Metabolic syndrome, insulin resistance and kidney function in non-diabetic individuals

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Abstract

Background. Metabolic syndrome has been recently identified as a risk factor for chronic kidney disease (CKD). Since the five individual components of the metabolic syndrome have also been identified as risk factors for CKD, the metabolic syndrome diagnosis may represent an aggregate of CKD risk factors. On the other hand, the components of the metabolic syndrome are also associated with insulin resistance, which may directly mediate the increased CKD risk.

Methods. This study was a cross-sectional evaluation of the relationship between metabolic syndrome, insulin resistance and estimated glomerular filtration rate (eGFR) in 574 non-diabetic individuals. Insulin resistance was directly quantified using the insulin suppression test, and the metabolic syndrome components were measured. eGFR was calculated using the three validated estimation equations: the Chronic Kidney Disease Epidemiology Collaboration equation, the Mayo quadratic equation and the Modification of Diet in Renal Disease study equation.

Results. While CKD prevalence was higher and mean eGFR was lower in individuals who met the metabolic syndrome criteria compared with those who did not, we did not observe a significant relationship between insulin resistance and eGFR. Of all of the components of the metabolic syndrome, only hypertension was significantly associated with CKD prevalence [odds ratio (95% confidence interval), 3.5 (1.2–10.1), $P = 0.02$].

Conclusion. Although CKD is more common among individuals with the metabolic syndrome, insulin resistance is not a common factor.

Keywords: chronic kidney disease; estimated glomerular filtration rate; insulin resistance; metabolic syndrome

increased risk may be due to the aggregation of known risk factors for CKD in the metabolic syndrome diagnosis. On the other hand, the metabolic syndrome diagnosis may indicate the presence of insulin resistance, which may directly increase the risk for CKD. A few studies have suggested a link between insulin resistance and CKD [2, 5, 6]; however, these studies used surrogate measures of insulin resistance based on fasting insulin concentration. Unfortunately, fasting insulin concentration captures <40% of the variability in insulin resistance [7, 8], indicating that insulin concentration is a less precise estimate of insulin action.

The few studies that have used direct measures of insulin action to evaluate the relationship between insulin resistance and kidney function were conducted in individuals with pre-existing kidney disease [9–11]. Although a relationship was identified, it is not clear whether declining kidney function engenders insulin resistance or whether insulin resistance predisposes to declining kidney function.

To better understand the relationship between kidney function and insulin resistance, we evaluated the association between estimates of glomerular filtration rate (eGFR) and a direct measure of insulin resistance, using the insulin suppression test, in 574 relatively healthy individuals without diabetes or known kidney disease. The purpose was to evaluate the association between kidney function and insulin resistance in a population prior to overt kidney disease. We concurrently evaluated the impact of the diagnosis of metabolic syndrome on eGFR. We hypothesized that although the diagnosis of metabolic syndrome would be associated with lower eGFR, with direct measurement of insulin resistance, there would be no association between insulin resistance and eGFR.

Materials and methods

The study population consisted of 574 non-diabetic individuals (348 women and 226 men) who have been enrolled for our cross-sectional study of insulin resistance since 2000. The study was approved by Stanford University's Internal Review Board and was in compliance with the principles outlined in the Declaration of Helsinki. All subjects provided written informed consent for participation. All subjects were generally healthy and had the following

Introduction

Recent studies have suggested that individuals with metabolic syndrome are at increased risk for developing chronic kidney disease (CKD) [1–4]. The mechanism behind this

procedures on the same day: measurement of height, weight, waist circumference, blood pressure, lipid assessment, serum creatinine and insulin suppression test to measure insulin sensitivity.

All procedures were performed in the Clinical and Translational Research Unit after 12 h of fasting. Blood pressure was measured using a Dinamap automatic blood pressure recorder (GE Healthcare, Tampa, FL). Before the blood pressure measurements, patients were seated quietly in a chair for 5 min with their feet on the floor and one arm supported at heart level. Using an appropriately sized cuff, three blood pressure readings were taken at 1-min intervals, and the mean of these readings was used for data analysis. Waist circumference was measured by placing a measuring tape around the waist at the upper point of the iliac crest and determined during minimal inspiration as previously described [12].

Lipid panel and serum creatinine were measured in the core laboratory at Stanford. As our population was generally healthy, we used two eGFR estimations recently developed for the general population including the Mayo Clinic Quadratic formula [13] and the Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation [14]. For comparison, prevalence of CKD was also calculated using the traditional Modification of Diet in Renal Disease (MDRD) study equation (abstract by Levey *et al.*, *J Am Soc Nephrol* 2000). CKD was defined as having an eGFR <60 mL/min.

Insulin sensitivity was directly measured using a modified version [15] of the insulin suppression test. Insulin sensitivity measurements from the insulin suppression test are highly correlated with results from the hyperinsulinemic euglycemic clamp ($r = 0.93$) [16]. Following an overnight fast, an intravenous catheter was placed in each of the subjects' arms. One arm was used for the administration of a 180-min infusion of octreotide ($0.27 \mu\text{g}/\text{m}^2/\text{min}$), insulin ($32 \text{ mU}/\text{m}^2/\text{min}$) and glucose ($267 \text{ mg}/\text{m}^2/\text{min}$); the other arm was used for drawing blood. Plasma glucose and insulin concentrations were measured every 10 min from 150 to 180 min and averaged to obtain the steady-state plasma glucose (SSPG) and insulin concentrations. Since steady-state plasma insulin concentrations are comparable in all individuals and glucose infusion rate is identical, the SSPG concentration provides a direct measure of insulin resistance; the higher the SSPG concentration, the more insulin resistant the individual. To evaluate the relationship between insulin resistance and kidney function, subjects were grouped into tertiles based on SSPG concentrations, with the most insulin-sensitive individuals in Tertile 1 and the most insulin-resistant

individuals in Tertile 3. Glucose concentrations were measured by the oxidase method (Beckman Analyzer 2, Brea, CA).

For the diagnosis of metabolic syndrome, we used the 2001 ATP III definition [17], with modifications as outlined in the 2005 statement from the American Heart Association/National Heart, Lung and Blood Institute [18]. The five components of the metabolic syndrome are as follows: (i) waist circumference >102 cm in men or >88 cm in women; (ii) blood pressure $\geq 130/85$ mmHg or on drug treatment for hypertension; (iii) serum triglycerides ≥ 1.7 mmol/L or on drug treatment for hypertriglyceridemia, (iv) serum high-density lipoprotein cholesterol (HDL-C) <1.03 mmol/L in men and <1.3 mmol/L in women or on drug treatment for low HDL-C and (v) fasting plasma glucose ≥ 5.6 mmol/L. Metabolic syndrome is considered to be present if any three of the five traits are present.

Statistical analysis was performed using SPSS (version 17 for Windows; SPSS, Chicago, IL). All data are median (interquartile range) unless otherwise specified. Analysis of variance or chi-square tests for categorical variables were used to compare clinical and laboratory characteristics. A linear model, adjusted for age, gender and ethnicity, was used to evaluate the relationship between insulin resistance (SSPG) and eGFR. In a second model, we also adjusted for use of medications that may prevent or slow progression of kidney disease, including angiotensin-converting enzyme (ACE) inhibitors [19, 20] or angiotensin receptor blockers (ARB) [21, 22] and 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins) [23, 24]. Variables that were not normally distributed were log transformed.

Results

We first categorized our study population by diagnosis of metabolic syndrome (Table 1). Overall, 42% of the study population met the criteria for metabolic syndrome. Individuals meeting this criteria were older, more likely to be male and heavier compared with individuals who did not. As expected, all components of the metabolic syndrome were more unfavorable in those who met the metabolic syndrome criteria. In addition, individuals with metabolic

Table 1. Characteristics of individuals with and without metabolic syndrome^a

Variables	Metabolic syndrome		P
	Absent	Present	
N	334	240	
Age (years)	50 (43–55)	53 (45–59)	<0.001
Body mass index (kg/m^2)	27.7 (25.3–30.8)	31.6 (29.3–34.8)	<0.001
Men (%)	35.3	45.0	0.019
Non-Hispanic White (%)	65.3	65.8	0.89
Metabolic syndrome components			
Waist circumference (cm)	93 (87–101)	106 (98–113)	<0.001
Systolic blood pressure (mmHg)	116 (109–126)	131 (117–140)	<0.001
Diastolic blood pressure (mmHg)	71 (66–78)	75 (69–83)	<0.001
Plasma glucose (mmol/L)	5.2 (4.9–5.4)	5.6 (5.3–6.1)	<0.001
Triglycerides (mmol/L)	0.99 (0.71–1.33)	1.73 (1.18–2.29)	<0.001
HDL-C (mmol/L)	1.30 (1.06–1.56)	1.01 (0.88–1.21)	<0.001
Insulin resistance			
SSPG (mmol/L)	6.2 (4.1–9.4)	11.1 (7.7–13.5)	<0.001
Medications			
Use of ACE inhibitor or ARB (%)	5.4	22.5	<0.001
Use of statin (%)	9.3	15.4	0.03
Kidney function estimates			
Serum creatinine ($\mu\text{mol}/\text{L}$)	65.2 (54.0–76.3)	68.6 (60.2–76.3)	0.03
eGFR, Mayo ($\text{mL}/\text{min}/1.73\text{m}^2$)	101.7 (96.2–110.9)	100.2 (93.3–110.3)	0.07
eGFR, CKD-EPI ($\text{mL}/\text{min}/1.73\text{m}^2$)	89.3 (78.5–100.9)	87.5 (75.9–96.7)	0.06
eGFR, MDRD ($\text{mL}/\text{min}/1.73\text{m}^2$)	84.4 (78.5–100.9)	83.7 (73.5–94.2)	0.36
CKD, Mayo (%)	0.3	0.8	0.74
CKD, CKD-EPI (%)	2.4	5.8	0.03
CKD, MDRD (%)	3.0	5.8	0.09

^aValues represent median (interquartile range) unless otherwise specified.

syndrome had higher degrees of insulin resistance as quantified by SSPG concentration. Finally, individuals with metabolic syndrome were more likely to be treated with ACE inhibitors, ARBs or statins.

The prevalence of CKD was generally low in the study population but varied greatly depending on the eGFR calculation. We calculated the overall prevalence of CKD to be 0.7% (4/574) with the Mayo Quadratic equation, 3.8% (22/574) with the CKD-EPI equation and 4.2% (24/574) with the traditional MDRD equation. Despite differences in the prevalence of CKD, estimates of kidney function tended to be lower in those with metabolic syndrome compared with those without the syndrome (Table 1). For example, serum creatinine was significantly higher, and CKD prevalence was ≥ 2 -fold in those with the metabolic syndrome compared with those without the diagnosis. The difference in CKD prevalence was only significant when eGFR was calculated using the CKD-EPI equation.

Of all of the components of the metabolic syndrome, hypertension was most strongly associated with CKD. Using the CKD-EPI equation to calculate eGFR, we found a 4-fold increase in the prevalence of CKD in individuals with hypertension compared with those without hypertension (6.5 versus 1.6%, $P = 0.002$). Similar trends were obtained when eGFR was calculated *via* the Mayo (1.1 versus 0.3%, $P = 0.34$) and MDRD (6.9 versus 1.9%, $P = 0.005$) equations. Hypertension remained a significant predictor of CKD in a logistic regression model even when adjusted for age, gender and ethnicity [odds ratio 3.5 (95% confidence interval, 1.2–10.1), $P = 0.02$ using CKD-EPI and 3.2 (1.2–8.7), $P = 0.02$ using MDRD]. In contrast, none of the other metabolic syndrome components was significantly associated with the presence of CKD.

To determine the impact of insulin resistance on kidney function, we also categorized our study population by tertiles

of insulin resistance (Table 2) and evaluated the relationship between insulin resistance and baseline characteristics. As the degree of insulin resistance increased, body mass index also increased. In terms of ethnicity, the prevalence of non-Hispanic Whites significantly decreased with increasing degrees of insulin resistance. Age and gender were similar across the three tertiles.

As expected, all components of metabolic syndrome became more unfavorable with increasing degrees of insulin resistance. Therefore, the prevalence of metabolic syndrome (three or more components) also increased with increasing degrees of insulin resistance. However, there were discrepancies between the diagnosis of metabolic syndrome and the degree of insulin resistance. For example, 16% of the most insulin-sensitive individuals (Tertile 1) actually met the criteria for metabolic syndrome. Conversely, 30% of the most insulin-resistant individuals failed to meet the criteria for metabolic syndrome. These findings highlight the limitations of using the metabolic syndrome diagnosis as a surrogate measure for insulin resistance.

With regard to kidney function, there was no relationship between insulin resistance and eGFR. Although all individuals with CKD defined by the Mayo Quadratic equation were categorized into the most insulin-resistant tertile, this group consisted of only four individuals. We also did not observe a relationship between insulin resistance and eGFR calculated by the other two equations.

Figure 1 illustrates the lack of relationship between SSPG concentration and eGFR calculated with the Mayo Quadratic formula (A) and CKD-EPI (B). Although there was a 6-fold difference in SSPG concentration among individuals, there was no obvious relationship between insulin resistance and eGFR calculated with either equation. Moreover, in a linear model, there was no significant relationship between SSPG

Table 2. Characteristics of individuals by tertile of insulin resistance^a

	Insulin sensitive SSPG 1	Insulin intermediate SSPG 2	Insulin resistant SSPG 3	P
N	193	189	192	
SSPG	4.2 (3.4–5.1)	8.2 (7.1–9.3)	13.0 (11.7–14.5)	<0.001
Age (years)	51 (45–57)	51 (42–57)	51 (42–57)	0.57
Body mass index (kg/m ²)	26.9 (24.3–28.9)	29.9 (27.0–32.7)	33.2 (29.3–35.2)	<0.001
Men (%)	37.8	38.6	41.7	0.72
Non-Hispanic White (%)	75.1	63.5	57.8	0.001
Metabolic syndrome components				
Waist circumference (cm)	91 (84–99)	100 (92–109)	105 (97–113)	<0.001
Systolic blood pressure (mmHg)	116 (108–130)	121 (111–133)	126 (114–137)	<0.001
Diastolic blood pressure (mmHg)	72 (66–78)	73 (67–80)	74 (69–81)	0.05
Plasma glucose (mmol/L)	5.1 (4.8–5.4)	5.3 (5.1–5.6)	5.6 (5.2–6.0)	<0.001
Triglycerides (mmol/L)	0.90 (0.68–1.37)	1.20 (0.86–1.70)	1.53 (1.13–2.27)	<0.001
HDL-C (mmol/L)	1.30 (1.06–1.62)	1.17 (0.98–1.40)	1.04 (0.91–1.24)	<0.001
Metabolic syndrome (%)	15.5	39.7	71.9	<0.001
Medications				
Use of ACE inhibitor or ARB (%)	8.8	10.1	18.8	0.006
Use of statin (%)	9.3	12.2	14.1	0.35
Kidney function estimates				
Serum creatinine (μ mol/L)	68.6 (57.6–76.3)	67.1 (57.2–76.3)	67.9 (55.1–76.3)	0.93
eGFR, Mayo (mL/min/1.73m ²)	100.9 (95.5–109.1)	101.6 (94.5–110.5)	101.8 (95.5–111.8)	0.56
eGFR, CKD-EPI (mL/min/1.73m ²)	88.0 (74.2–99.1)	89.8 (78.3–98.6)	89.0 (76.5–100.7)	0.48
eGFR, MDRD (mL/min/1.73m ²)	83.7 (72.9–95.1)	84.2 (76.2–95.0)	84.4 (74.2–96.7)	0.44
CKD, Mayo (%)	0	0	2.1	0.02
CKD, CKD-EPI (%)	4.7	3.2	3.6	0.74
CKD, MDRD (%)	5.7	3.2	3.6	0.42

^aValues represent median (interquartile range) unless otherwise specified.

Fig. 1. (A) The relationship between SSPG concentration (mmol/L) and eGFR (mL/min) as determined by the Mayo quadratic formula. (B) The relationship between SSPG concentration (mmol/L) and eGFR (mL/min) as determined by the CKD-EPI formula.

concentration and eGFR even after adjustment for age, gender and ethnicity ($P = 0.72$ for CKD-EPI, $P = 0.72$ for Mayo and $P = 0.58$ for MDRD). Further adjustment for treatment of individuals with ACE inhibitors/ARBs or statins did not alter the relationship between SSPG concentration and eGFR ($P = 0.40$ for CKD-EPI, $P = 0.29$ for Mayo and $P = 0.32$ for MDRD).

Since prior publications examining the relationship between metabolic syndrome and eGFR used the old glucose cutoff of ≥ 6.1 mmol/L as a criterion for the metabolic syndrome [2, 5], we re-analyzed our data using this cut-point. There was still no fundamental change in the relationship among metabolic syndrome, insulin resistance and eGFR (data not shown), with the exception that the prevalence of the metabolic syndrome diagnosis decreased from 42 to 34% using the higher glucose cut-point.

Discussion

Previous studies have suggested an association between the diagnosis of the metabolic syndrome and an increased risk for developing CKD. In this study, we also observed an association between the diagnosis of the metabolic syndrome and a modest decline in eGFR. Interestingly, of all the components of metabolic syndrome, we found that only

hypertension was significantly associated with an increased risk for CKD. In contrast, insulin resistance, directly measured by the insulin suppression test, was not associated with a decline in eGFR. Our findings indicate that the relationship between metabolic syndrome and kidney function may be explained by risk conferred by individual components of the syndrome, such as hypertension, rather than by insulin resistance.

Our study is different from earlier studies reporting an association between insulin resistance and CKD because these studies used surrogate markers of insulin resistance [2, 5, 6]. The most commonly used marker has been the homeostasis model assessment of insulin resistance (HOMA-IR), which is a calculation based on fasting glucose and insulin. HOMA-IR is a limited surrogate marker because it accounts for <40% of the variability as quantified by more direct measures of insulin resistance [7, 25]. The metabolic syndrome diagnosis has also been used as a surrogate measure of insulin resistance. However, as seen in Table 2, the relationship between metabolic syndrome and insulin resistance is not perfect, with 16% of the most insulin-sensitive individuals qualifying for the diagnosis of metabolic syndrome. Therefore, it is not entirely surprising to find conflicting results between studies using surrogate markers and direct measures of insulin resistance.

Although we did not find a relationship between insulin resistance and kidney function, our results do support previous findings showing an association between the metabolic syndrome diagnosis and impaired kidney function. The marginal significance levels seen in our study may relate to our smaller sample size compared with those of previous studies, which included 6000 to 10 000 subjects [1, 2]. The relationship between the metabolic syndrome and CKD likely reflects two major factors known to be associated with CKD initiation or progression. Firstly, individuals with metabolic syndrome are generally older than their counterparts without metabolic syndrome [1, 2]. Older age is known to be a strong risk factor for CKD [25]. Secondly, each of the components of the metabolic syndrome has been identified to be associated with CKD [26–32]; thus, the diagnosis may reflect additive effects of the individual components on CKD risk. The risk conferred by each component, however, is probably not equal. In our study, hypertension had the strongest association with CKD, which is consistent with findings from other studies [1, 2]. For example, in 10 096 non-diabetic participants enrolled in the Atherosclerosis Risk in Communities Study [2], a greater proportion of hypertensive individuals developed CKD compared with individuals with any other single component of the metabolic syndrome (11 versus <9%). Notably, hypertensive individuals accounted for 46% of the total number of individuals who developed CKD; in comparison, individuals with metabolic syndrome diagnosis accounted for 30% of the total number of individuals who developed CKD.

The strong association between hypertension and CKD is particularly interesting because hypertension is the component of the metabolic syndrome least associated with insulin resistance [33, 34]. Although insulin-resistant individuals are more likely to be hypertensive compared with insulin-sensitive individuals, only half of hypertensive

individuals are insulin-resistant (in upper tertile of insulin resistance) [35]. Moreover, using factor analysis to identify related variables among the metabolic syndrome components and insulin resistance, Ferrannini [33] demonstrated that triglyceride and HDL-C concentration but not hypertension cluster with insulin resistance as measured by the hyperinsulinemic euglycemic clamp method.

Our findings highlight two main limitations of the metabolic syndrome diagnosis. Firstly, this diagnosis does not accurately stratify individuals with varying degrees of insulin resistance compared to direct measures of insulin sensitivity. Secondly, although the metabolic syndrome diagnosis may predict cardiovascular disease and CKD, the predictive power of this diagnosis is likely driven by individual components of the syndrome such as glucose intolerance, dyslipidemia and hypertension. Thus, the metabolic syndrome diagnosis does not convey additional prognostic information when compared to that provided by the sum of its individual components. Due to these limitations, the clinical utility of the metabolic syndrome has been recently debated [36–38].

In comparison to previous studies employing direct measures of insulin sensitivity to evaluate the association between insulin resistance and kidney function [9–11], our study differed significantly. These prior studies examined insulin resistance in individuals with significant kidney disease, and although a relationship between insulin resistance and kidney function was identified, it is not clear whether insulin resistance is a consequence or a cause of overt kidney disease. For example, DeFronzo *et al.* [9] used the euglycemic clamp technique to evaluate insulin sensitivity in patients with end-stage renal disease ($n = 10$) and reported lower degrees of insulin sensitivity compared to that of controls ($n = 8$). Kobayashi *et al.* [10] also reported lower mean insulin sensitivity in patients diagnosed with CKD ($n = 29$) compared with controls ($n = 10$). Within the group of individuals with kidney disease, there was a modest association between serum creatinine concentration and insulin sensitivity ($r = -0.449$). Finally, a recent study suggested a linear association between insulin sensitivity and eGFR in older men ($n = 1070$) with a mean age of 71 and a cystatin-based eGFR of $61.5 \text{ mL/min/1.73m}^2$ [11]. The relationship was modest, with a large (one unit) decrease in insulin sensitivity correlating with a small ($0.85\text{--}1.19 \text{ mL/min/1.73m}^2$) decline in eGFR. Collectively, these studies suggest a relationship between insulin resistance and overt kidney disease but it is not clear what is the nature of this relationship. To circumvent the potential confounding factor of the presence of advanced kidney disease contributing to insulin resistance, we evaluated the association between kidney function and insulin resistance in a population prior to overt kidney disease and found no meaningful relationship.

There are several limitations to our study. Firstly, we examined a cross-sectional study of individuals with a low prevalence of CKD. Nevertheless, the prevalence of CKD estimated by the MDRD equation was higher than that found in the NHANES population without diabetes (4.2% in this study compared with 1.9% in NHANES [5]). Secondly, although we studied a population that was much larger than those of previous studies using direct

measures of insulin resistance [9, 10], our sample size was still smaller than those of epidemiological studies using indirect measures of insulin resistance [1, 2]. Therefore, we could have missed smaller associations between insulin resistance and kidney function that would have been apparent with larger samples. Thirdly, we evaluated only the association between insulin resistance and kidney function and therefore cannot exclude the possibility that insulin resistance could influence the future development of kidney disease. Finally, to assess kidney function, we did not evaluate other markers of kidney disease such as microalbuminuria in our study. We primarily used estimation equations for glomerular filtration rate, which are surrogates for direct measurements of glomerular filtration. To address this inherent limitation, we did employ two newer equations, CKD-EPI and Mayo, which have been specifically developed for calculating eGFR in healthier populations. Although the prevalence of CKD varied with the method used to calculate eGFR, the direction of the association between the metabolic syndrome diagnosis and eGFR remained similar to and consistent with past studies.

In conclusion, we analyzed the association among insulin resistance, the metabolic syndrome and eGFR in 574 relatively healthy individuals and found no meaningful correlation between insulin resistance and eGFR. While decreased kidney function may be more common in individuals with the metabolic syndrome than in those without it, our findings argue against the role of insulin resistance as a common factor for CKD.

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Conflict of interest statement. None declared.

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