Association of Albuminuria With Intraglomerular Hydrostatic Pressure and Insulin Resistance in Subjects With Impaired Fasting Glucose or Impaired Glucose Tolerance

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OBJECIVE

Little is known about the relationships between insulin resistance, intrarenal hemodynamics, and urinary albumin excretion (UAE) in humans with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). The aim of the current study was to examine intrarenal hemodynamic abnormalities, insulin resistance, and UAE in subjects with IFG or IGT. We hypothesized that intrarenal hemodynamic abnormalities would be associated with insulin resistance.

RESEARCH DESIGN AND METHODS

Fifty-four kidney donors underwent 75-g oral glucose tolerance and inulin and para-aminohippuric acid clearance testing. Insulin sensitivity index (ISI) was evaluated by the Matsuda index. Intrarenal hemodynamic parameters were calculated by the Gomez formulae.

RESULTS

Of the 54 subjects, 33 exhibited IFG or IGT and 31 exhibited normal glucose tolerance (NGT). Glomerular hydrostatic pressure (P_{glo}) and UAE were significantly higher in the IFG or IGT subjects with obesity (P = 0.015 and 0.0001, respectively). Log ISI correlated significantly and negatively with P_{glo} (r = −0.351, P = 0.009) in all subjects. In multiple regression analyses among all subjects, log ISI was associated significantly and independently with P_{glo} (β = −0.316, P = 0.015), after adjustment for age, sex, and systolic blood pressure. Further, BMI (β = 0.517, P = 0.0004), P_{glo} (β = 0.420, P = 0.004), and log ISI (β = −0.366, P = 0.008) were each associated significantly and independently with UAE after adjustment.

CONCLUSIONS

We demonstrated that increased insulin resistance is associated with increased P_{glo} and UAE in IFG or IGT subjects. These hemodynamic burdens and insulin resistance may cause injury to the glomeruli even in subjects with IFG or IGT.

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It has been reported that the development and progression of diabetic nephropathy are associated with glomerular hypertension and hyperfiltration in both patients with type 1 diabetes and patients with type 2 diabetes (1,2). Glomerular hyperfiltration in patients with diabetes contributes to the onset of nephropathy, its progression, and loss of renal function (3,4). Increased albuminuria is associated with obesity and diabetes and is a risk factor for cardiovascular and renal diseases (5,6). Further, albuminuria in the high normal range (10–30 μg/mg) has been identified as a risk factor for cardiovascular disease (7). Recently, several studies have shown that sodium–glucose cotransporter 2 inhibitors, which have been demonstrated to reduce glomerular hypertension, slow the progression of decline of the estimated glomerular filtration rate (GFR) and that they decrease albuminuria in patients with type 2 diabetes (8,9). Obese patients and patients with type 2 diabetes are well-known to exhibit insulin resistance (10). These data suggest that there may be relationships between glomerular hypertension, insulin resistance, and urinary albumin excretion (UAE).

However, as little is known about the precise intrarenal hemodynamic abnormalities in subjects with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT), the relationships between glomerular hypertension, insulin resistance, and UAE remain to be elucidated. Glomerular hemodynamics can be examined using the Gomez formulae (11,12), in which both inulin clearance (C_{in}) and para-aminohippuric acid (PAH) clearance (C_{PAH}) are measured simultaneously. We recently reported a significant association between poor glycemic control and increased efferent arteriolar resistance in patients with diabetes using the Gomez formulae (13).

Thus, we hypothesized that intrarenal hemodynamic abnormalities would be associated with increased UAE and insulin resistance in subjects with prediabetes. The aim of the current study was to evaluate intrarenal hemodynamic abnormalities by measuring C_{in} and C_{PAH} in subjects with normal glucose tolerance (NGT) and in those with IFG or IGT. We further investigated the relationships between intrarenal hemodynamic abnormalities, insulin resistance, and UAE in these subjects.

RESEARCH DESIGN AND METHODS

Subjects

The study protocol was approved by the ethics committee of Osaka City University Graduate School of Medicine (no. 3955). Kidney donor candidates were admitted to Osaka City University Hospital between January 2006 and March 2017 for the evaluation of suitability for transplantation. A total of 54 subjects were enrolled consecutively after providing written informed consent. Two-hour 75-g oral glucose tolerance tests (75-g OGTTs) were performed and C_{in} and C_{PAH} were determined in all subjects. None of the subjects were undergoing treatment involving medication, including antihypertensives, i.e., ACE inhibitors or angiotensin II receptor blockers.

BMI was calculated as the body weight in kilograms divided by the square of the height in meters. Obesity was defined as BMI >25 kg/m^2, according to the Japan Society for the Study of Obesity, which has defined obesity among Japanese subjects based on a number of epidemiological studies (14). Subjects were divided into four groups: NGT without obesity (group 1), NGT with obesity (group 2), IFG or IGT without obesity (group 3), and IFG or IGT with obesity (group 4).

Measurements of C_{in} and C_{PAH} and Calculation of Intrarenal Hemodynamic Parameters

GFR and renal plasma flow (RPF), as measured by C_{in} and C_{PAH}, respectively, were determined simultaneously by the input clearance technique (13,15–17), using constant infusion of 1% inulin (Inulead; Fuji Yakuhin Co., Ltd., Saitama, Japan) and 0.5% PAH (sodium p-aminohippurate; Daiichi-Sankyo Co. Ltd., Tokyo, Japan), respectively. Inulin concentrations were measured enzymatically (16). PAH concentrations were measured photometrically by means of the N-1 naphthylethylenediamine and the anthrone method using a Corning 258 spectrophotometer (18). Since the direct measurement of glomerular hemodynamics parameters is not feasible in humans, the formulae introduced by Gomez (11) allow indirect assessment of glomerular hemodynamics, as reported previously by others (12,19,20) and ourselves (13,15,21,22). The Gomez formulae were calculated from the original report describing the formulae (11), as described in detail in our previous studies (13,15,21,22). In the formulae, GFR (C_{in}), afferent arteriolar resistance (R_a), efferent arteriolar resistance (R_e), and glomerular hydrostatic pressure (P_{glo}) are calculated. Filtration fraction was calculated by dividing the GFR (C_{in}) by the RPF (C_{PAH}). According to the Gomez formulae, in which inulin clearance greater than 60 mL/min could be applied (11), we excluded those with inulin clearance values that were <60 mL/min ($n = 5$) from further analyses.

The Gomez formulae, according to the original publication, are as follows:

$$\Delta P_F = GFR/K_{FG}$$
$$P_{glo} = \Delta P_F + P_{Bow} + \pi G$$
$$\pi G = 5 \cdot (C_M - 2)$$
$$C_M = TP/FF \cdot \ln(1/(1 - FF))$$

where ΔP_F was the filtration pressure across the glomerular capillary, K_{FG} (the gross filtration coefficient) was estimated as 0.0406 mL/s · mmHg per kidney, P_{Bow} (the hydrostatic pressure in Bowman's space) was estimated as 10 mmHg, and πG (the oncotic pressure within the glomerular capillaries) was obtained from the C_M (plasma protein concentration within the glomerular capillaries) and calculated from the TP (total protein concentration) and filtration fraction (FF).

From Ohm's law:

$$R_a = ((MBP - P_{glo})/RBF) \cdot 1,328$$
$$R_e = (GFR/KFG \cdot (RBF - GFR)) \cdot 1,328$$

where the conversion factor to dyne · s · cm^{-5} is 1,328; GFR, RPF, and RBF (renal blood flow) are expressed in mL/s; and the MBP (mean blood pressure) is calculated as (2 × diastolic blood pressure + systolic blood pressure)/3. RBF can be calculated from the RPF and hematocrit (Ht) using the standard formula:

$$RBF = RPF/(1 - Ht)$$

OGTT and Insulin Sensitivity Index

Two-hour 75-g OGTT was performed in the morning after an overnight fast. Blood was collected via an intravenous catheter before and 30, 60, and 120 min after glucose ingestion for measurement of plasma glucose and insulin levels.

According to the American Diabetes Association, the diagnosis of prediabetes

(IGT or IFG) is made on the basis of one of the following clinical biochemistry criteria: *1*) 2-h plasma glucose of 140–199 mg/dL during OGTT for IGT and *2*) fasting plasma glucose of 100–125 mg/dL for IFG (23,24).

For the assessment of insulin resistance, the insulin sensitivity index (ISI) was evaluated by the Matsuda Index and calculated from the pretest (0 min) and 120-min data from the 75-g OGTT (25) according to the following formula:

$$\mathrm{ISI} = 10,000/\left[(\mathrm{FPG} * \mathrm{FPI}) * (\overline{\mathrm{G}} * \overline{\mathrm{I}})\right]^{\hat{}0.5}$$

where FPG is fasting plasma glucose, FPI is fasting plasma insulin, $\overline{\mathrm{G}}$ is mean plasma glucose concentration during 75 g-OGTT, and $\overline{\mathrm{I}}$ is mean plasma insulin concentration during the 75 g-OGTT.

Biochemical and Physiological Parameters

Blood and urine samples were obtained after overnight fasting. Plasma glucose levels were measured with the glucose oxidase method. Plasma insulin and urinary albumin were determined by electrochemical luminescence immunoassay (Roche Co., Tokyo, Japan) and turbidimetric immunoassay (Wako Co., Tokyo, Japan), respectively.

Statistical Methods

The results are expressed as the mean ± SD. Multiple comparisons of the differences of the characteristics between each of the groups (group 1, NGT subjects without obesity; group 2, NGT subjects with obesity; group 3, IFC and/or IGT subjects without obesity; and group 4, IFC and/or IGT subjects with obesity) were evaluated by two-way ANOVA and the Scheffé multiple means comparisons. Correlations between variables were examined using the Pearson correlation coefficient. Multiple regression analyses were performed to examine the relationships between P_{glo} and the clinical parameters and between UAE and the clinical parameters. All analyses were performed using StatView 5.0 (SAS Institute, Cary, NC) for Windows. The level of statistical significance was set at $P < 0.05$.

RESULTS

The characteristics of the 54 subjects examined in the current study are presented in Table 1. The patients were mean ± SD age 56.2 ± 12.0 years old, and 29 (51.9%) were male. As shown in Table 1, of the 54 subjects who underwent 75 g-OGTT, 26 exhibited NGT without obesity (group 1), five exhibited NGT with obesity (group 2), 12 exhibited IFG or IGT without obesity (group 3), and 11 exhibited IFG or IGT with obesity (group 4).

P_{glo} ($P = 0.0015$), UAE ($P = 0.0001$), and FF ($P = 0.016$) were significantly higher in the IFG or IGT subjects with obesity (group 4) than in the other groups. R_e in the IFC or IGT subjects with obesity (group 4) tended to be higher than in the other groups (FF, $P = 0.088$; R_e, $P = 0.066$). ISI in subjects with obesity (group 2 and

Table 1—Clinical characteristics of the 54 subjects

	NGT		IFG or IGT		
	Without obesity (group 1)	With obesity (group 2)	Without obesity (group 3)	With obesity (group 4)	*P*
N (total = 54)	26	5	12	11	—
Age (years)	55.5 ± 13.1	61.0 ± 12.7	56.3 ± 11.9	55.5 ± 3.1	n.s.
Sex (*n* male/*n* female)	11/15	4/1	3/9	6/3	0.037#1a, 0.021#1b
BMI (kg/m^2)	21.0 ± 1.8	26.2 ± 1.8	21.5 ± 2.1	27.1 ± 1.3	<0.0001#2
Arterial pressure (mmHg)	87.9 ± 13.3	87.3 ± 10.3	83.0 ± 12.3	95.3 ± 14.0	0.033#3
Systolic blood pressure (mmHg)	122.3 ± 19.3	117.8 ± 12.9	117.9 ± 16.5	128.6 ± 14.2	n.s.
Diastolic blood pressure (mmHg)	70.9 ± 12.3	71.4 ± 8.7	67.3 ± 11.6	78.6 ± 14.3	0.033#3
Blood urea nitrogen (mg/dL)	13.2 ± 3.9	12.4 ± 1.1	13.3 ± 2.9	12.7 ± 1.7	n.s.
Creatinine (mg/dL)	0.7 ± 0.1	0.7 ± 0.1	0.7 ± 0.2	0.8 ± 0.1	0.01#4
Estimated GFR (mL/min/1.73 m^2)	78.7 ± 11.9	70.9 ± 5.3	81.1 ± 16.4	74.0 ± 11.7	n.s.
GFR (C_{in}) (mL/min)	80.4 ± 18.9	78.3 ± 9.3	85.8 ± 25.5	88.2 ± 18.9	n.s
GFR (C_{in}) (mL/min/1.73 m^2)	89.2 ± 18.7	81.3 ± 10.8	95.5 ± 25.4	88.9 ± 18.6	n.s.
RPF (C_{PAH}) (mL/min)	380.9 ± 118.0	371.2 ± 71.8	402.1 ± 124.4	362.5 ± 74.2	n.s.
UAE (mg/day)	5.2 ± 2.8	6.0 ± 2.0	4.4 ± 3.6	10.1 ± 7.4	0.0001#5
FF (%)	0.22 ± 0.03	0.21 ± 0.03	0.22 ± 0.04	0.25 ± 0.04	0.016#6
P_{glo} (mmHg)	54.3 ± 4.5	54.8 ± 3.5	55.9 ± 5.0	58.4 ± 4.4	0.015#7
R_a (dyne·s·cm^{-5})	4,629.3 ± 2,233.2	4,267.0 ± 1,536.8	3,648.0 ± 2,532.4	5,001.0 ± 2,441.8	n.s.
R_e (dyne·s·cm^{-5})	2,440.5 ± 366.5	2,376.2 ± 491.9	2,476.9 ± 547.9	2,783.1 ± 723.0	0.066#8
Fasting plasma glucose (mg/dL)	89 ± 6	90 ± 3	100 ± 8	104 ± 12	0.007#9
Hemoglobin A_{1c} (%)	5.6 ± 0.3	5.5 ± 0.2	5.7 ± 0.2	5.7 ± 0.2	n.s.
2-h plasma glucose on 75-g OGTT	102 ± 20	104 ± 22	150 ± 41	139 ± 35	<0.0001#10
Log ISI (Matsuda index)	0.9 ± 0.2	0.9 ± 0.3	0.8 ± 0.2	0.4 ± 0.2	<0.0001#11

Data are mean ± SD unless otherwise indicated. *P* values were evaluated by two-way ANOVA and Scheffé multiple means comparisons. #1aP = 0.037 (group 1 vs. group 2). #1bP = 0.021 (group 2 vs. group 3). #2$P < 0.0001$ (groups 1 and 3 vs. groups 2 and 4). #3P = 0.033 (group 3 vs. group 4). #4P = 0.01 (groups 1 and 3 vs. group 4). #5P = 0.0001 (groups 1, 2, and 3 vs. group 4). #6P = 0.016 (group 1 vs. group 4). #7P = 0.015 (group 1 vs. group 4). #8P = 0.066 (group 1 vs. group 4). #9P = 0.007 (groups 1 and 2 vs. groups 3 and 4). #10$P < 0.0001$ (groups 1 and 2 vs. groups 3 and 4). #11$P < 0.0001$ (groups 1, 2, and 3 vs. group 4).

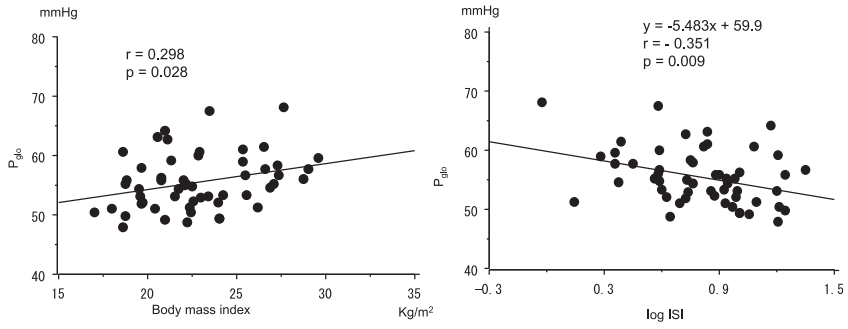

Figure 1—Relationship between P_{glo} and BMI and between P_{glo} and ISI. There was a significant and positive correlation between BMI and P_{glo} and a significant and negative correlation between log ISI and P_{glo}.

group 4) was significantly lower than in those without obesity ($P < 0.0001$ vs. group 1 and group 3). It is well-known that insulin resistance is related to obesity (26,27). When we examined the association between BMI and ISI, log ISI was associated significantly and negatively with BMI ($r = -0.593$, $P < 0.0001$). As shown in Fig. 1, P_{glo} correlated significantly and positively with BMI ($r = 0.298$, $P = 0.028$) and correlated significantly and negatively with the log ISI ($r = -0.351$, $P = 0.009$). There were no significant relationships between the log ISI and the following parameters; GFR ($r = 0.067$, $P = 0.628$), RPF ($r = 0.149$, $P = 0.283$), R_a ($r = 0.023$, $P = 0.867$), R_e ($r = 0.103$, $P = 0.460$), and FF ($r = 0.094$, $P = 0.498$). Since there was a significant association between BMI and log ISI, we performed multiple regression analyses, in which BMI and log ISI were entered as independent variables. In these analyses, BMI tended to be associated with P_{glo} ($\beta = 0.269$, $P = 0.064$) (Table 2) (model 1) and the log ISI was associated significantly and independently with P_{glo} ($\beta = -0.316$, $P = 0.015$) (Table 2) (model 2) after adjustment for age, sex, and systolic blood pressure.

Next, we examined the associations between UAE and several factors. As shown in Fig. 2, BMI ($r = 0.505$, $P = 0.0001$) and P_{glo} ($r = 0.364$, $P = 0.006$) correlated significantly and positively and log ISI ($r = -0.386$, $P = 0.001$) correlated significantly and negatively with UAE. For analysis of the factors associated with UAE, multiple regression analyses were performed after adjustment for age, sex, and systolic blood pressure. Since P_{glo} was associated significantly with BMI and log ISI (Fig. 1), multiple regression analyses were performed in which BMI, P_{glo}, and log ISI were entered as independent variables. As shown in models 3, 4, and 5 in Table 2, BMI ($\beta = 0.517$, $P = 0.0004$), P_{glo} ($\beta = 0.420$, $P = 0.004$), and log ISI ($\beta = -0.366$, $P = 0.008$) were each significantly and independently associated with UAE after these adjustments.

CONCLUSIONS

In the current study, we examined C_{in} and C_{PAH} and calculated the intrarenal hemodynamic parameters in kidney donor candidates using the Gomez formulae as described in detail in our previous studies (13,21). In all subjects, GFR, as measured by C_{in}, was >60 mL/min and UAE was <30 mg/day, i.e., within the normal range. Glucose metabolism pattern was evaluated by 2-h 75-g OGTT in all subjects, and insulin resistance was evaluated by calculation of the ISI (Matsuda index) (25). In this study, we demonstrated that P_{glo} and the degree of UAE, even within a normal range (13.7 ± 8.4 mg/day), were significantly higher in obese patients with IFG or IGT (group 4) compared with the other groups. We also demonstrated that the R_e and FF in the obese subjects with IFG or IGT (group 4) tended to be higher than in the other groups. Further, we demonstrated that log ISI and BMI were associated significantly with P_{glo} and that ISI, BMI, and P_{glo} were associated significantly with UAE. These results indicate that lower ISI, i.e., worse insulin resistance, even in subjects with IFG or IGT, is associated with increased P_{glo} and suggest that increased P_{glo} may, in turn, be associated with increased UAE, even within the normal range. BMI was associated with insulin resistance in the current study, which has been well established (28). Thus, the associated increased insulin resistance in subjects with IFG or IGT likely increases the burden on the glomeruli, thus affecting deterioration of the glomeruli in patients with prediabetes.

Increased GFR has previously been reported in diabetic nephropathy (1,29). Glomerular hyperfiltration is observed in the early stages of most patients with diabetes and is considered to precede the development of microalbuminuria by several years (1,30). In animals, the increase in GFR in diabetes is

Table 2—Factors associated with P_{glo} and UAE

	P_{glo}				UAE					
	Model 1		Model 2		Model 3		Model 4		Model 5	
	β	*P*	β	*P*	β	*P*	β	*P*	β	*P*
Age (years)	−0.357	0.010	−0.327	0.015	0.061	0.633	0.222	0.124	0.103	0.452
Sex (male = 0, female = 1)	−0.083	0.565	−0.188	0.146	−0.004	0.974	−0.137	0.314	−0.211	0.119
SBP (mmHg)	0.143	0.299	0.108	0.427	−0.103	0.436	−0.124	0.375	−0.124	0.380
BMI (kg/m^2)	0.269	0.064			0.517	0.0004				
P_{glo}							0.420	0.004		
Log ISI			−0.316	0.015					−0.366	0.008
R^2/P	0.357/0.010		0.327/0.015		0.265/0.004		0.201/0.024		0.181/0.041	

SBP, systolic blood pressure.

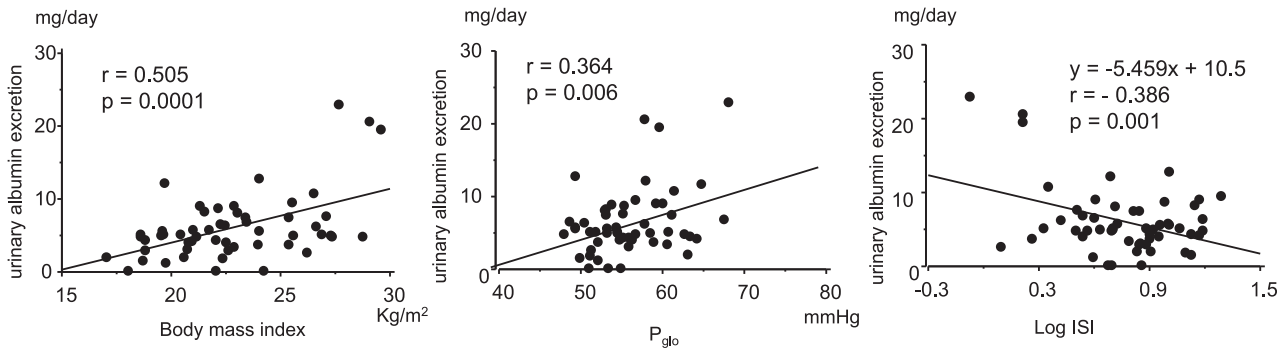

Figure 2—Relationship between UAE and BMI, ISI, and P_{glo}. There were significant and positive correlations between BMI and UAE and between P_{glo} and UAE. There was a significant and negative correlation between log ISI and UAE.

caused by imbalances of afferent and efferent arteriolar tone with a disproportionate decrease in afferent arteriolar resistance and relatively higher efferent arteriolar tone, leading to increases in glomerular capillary pressure (30). However, imbalances between afferent and efferent arteriolar resistance have not been demonstrated clinically in the early stages in humans with diabetes. We recently demonstrated that poor glycemic control is associated significantly with glomerular hemodynamic abnormalities in humans (13). In our previous study, we reported that poor glycemic control increased the filtration fraction, P_{glo}, and R_e but not R_a (13). While all of these experimental and clinical studies have examined patients with diabetes or diabetic experimental animals, to date there has been no report in which renal hemodynamic abnormalities were evaluated by C_{in} and C_{PAH} with respect to the relationship with insulin resistance in human subjects without diabetes. Further, there have been no reports in which UAE was examined in relation to glomerular hemodynamics and insulin resistance in these subjects. Thus, this is the first study to demonstrate that insulin resistance is associated significantly with glomerular hemodynamic changes and UAE in subjects with IFG or IGT.

Based on the current findings, the mechanism underlying increased P_{glo}, under the condition of insulin resistance, remains unknown. Evidence suggests that insulin resistance and obesity could activate the intrarenal renin angiotensin system (RAS) (2). RAS activation increases efferent arteriolar resistance, leading to glomerular hypertension and hyperfiltration (1,31). From the results of the current study, we consider that intrarenal RAS may be activated even in subjects with IFG or IGT in obesity. Concerning P_{glo}, in a model in which both BMI and log ISI were entered simultaneously as independent variables, neither BMI nor log ISI was significantly, independently associated with P_{glo} (data not shown). We consider that the results of these additional analyses could indicate that there is a high level of confounding between BMI and log ISI, leading to the nonsignificant associations between the two variables and P_{glo}.

On the other hand, it is well-known that UAE is caused by glomerular hypertension induced by poor glycemic control or obesity in animal studies (32). It was reported that UAE was preceded by glomerular hypertension under high glucose conditions through increased shear stress (33). Nakagawa (34) reported that the reduction of nitric oxide synthesis from endothelial cells in the glomeruli, as a consequence of insulin resistance, induces continuous increases in renal vascular endothelial growth factor expression and marked macrophage infiltration in an animal model. Furthermore, in humans, Pistrosch et al. (35) reported that an insulin-sensitizing drug, rosiglitazone, ameliorated glomerular hyperfiltration and reduced UAE in patients with early type 2 diabetes with microalbuminuria. Denic et al. (36) demonstrated that obesity was associated with a higher single-nephron GFR in chronic kidney disease among otherwise healthy adult kidney donor candidates. Bjornstad et al. (37) demonstrated relationships between whole-body, central adiposity and intrarenal hemodynamic function in adults with long-standing type 1 diabetes. We consider that mechanisms similar to those described above may be underlying the increase in UAE in the current study, in which subjects with IFG or IGT were examined.

Concerning UAE, in additional analyses in which two or three measures, out of BMI, P_{glo}, and log ISI, were included simultaneously as independent variables, BMI and P_{glo} were independently, significantly associated with UAE (data not shown). However, log ISI was not associated significantly with UAE (data not shown). These results may indicate that BMI, which is very strongly associated with log ISI, may be a stronger factor that is associated with UAE. It is possible that obesity itself may affect the increased UAE. However, the analyses presented in Table 1 demonstrate that, among four groups, only group 4 (IFG or IGT with obesity) showed significantly higher P_{glo} and UAE. This result may indicate that the presence of IFG or IGT and obesity cause significantly increased P_{glo} and UAE. Thus, we suggest that a significant increase in P_{glo} is caused by the presence of both increased log ISI (as represented by IFG or IGT) and increased BMI should be considered. In the current study, we have demonstrated, for the first time, that increased P_{glo} is associated with increased UAE in humans and that obesity is also significantly associated with UAE, as has previously been reported by others (38,39). The reason obesity is associated with increased UAE remains unknown from the results of the present study. We consider that the presence of both insulin resistance and obesity may cause increased P_{glo}, which may be followed by increased UAE.

In the current report, we show that P_{glo}, insulin resistance, and BMI were associated significantly with UAE in subjects with IFG or IGT, even within the normal range. Some reports have shown that higher levels of UAE, even within the

normal range, predict the decline in GFR in patients with diabetes (40), as well as the development of cardiovascular disease (41) and coronary heart disease (42). These studies and the results of the current study may support the need to redefine the range of microalbuminuria, even at the levels currently considered to be normal. The current findings suggest that albuminuria, even at levels currently considered to be within the normal range, may be increased as a consequence of insulin resistance in subjects with IFG or IGT, likely through increasing the intraglomerular hydrostatic pressure.

There are some limitations to the current study. First, the study was performed in a small number of Japanese subjects, and a large-scale study is needed to confirm the relationship among UAE, insulin resistance, and glomerular hemodynamic abnormalities in subjects with IFG or IGT. Secondly, this is a cross-sectional study. Further studies may be needed to explore the consequence of insulin resistance on glomerular hypertension and UAE. However, this is the first study in which insulin resistance was associated significantly with P_{glo} and UAE in human subjects with IFG or IGT. Thirdly, we were not able to directly measure R_a, R_e, or P_{glo} in the current study, as it is not possible to directly measure these parameters in humans—as opposed to animal studies. Thus, we used the Gomez formulae to assess intrarenal hemodynamics, as in the previous studies reported by others (12,19,20,43) and by ourselves (13,15,21,22).

In conclusion, in the current study, by measuring C_{in} and C_{PAH}, we showed that increased insulin resistance is associated significantly with increased P_{glo} and UAE, even at levels currently considered to be within the normal range in human subjects with IFG or IGT. These hemodynamic burdens may lead to glomerular injury in subjects with IFG or IGT. We also suggest that the clinically significant levels of microalbuminuria, as currently defined, could be redefined based upon several human studies, including the current study.

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