plays an essential role in the clearance and degradation of circulating insulin (23,24). In addition, experiments in laboratory animals and human subjects have indicated that the kidney plays an important role in glucose metabolism (25,26). Animal and human studies indicate that acute renal failure results in a reduction in the systemic removal of insulin (27). Therefore, the elevated level of serum insulin and C-peptide observed in our study in CKD patients may be a consequence of a decline in renal function. However, patients with kidney failure were excluded from our analysis. In addition, our data indicate that both serum insulin and plasma glucose levels are increased in patients with CKD, which suggests the presence of insulin resistance among these patients. A reduced clearance of insulin in acute renal failure

Table 3. Age, gender, and race/ethnicity- or multivariate-adjusted odds ratios of chronic kidney disease according to quartiles of glucose, insulin, C-peptide, HbA1c, and HOMA-insulin resistance among 6453 persons without diabetes[a]

	Age, Gender, Race/Ethnicity Adjusted		Multivariate-Adjusted	
	Odds Ratio (95% CI)	*P*-Trend	Odds Ratio (95% CI)	*P*-Trend
Plasma glucose, mg/dl				
<88.9	1.00		1.00	
88.9 to 95.1	1.19 (0.55 to 2.58)		1.04 (0.46 to 2.33)	
		0.23		0.56
95.2 to 101.9	1.36 (0.55 to 3.37)		1.11 (0.45 to 2.70)	
≥102.0	1.55 (0.71 to 3.42)		1.20 (0.57 to 2.53)	
Serum insulin, μU/ml				
<6.61	1.00		1.00	
6.62 to 9.08	1.91 (1.05 to 3.50)		1.77 (0.93 to 3.37)	
		<0.001		0.001
9.09 to 12.88	2.48 (1.32 to 4.63)		2.30 (1.20 to 4.40)	
≥12.89	4.41 (2.42 to 8.05)		4.03 (1.81 to 8.95)	
Serum C-peptide, ρmol/ml				
<0.403	1.00		1.00	
0.404 to 0.636	1.30 (0.48 to 3.58)		1.23 (0.43 to 3.55)	
		<0.001		<0.001
0.637 to 0.937	3.09 (1.29 to 7.44)		3.21 (1.23 to 8.52)	
≥0.938	9.76 (4.22 to 23.0)		11.4 (4.07 to 32.1)	
HbA1c, %				
<5.0	1.00		1.00	
5.1 to 5.3	1.47 (0.66 to 3.30)		1.24 (0.56 to 2.78)	
		0.001		0.002
5.4 to 5.6	1.67 (0.90 to 3.11)		1.46 (0.81 to 2.62)	
≥5.7	3.17 (1.49 to 6.74)		2.67 (1.31 to 5.46)	
HOMA-insulin resistance				
<1.493	1.00		1.00	
1.493 to 2.147	1.08 (0.56 to 2.07)		0.93 (0.49 to 1.78)	
		<0.001		0.008
2.148 to 3.153	1.44 (0.71 to 2.91)		1.26 (0.62 to 2.59)	
≥3.154	3.15 (1.72 to 5.77)		2.65 (1.25 to 5.62)	

[a] Adjusted for age, race-ethnicity, gender, systolic BP, body mass index, total cholesterol, education, physical activity, cigarette smoking, NSAID usage in the past month, and alcohol consumption.

patients has been associated with a decrease in levels of blood glucose (27). Furthermore, using a more precise method for measurement of insulin resistance (minimal-model technique), insulin resistance has been documented in nondiabetic CKD patients (13,14). In these studies, plasma insulin levels were highly correlated with measured insulin resistance (13,14).

Finally, serum creatinine levels and calculated GFR were used to identify and classify kidney disease in our study. Although inulin or iothalamate clearance techniques may provide a more sensitive estimate of renal function, serum creatinine has been used widely in large epidemiologic studies and in clinical practice for estimation of renal function. As such, the findings from our study are applicable to clinical and public health practice settings.

Diabetes has been identified as a major underlying cause of ESRD in the US population (1–4). Several prospective cohort studies have documented that diabetes is associated with an increased risk of diabetic and nondiabetic ESRD (28–31). Clinical trials have also demonstrated that intensive glycemic control slows the progression of diabetic nephropathy in both type 1 and type 2 diabetic patients (32–34). Our data indicate that glycosylated hemoglobin A, an index of long-term glycemic level, is linearly related to the risk of CKD in persons without diabetes. In our study, a HbA1c level greater than or equal to 5.7% was associated with an elevated risk of CKD. These findings support the notion that intensive glycemic control in diabetics as well as a reduction of glycemic level in persons with an impaired fasting glucose may be important

Table 4. Age, gender, and race/ethnicity- or multivariate-adjusted odds ratios of chronic kidney disease associated with one SD higher level of glucose, insulin, C-peptide, HbA1c, and HOMA-insulin resistance among 6453 persons without diabetes

	Age, Gender, and Race/Ethnicity-Adjusted	Multivariate-Adjustment[a]
Glucose (10.91 mg/dl)	1.13 (0.86 to 1.48)	1.04 (0.79 to 1.37)
Insulin (7.14 μU/ml)	1.39 (1.18 to 1.63)	1.35 (1.16 to 1.57)
C-peptide (0.45 ρmol/ml)	2.46 (1.98 to 3.05)	2.78 (2.25 to 3.42)
HbA1c (0.52%)	1.73 (1.34 to 2.24)	1.69 (1.28 to 2.23)
HOMA-insulin resistance (1.93)	1.35 (1.15 to 1.58)	1.30 (1.13 to 1.50)

[a] Adjusted for age, race-ethnicity, gender, systolic BP, body mass index, total cholesterol, education, physical activity, cigarette smoking, NSAID usage in the past month, and alcohol consumption.

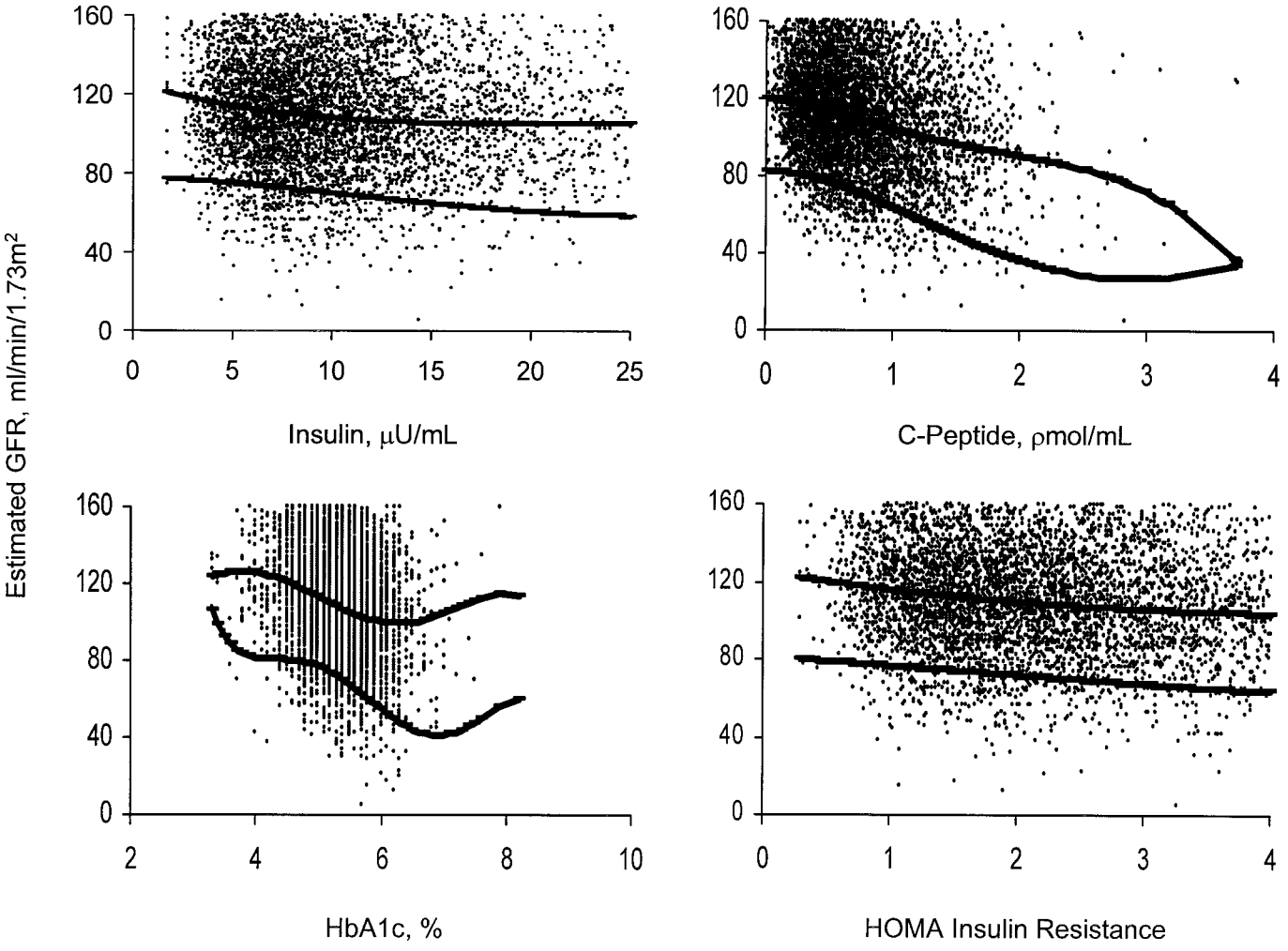

Figure 1. Scatter plot of insulin, C-peptide, glycosylated hemoglobin A (HbA1c), and Homeostasis Model Assessment (HOMA)-insulin resistance *versus* estimated GFR. Lines represent the age-adjusted median (top line) and fifth percentile (bottom line) of estimated GFR using a fifth-order polynomial for each independent variable (*i.e.*, insulin, C-peptide, HbA1c, and HOMA-insulin resistance).

strategies for primary prevention of CKD and slowing the progression of CKD.

Epidemiologic studies have demonstrated that insulin resistance and concomitant hyperinsulinemia play a central role in the development of arteriosclerotic vascular disease (9,12). Insulin resistance has been associated with type 2 diabetes, hypertension, central obesity, and dyslipidemia, all of which are important risk factors for CKD (28–31,35–38). In addition, clinical studies have indicated that a greater degree of insulin resistance may predispose to renal injury by worsening renal hemodynamics through

Table 5. Age, gender, and race/ethnicity or multivariate-adjusted changes of GFR associated with one SD higher level of glucose, insulin, C-peptide, HbA1c, and HOMA-insulin resistance among 6453 persons without diabetes

	Age, Gender, and Race/Ethnicity-Adjusted		Multivariate-Adjustment[a]	
	Δ (95% CI)	*P*	Δ (95% CI)	*P*
Glucose (10.91 mg/dl)	−1.23 (−2.32 to −0.15)	0.03	−0.94 (−2.07 to 0.19)	0.10
Insulin (7.14 μU/ml)	−1.41 (−2.55 to −0.28)	0.02	−1.51 (−2.64 to −0.37)	0.01
C-peptide (0.45 ρmol/ml)	−3.23 (−4.24 to −2.22)	<0.001	−4.27 (−5.48 to −3.06)	<0.001
HbA1c (0.52%)	−2.33 (−3.48 to −1.18)	<0.001	−2.86 (−4.07 to −1.65)	<0.001
HOMA-insulin resistance (1.93)	−1.57 (−2.63 to −0.52)	0.004	−1.71 (−2.76 to −0.66)	0.002

[a] Adjusted for age, race-ethnicity, gender, systolic BP, body mass index, total cholesterol, education, physical activity, cigarette smoking, NSAID usage in the past month, and alcohol consumption.

the elevation of glomerular filtration fraction and resultant glomerular hyperfiltration among hypertensives (39).

There are sparse data on the relationship between insulin resistance and CKD in nondiabetic patients. Several small clinical studies have suggested that insulin resistance might be present in kidney disease patients without diabetes (13–15). Vareesangthip *et al.* (13) found that insulin sensitivity was significantly lower and fasting plasma insulin was significantly higher in 15 adult polycystic kidney disease patients compared with 20 age- and sex-matched subjects with normal renal function. Fliser *et al.* (14) examined 29 patients with IgA glomerulonephritis, 21 patients with adult polycystic kidney disease in different stages of renal failure, and 16 healthy age-matched controls. Insulin sensitivity (minimal-model technique) was significantly lower and plasma insulin concentration was significantly higher in the kidney disease patients compared with their matched controls. Insulin sensitivity was not significantly different in patients with different underlying causes of renal disease and was similar in renal patients with a GFR within the normal range, mild to moderate renal failure, or advanced renal failure (14). These data suggest that insulin resistance and concomitant hyperinsulinemia are present early in the course of kidney disease, irrespective of underlying cause. DeFronzo *et al.* (40) examined insulin sensitivity with the euglycemic insulin clamp technique in 17 patients with chronic renal failure and 36 control subjects. They found that insulin-mediated glucose metabolism was reduced by 47%, whereas splanchnic glucose production was similar in the patients with renal failure compared with the controls. Their results suggest that insulin-mediated glucose uptake by the liver is normal in persons with chronic renal failure, and tissue insensitivity to insulin is the primary cause of insulin resistance in patients with CKD (40).

Several epidemiologic studies have reported a positive relationship between insulin resistance and the risk of microalbuminuria in nondiabetic patients (41,42). In the Insulin Resistance Atherosclerosis Study, Mykkanen *et al.* (41) examined the relationship of insulin sensitivity, estimated by a frequently sampled intravenous glucose tolerance test and the minimal model and fasting plasma insulin concentration, to microalbuminuria in a cross-sectional study of 982 nondiabetic patients aged 40 to 69 yr. They reported that decreased levels of insulin sensitivity were related to an increased prevalence of microalbuminuria (41). Fujikawa *et al.* (42) conducted a 6-yr prospective study to examine the relationship between insulin resistance and risk of microalbuminuria in 116 nondiabetic Japanese Americans living in Hawaii. Their study indicated that fasting insulin levels and HOMA-insulin resistance were significantly higher in participants who developed microalbuminuria or proteinuria during follow-up compared with those who did not. They concluded that insulin resistance appeared earlier than the appearance of microalbuminuria (42).

Our findings of a positive and significant association among insulin resistance, hyperinsulinemia, and kidney disease in nondiabetic patients have both clinical and public health implications. First, they suggest that it may be beneficial to detect and treat insulin resistance and concomitant hyperinsulinemia in nondiabetic patients with CKD. Second, they suggest that a more aggressive approach to reducing insulin resistance in individual patients and in populations would substantially lower the risk of CKD. Many lifestyle modification measures, such as a reduction in dietary fat intake and an increase in physical activity, have been demonstrated to reduce insulin resistance.

In conclusion, our study documents the presence of a strong, positive, independent, and dose-response relationship between insulin resistance and CKD among nondiabetic patients. These findings combined with knowledge from previous studies suggest that the insulin resistance and concomitant hyperinsulinemia are presented in CKD patients without clinical diabetes. Detection and treatment of insulin resistance should be considered even in nondiabetic patients with CKD. Prevention and treatment of insulin resistance in the community might substantially reduce the societal burden of CKD. Further studies are warranted to establish the causal relationship between insulin resistance and CKD.

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