Correlation between the Indexes of Insulin Resistance and Renal Function in the Presence of Hypertension

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Key Words

Insulin sensitivity • Homeostasis model assessment • Glomerular filtration rate • Chronic kidney disease

Abstract

Background/Aims: It is important to establish the association between insulin resistance and renal function; however, the reported associations differ across studies. Different underlying pathophysiologies of the studied populations may affect the associations. There have been no reports on the relationship between insulin resistance and renal function in the presence of hypertension (HT). We investigated the correlation between a homeostasis model assessment of insulin resistance (HOMA-IR) and the estimated glomerular filtration rate (eGFR) in subjects with and without HT. **Methods:** The study included 214 individuals (mean age: 65.6 years) who were nonmedicated and cardiovascular disease-free. Clinical variables, including blood pressure (BP), creatinine, glucose and lipid panels, were measured. **Results:** The HT group showed significantly higher levels of systolic/diastolic BP than the non-HT group. A multiple linear regression analysis revealed that the eGFR in the non-HT group was independently, significantly and inversely correlated with HOMA-IR, while the eGFR in the HT group was independently, significantly and inversely correlated with systolic BP, but not with HOMA-IR. **Conclusions:** A clearer correlation between HOMA-IR and eGFR was observed in the non-HT group than

the HT group, suggesting that HT may attenuate the direct correlation between the insulin resistance and renal function indices.

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Introduction

Insulin resistance (IR) is an underlying pathology of cardiometabolic disorders, such as hypertension (HT), which leads to damage of various organs including the kidney [1, 2]. Chronic kidney disease (CKD) is a public health concern because the incidence is increasing [3]. Establishing the association between IR and CKD will be useful for the prevention of CKD at earlier stages.

Conflicting results have been presented on the association between the indices of IR and CKD traits. Some studies have reported significant inverse relationships between a homeostasis model assessment of insulin resistance (HOMA-IR, an index of IR) and the estimated glomerular filtration rate (eGFR, an index of renal function)

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in type-1 diabetic patients with mild nephropathy [4] and in non-diabetic men [5], as well as between HOMA-IR and inulin clearance (the gold standard of GFR) in obese type-2 diabetic patients with renal insufficiency [6]. On the other hand, others have reported no significant relationships between HOMA-IR and eGFR in non-diabetic patients with CKD [7] or obese non-diabetic patients [8], or between HOMA-IR and urinary albumin excretion rate in type-1 diabetic patients with mild nephropathy [9]. One study has also demonstrated that visceral adiposity (an IR-related manifestation), not HOMA-IR, is inversely associated with the eGFR in obese subjects [10]. An additional report has documented that waist circumference and metabolic syndrome (IR-related manifestations) are associated with micro-albuminuria, not eGFR, in type-2 diabetic patients [11].

These discrepancies seem largely due to the differences in such characteristics of the study population as the absence/presence of obesity and diabetes or the stage of CKD. Because renal function appears to be modulated by the states of obesity and diabetes, it is crucial to determine the situation in which the relationship between IR and renal function is most critical. While hypertensive states may also be associated with both IR and renal function, there are no reports that have examined the association of both indexes in the presence of HT. The present study therefore investigated the correlation between HOMA-IR and eGFR in the subjects with or without HT.

Subjects and Methods

A total of 214 nonmedicated participants (males/females = 80/134, mean age = 65.6 years, range = 30–80) were recruited from health check-ups. The eligible subjects had no severe CKD (defined as an eGFR level <50 ml/min/1.73 m² in this study [12]) or diabetes mellitus (defined as ≤ 7.0 mmol/l of fasting plasma glucose [13]; HOMA-IR is not applicable for diabetics), as well as no apparent histories of cardiovascular, thyroid, hematological or liver diseases. The study population was composed of the HT group (n = 101) and the non-HT group (n = 113; table 1). The study was approved by the Jichi Medical University Ethics Committee, and all subjects gave their informed consent.

Current smoking habits were self-reported. In addition to body mass index (BMI), fasting serum total cholesterol, triglyceride, high-density lipoprotein cholesterol, creatinine and plasma glucose levels were measured by standard enzymatic methods. The plasma insulin was measured using an ELISA method (Tosoh Co. Ltd., Tokyo, Japan). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured in the seated subject's right-arm with a mercury sphygmomanometer after 5 min of rest. HT was diagnosed in subjects with ≥ 140 mm Hg of SBP and/or ≥ 90 mm Hg of DBP [14]. HOMA-IR was calculated using the fol-

lowing formula: (fasting plasma insulin $\times$ plasma glucose)/22.5 [15]. The eGFR was calculated using the following formula (the Modification of Diet in Renal Disease Study Group equation): $0.741 \times 175 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203}$ ($\times 0.742$ if female) [12].

The data were expressed as the mean $\pm$ standard deviation (SD) or the median plus interquartile range. The data between the groups were compared using a t test or χ^2 test. A simple and multivariate-adjusted linear regression model was utilized to observe the correlation between eGFR and HOMA-IR. In a multivariate-adjusted analysis, all the measured variables were used. Because of a close correlation between glucose and HOMA-IR, these variables were not simultaneously entered in the multivariate-adjusted analysis model in this study. The triglyceride, HOMA-IR and eGFR data were log-transformed for all the analyses because of their skewed distributions. A p value of ≤ 0.05 was considered to be statistically significant.

Results

The clinical characteristics of the HT and non-HT groups are listed in table 1. The HT group showed significantly higher levels of BMI, SBP and DBP than the non-HT group. The HOMA-IR and eGFR levels were similar between these groups.

In the simple linear regression analysis, the eGFR was inversely and significantly correlated with HOMA-IR ($r = -0.196$, $p = 0.038$) in the non-HT group, but the eGFR showed an inverse correlation with HOMA-IR at a non-significant level ($r = -0.182$, $p = 0.070$) in the non-HT group. The results of the multivariate-adjustments are listed in table 2. The eGFR in the non-HT group was independently, significantly and inversely correlated with HOMA-IR, along with age. In the HT group, the eGFR was independently, significantly and inversely correlated only with SBP, and a weak correlation between the eGFR and HOMA-IR was observed.

Discussion

The present study found a significant and inverse correlation between HOMA-IR and eGFR in the non-HT group, but not in the HT group, suggesting that HT can affect the association between IR and renal function. This may be partly accounted for by the fact that HT displays glomerular hyperfiltration (via the sympathetic nervous system, angiotensin II and nitric oxide pathway) [16, 17], thus indicating that the modified (probably compensatory) levels of eGFR in such a situation may alter the direct correlation between HOMA-IR and eGFR.

Table 1. Clinical characteristics between groups of subjects with and without hypertension

Group variables	Non-hypertension (n = 113)	Hypertension (n = 101)	p
Age, years	65.7 ± 10.5	65.5 ± 8.9	0.846
Males/females	47/66	33/68	0.178
Current smoker	18	10	0.192
Body mass index	23.6 ± 2.8	24.6 ± 3.1	0.014*
Systolic blood pressure, mm Hg	124.1 ± 10.7	153.9 ± 12.8	<0.0001**
Diastolic blood pressure, mm Hg	70.9 ± 8.0	84.2 ± 10.8	<0.0001**
Total cholesterol, mmol/l	4.87 ± 0.94	4.91 ± 0.91	0.746
Triglyceride, mmol/l	0.94 (0.75–1.34)	1.10 (0.88–1.39)	0.117
HDL-cholesterol, mmol/l	1.43 ± 0.39	1.39 ± 0.31	0.458
HOMA-IR	1.30 (0.80–2.12)	1.39 (0.88–2.18)	0.954
Plasma glucose, mmol/l	5.17 ± 0.68	5.14 ± 0.62	0.752
Plasma insulin, µU/ml	6.0 (3.6–8.7)	6.3 (3.9–9.4)	0.867
eGFR, ml/min/1.73 m ²	66.0 (59.0–77.3)	67.0 (57.1–75.5)	0.397

Values are expressed as the mean ± SD in parametrically distributed variables or median (interquartile range) in nonparametrically distributed variables. The triglyceride, HOMA-IR, insulin and eGFR data were analyzed after log-transformation because of their skewed distributions. Significance level (by t test): * p ≤ 0.05; ** p ≤ 0.01. HDL = High-density lipoprotein.

Table 2. Multivariate-adjusted correlations of each variable on eGFR (ml/min/1.73 m²) in the respective groups of subjects with and without hypertension

Group variables	Non-hypertension		Hypertension	
	β-coefficient	p	β-coefficient	p
Age, year	−0.352	0.001**	−0.160	0.129
Gender, male	−0.028	0.794	0.023	0.841
Current smoking	−0.178	0.109	0.005	0.961
Body mass index	−0.183	0.061	−0.018	0.872
Systolic blood pressure, mm Hg	−0.020	0.987	−0.270	0.019*
Diastolic blood pressure, mm Hg	−0.137	0.188	0.169	0.162
Total cholesterol, mmol/l	−0.190	0.120	0.040	0.750
Triglyceride, mmol/l	0.198	0.091	−0.122	0.306
HDL-cholesterol, mmol/l	0.069	0.559	0.148	0.228
HOMA-IR	−0.211	0.050*	−0.094	0.409

The triglyceride, HOMA-IR and eGFR data were analyzed after log-transformation because of their skewed distributions. Significance level (by multiple linear regression model analysis): * p ≤ 0.05; ** p ≤ 0.01. HDL = High-density lipoprotein.

Our study had some potential limitations. The study was performed with a relatively small sample size. Because of the cross-sectional study design, we have not precisely defined any cause-and-effect relationship in the results. Prospective studies with larger sample sizes will be necessary. Furthermore, the following background should be considered: CKD is a very heterogeneous entity regardless of the causes, and the eGFR is not always

an accurate estimate of true GFR (while the eGFR is more accurate than serum creatinine or the Cockcroft-Gault formula [18, 19]). In addition, measurement of micro-albuminuria was not available for our study population. Although the single usage of eGFR to define CKD, as in our present study, has been a common approach in many epidemiological studies [5, 8, 10], we acknowledge that this is a weakness in describing CKD in comparison with

the other cases, where micro-albuminuria is included in the assessment of renal function. Micro-albuminuria is prevalent in diabetic and/or hypertensive patients [20, 21]. Because our study population excluded subjects with overt diabetes mellitus (only subjects with impaired glucose tolerance, impaired fasting glucose and diabetes diagnosed by the 2-hour plasma glucose concentration from an oral glucose tolerance test could not be completely excluded), there was a possibility that the measurement of micro-albuminuria was convenient for describing CKD in detail. The inclusion of micro-albuminuria measurements in such study populations as ours should be performed in the future.

In summary, the correlation between HOMA-IR and eGFR can be more clearly observed in the non-HT group than in the HT group. The presence of HT may attenuate the direct correlation between the indexes of insulin resistance and renal function. Further studies will confirm our prediction and clarify the causality of these factors.

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