The relationship between chronic kidney function and homeostasis model assessment of insulin resistance and beta cell function in Korean adults with or without type 2 diabetes mellitus

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Abstract. The present study was conducted to assess the relationship between chronic kidney disease (CKD) and the homeostasis model assessment of insulin resistance (HOMA-IR) and beta cell function (HOMA-B) in Korean adults with or without type 2 diabetes mellitus (T2DM). This study included 5,188 adults aged 20 or older using the 2015 Korea National Health and Nutrition Examination Survey (KNHANES) data, which represents national data in Korea. A covariance test adjusted for covariates was performed for HOMA-IR and HOMA-B in relation to CKD. The present study has several key findings. First, in T2DM, HOMA-IR ($p = 0.035$) was higher in the CKD group than in the non-CKD group after adjusting for the related variables but HOMA-B ($p = 0.141$) was not significant. Second, in non-T2DM, HOMA-IR ($p = 0.163$) and HOMA-B ($p = 0.658$) were not associated with CKD after adjusting for the related variables (except age). However, when further adjusted for age, HOMA-IR ($p = 0.020$) and HOMA-B ($p = 0.006$) were higher in the CKD group than in the non-CKD group. In conclusion, insulin resistance was positively associated CKD with in Korean adults with or without T2DM. Beta cell function was positively associated CKD with in Korean adults without T2DM but not in Korean adults with T2DM.

Key words: CKD, HOMA-IR, HOMA-B, T2DM

DIABETES mellitus (DM) is a common endocrine disease that results from the interaction of genetic and environmental factors [1, 2]. In the progression of type 2 diabetes mellitus (T2DM), which accounts for approximately 90% of diabetes cases, it is important to monitor insulin resistance (IR) and beta cell function [3]. In study of the insulin resistance and beta cell function, the homeostasis model assessment of insulin resistance (HOMA-IR) and beta cell function (HOMA-B) are appropriate for use in large epidemiological studies [4].

Chronic kidney disease (CKD) is a common global

public health problem and is defined by estimating the glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² [5, 6]. Diabetes is the most prevalent independent risk factor in the progression of CKD [7] and diabetic nephropathy, a diabetes-related kidney disease, is the leading cause of end-stage renal disease (ESRD) [8]. It is estimated that the number of adults with diabetes around the world will increase to 300 million by the year 2025 [9]. Therefore, the prevention of diabetes-related kidney disease may be a key to decreasing the societal and economic burden of illness due to ESRD [10].

Recently, research into CKD and IR has been conducted all over the world. However, these relationships are not consistent across ethnic groups and countries [11–13]. In addition, the research into the relationship between CKD and beta cell function is rare and the relationship between CKD and beta cell function may differ by subjects with or without T2DM because

Submitted Jun. 30, 2017; Accepted Aug. 14, 2017 as EJ17-0274

Released online in J-STAGE as advance publication Sep. 9, 2017

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differences in the function or mass of beta cells. Therefore, the present study aims to investigate the relationships between CKD and IR and beta cell function in adults with or without T2DM using the sixth Korea National Health and Nutrition Examination Survey (KNHANES VI-3) data, which is representative for the entire population of Korea.

Methods

Study Subjects

This study was based on data from the KNHANES VI-3 (2015), which are the most recent data for HOMA. The KNHANES is a cross-sectional survey conducted nationwide by the Division of Korean National Health and Welfare. The KNHANES VI-3 (2015) was performed from January 2015 to December 2015. In the KNHANES VI-3 (2015), 7,380 individuals over 1 year of age were sampled for the survey. Among the 5,855 subjects who participated in the KNHANES VI-3, we limited the analyses to adults aged ≥ 20 years. We excluded 667 subjects whom data were missing for important analytic variables, such as the HOMA-IR, HOMA-B, and various blood chemistry tests. Finally 5,188 subjects were included in the statistical analysis. The KNHANES VI-3 (2015) study was conducted according to the principles expressed in the Declaration of Helsinki (Institutional Review Board No, 2015-01-02-6C). All participants in the survey provided written informed consent. Further information can be found in "The KNHANES VI-3 (2015) Sample," which is available on the KNHANES website. The data from KNHANES are available on request by email if the applicant logs onto the "Korea National Health and Nutrition Examination Survey" website.

General Characteristics and Blood Chemistry

Research subjects were classified by sex (men and women), smoking (non-smoker or ex-smoker or current smoker), alcohol drinking (yes or no), and regular exercise (yes or no). In the smoking category, participants who smoked more than one cigarette a day, those who had previously smoked but do not presently smoke, and those who never smoked were classified into the current smoker, ex-smoker, and non-smoker groups, respectively. Alcohol drinking was indicated as "yes" for participants who had consumed at least one glass of alcohol every month over the last year. Regular exercise was indicated as "yes" for partici-

pants who had exercised on a regular basis regardless of indoor or outdoor exercise. (Regular exercises was defined as 30 min at a time and 5 times/wk in the case of moderate exercise, such as swimming slowly, doubles tennis, volleyball, badminton, table tennis, and carrying light objects; and for 20 min at a time and 3 times/wk in the case of vigorous exercise, such as running, climbing, cycling fast, swimming fast, football, basketball, jump rope, squash, singles tennis, and carrying heavy objects). Anthropometric measurements included measurement of body mass index (BMI) and waist measurement (WM), as well as final measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP). Blood chemistries included measurements of total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), triglycerides (TGs), fasting blood glucose (FBG), insulin, blood urea nitrogen (BUN), and serum creatinine (Crea), high sensitivity C reactive protein (hs CRP). Metabolic Syndrome (MetS) was defined using the diagnostic criteria of the Revised National Cholesterol Education Program Adult Treatment panel III (Revised NCEP-ATP III) based on common clinical measures, including TGs, HDL-C, blood pressure (BP), FBG, and WM. TGs over 150 mg/dL was set as the criteria for elevated TGs. The criteria for reduced HDL were HDL of less than 40 mg/dL and 50 mg/dL for men and women, respectively. FBG over 100 mg/dL was set as the criteria for elevated FBG. SBP over 130 mmHg or DBP over 85 mmHg were set as the criteria for elevated BP. The criteria for abdominal obesity were abdominal measurements of over 90 cm and 80 cm for men and women, respectively, according to the Asia-Pacific criteria [14]. The presence of defined abnormalities in any three of these five measures constitutes a diagnosis of MetS.

Glomerular filtration rate and HOMA-IR and HOMA-B and T2DM

GFR was estimated from the simplified equation developed using MDRD data: $eGFR = 186.3 \times (\text{serum creatinine in mg/dL})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ for women}) \times (1.212 \text{ if African American})$ [15]. CKD was classified as $eGFR < 60 \text{ mL/min/1.73 m}^2$. HOMA-IR and HOMA-B constitute a method for assessing IR and beta cell function from basal glucose and insulin concentrations [16]. The formulas are as follows: $\text{HOMA-IR} = [\text{fasting insulin } (\mu\text{U/mL}) \times \text{fasting plasma glucose (mg/dL)}] / 405$; $\text{HOMA-B} = 360 \times \text{fasting insulin } (\mu\text{U/mL}) / [\text{fasting plasma glucose (mg/dL)} - 63]$.

T2DM was defined as a fasting blood glucose level of ≥ 126 mg/dL or through the subject's self-reported history of diabetes or use of diabetes medications [17].

Statistical analysis

The collected data were statistically analyzed using SPSS WIN version 18.0 (SPSS Inc., Chicago, IL, USA). The distributions of the participant characteristics were converted into percentages, and the successive data were presented as averages with standard deviations. The distribution and average difference in clinical characteristics according to subjects with or without T2DM and CKD were calculated using chi-squared and an independent *t*-test. In the case of analysis of covariance test (ANCOVA) for CKD, the 4 models constructed were: 1) adjusted for gender, smoking, drinking, and regular exercising; 2) further adjusted for SBP, DBP, BMI, and WM; 3) further adjusted for hs CRP, TC, and TGs; 4)

further adjusted for age. The significance level for all of the statistical data was set as $p < 0.05$.

Results

General clinical characteristics in subjects

The prevalence rate of CKD was 151 (3.2%) in non-T2DM (4,725 subjects), and the eGFR, insulin, FBG, hs CRP, HOMA-IR, and HOMA-B levels were 92.75 ± 18.81 mL/min/1.73 m², 8.05 ± 7.01 μ U/mL, 1.21 ± 2.27 mg/L, 95.54 ± 10.26 mg/dL, 1.94 ± 1.86 , and 91.76 ± 74.21 , respectively. Meanwhile, the prevalence rate of CKD was 31 (6.7%) in T2DM (463 subjects), and the eGFR, insulin, FBG, hs CRP, HOMA-IR, and HOMA-B level were 88.59 ± 20.53 mL/min/1.73 m², 14.67 ± 15.94 μ U/mL, 167.02 ± 47.97 mg/dL, 1.91 ± 2.94 mg/L, 6.30 ± 8.01 , and 55.29 ± 56.59 , respectively (Table 1).

Table 1 Clinical characteristics in subjects

		<i>n</i> (%), Mean $\pm$ SD (<i>n</i> = 5,188)			
Variables	Category	Total (<i>n</i> = 5,188)	Non-T2DM (<i>n</i> = 4,725)	T2DM (<i>n</i> = 463)	<i>P</i>
Age (years)	20-29	579 (11.2)	575 (12.2)	4 (0.9)	< 0.001
	30-39	726 (14.0)	703 (14.9)	23 (5.0)	
	40-49	949 (18.3)	894 (18.9)	55 (11.9)	
	50-59	1,110 (21.4)	1,015 (21.5)	95 (20.5)	
	≥ 60	1,824 (35.2)	1,538 (32.6)	286 (61.8)	
Gender	Men	2,288 (44.1)	2,039 (43.2)	249 (53.8)	< 0.001
Smoking	Current smoker	896 (17.3)	807 (17.1)	89 (19.2)	0.004
Alcohol drinking	Yes	2,724 (52.5)	2,493 (52.8)	231 (8.5)	0.238
Regular exercise	Yes	496 (9.6)	465 (9.8)	31 (6.7)	0.028
Metabolic syndrome	Yes	1,677 (32.3)	1,357 (28.7)	320 (69.1)	< 0.001
eGFR (mL/min/1.73 m ²)		92.37 $\pm$ 19.01	92.75 $\pm$ 18.81	88.59 $\pm$ 20.53	< 0.001
	eGFR ≥ 60	5,006 (96.5)	4,574 (96.8)	432 (93.3)	< 0.001
	eGFR < 60	182 (3.5)	151 (3.2)	31 (6.7)	
BMI (kg/m ²)		23.98 $\pm$ 3.48	23.83 $\pm$ 3.41	25.52 $\pm$ 3.87	< 0.001
WM (cm)		82.97 $\pm$ 9.94	82.38 $\pm$ 9.75	89.11 $\pm$ 9.87	< 0.001
SBP (mmHg)		119.41 $\pm$ 17.18	118.73 $\pm$ 17.06	126.38 $\pm$ 16.95	< 0.001
DBP (mmHg)		75.14 $\pm$ 10.29	75.18 $\pm$ 10.15	74.73 $\pm$ 11.63	0.380
TC (mg/dL)		190.12 $\pm$ 36.02	190.68 $\pm$ 35.47	184.39 $\pm$ 40.85	< 0.001
TGs (mg/dL)		137.74 $\pm$ 111.61	132.57 $\pm$ 101.54	190.48 $\pm$ 177.08	< 0.001
HDL-C (mg/dL)		50.83 $\pm$ 12.90	51.29 $\pm$ 12.94	45.65 $\pm$ 11.21	< 0.001
FBG (mg/dL)		101.92 $\pm$ 26.76	95.54 $\pm$ 10.26	167.02 $\pm$ 47.97	< 0.001
Insulin (μ U/mL)		8.64 $\pm$ 8.42	8.05 $\pm$ 7.01	14.67 $\pm$ 15.91	< 0.001
HOMA-IR		2.34 $\pm$ 3.23	1.94 $\pm$ 1.86	6.30 $\pm$ 8.01	< 0.001
HOMA-B		88.50 $\pm$ 73.54	91.76 $\pm$ 74.21	55.29 $\pm$ 56.59	< 0.001
BUN (mg/dL)		14.70 $\pm$ 4.96	14.55 $\pm$ 4.81	16.30 $\pm$ 6.01	< 0.001
Crea (mg/dL)		0.85 $\pm$ 0.36	0.84 $\pm$ 0.35	0.89 $\pm$ 0.46	0.013
hs CRP (mg/L)		1.27 $\pm$ 2.35	1.21 $\pm$ 2.27	1.91 $\pm$ 2.94	< 0.001

eGFR, estimated glomerular filtration rate; BMI, body mass index; WM, waist measurement; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TGs, triglycerides; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood glucose; HOMA-IR, Homeostasis model assessment of insulin resistance; HOMA-B, Homeostasis model assessment of beta cell function; BUN, blood urea nitrogen; Crea, serum creatinine; hs CRP, high sensitivity C reactive protein.

Clinical characteristics according to non-CKD and CKD in subjects with or without T2DM

In non-T2DM, men ($p = 0.037$), MetS ($p < 0.001$), age ($p < 0.001$), BMI ($p < 0.001$), WM ($p < 0.001$), SBP ($p < 0.001$), DBP ($p = 0.030$), FBG ($p < 0.001$), insulin ($p = 0.001$), HOMA-IR ($p = 0.048$), BUN ($p < 0.001$), Crea ($p < 0.001$), and hs CRP ($p < 0.001$) were higher in the CKD group than in the non-CKD group. HDL-C ($p < 0.001$) and GFR ($p = 0.004$) were lower in CKD group than in the non-CKD group and TC ($p = 0.069$) and HOMA-B ($p = 0.135$) were not significant (Table 2). In T2DM, age ($p < 0.001$), HOMA-IR ($p = 0.031$), BUN ($p < 0.001$), and Crea ($p < 0.001$) were higher in the CKD group than in the non-CKD group. DBP ($p < 0.001$) and GFR ($p < 0.001$) were lower in CKD group than in non-CKD group and MetS ($p = 0.271$), BMI ($p = 0.198$), WM ($p = 0.610$), SBP ($p = 0.910$), TC ($p = 0.218$), TGs ($p = 0.526$), HDL-C ($p = 0.135$), FBG ($p = 0.249$), insulin ($p = 0.051$), HOMA-B ($p = 0.315$), and hs CRP ($p = 0.750$) was not significant (Table 3).

Comparisons of HOMA-IR and HOMA-B according to non-CKD and CKD in subjects with or without T2DM

In non-T2DM, HOMA-IR ($p = 0.163$) and HOMA-B ($p = 0.658$) were not associated with CKD after adjusting for the related variables (except age). However, when further adjusted for age, both HOMA-IR ($p = 0.020$) and HOMA-B ($p = 0.006$) were higher in the CKD group than in the non-CKD group (Table 4). In T2DM, HOMA-IR ($p = 0.040$) was higher in the CKD group than in the non-CKD group after adjusting for the related variables (except age) but HOMA-B ($p = 0.172$) was not significant. In addition, when further adjusted for age, HOMA-IR ($p = 0.035$) was higher in the CKD group than in the non-CKD group but HOMA-B ($p = 0.141$) was not significant (Table 5).

Discussion

The present study investigated the gender difference in the relationship between CKD and IR and beta cell function in Korean adults with or without T2DM. There were several key findings in the present study; HOMA-IR was positively associated with CKD in Korean adults with or without T2DM. HOMA-B was positively associated with CKD in Korean adults without T2DM but not in Korean adults with T2DM.

Research on the association between CKD and IR

is being conducted all over the world. Some studies demonstrated that IR was associated with CKD [18–20]. Chen *et al.* and Srivastava *et al.* reported that CKD was positively associated with HOMA-IR in US ($p = 0.001$) [18] and Indian ($p = 0.001$) [19]. Kurella *et al.* reported that compared with the lowest quintile, the highest quintile of HOMA-IR had a 70% increased odds ratio for CKD (OR, 1.70; 95% CI, 1.26 to 2.30) [20]. In contrast, Satirapoj *et al.* and Trirogoff *et al.* reported that HOMA-IR was not significantly correlated with GFR in US and British [21, 22]. In the present study, in both non-T2DM ($p = 0.015$) and T2DM ($p = 0.036$), HOMA-IR in the CKD group was higher than those in the non-CKD group. Similarly, in both non-T2DM ($p = 0.012$) and T2DM ($p = 0.028$), insulin level in the CKD group was higher than those in the non-CKD group (Supplement table 1). IR and hyperinsulinaemia are prevalent in CKD patients and plays a role in declining renal function. Hyperinsulinemia and IR predispose to the development and progression of CKD, *via* mechanisms such as left ventricular hypertrophy, cardiac hyperreactivity, dyslipidemia, hyperglycemia, enhanced renin-angiotensin-aldosterone system activity, stimulating the sympathetic nervous system activity [23–26]. In particular, in continuous hyperglycemic state such as DM, an increase of hyperinsulinemia and IR can accelerate progression of CKD caused by leading glomerular microangiopathy and renal injury [27, 28]. In addition, renal function may be reduced by factors that have detrimental effects on inflammation and oxidative stress, and IR increases inflammation and oxidative stress [29, 30]. However, these association may be differ by the subjects with or without DM. Marouga *et al.* reported that HOMA-IR, tumor necrosis factor alpha (TNF- α), and hs CRP were positively associated eGFR loss in non-diabetic CKD patient [31]. However, Gohda *et al.* reported that eGFR loss in patients with DM is not associated with TNF- α level [32]. In the present study, in non-diabetes, hs CRP level in subjects with CKD is higher than in subject without CKD but not significant in T2DM.

Diabetes mellitus is the most common cause of CKD. Diabetic kidney disease occurs in 20–40% of patients with DM [33], and the essential for delay or prevent the onset of diabetic kidney disease is a glycemic control [34]. Beta cell function and mass are decreased from the clinical onset of both types 1 and 2 DM and this is accompanied by a correspondent deterioration of glycaemic control [35]. Therefore, some studies suggested that

Table 2 Clinical characteristics according to non-CKD and CKD in subjects without T2DM

<i>n</i> (%), Mean $\pm$ SD (<i>n</i> = 4,725)				
Variables	Category	non-CKD (<i>n</i> = 4,412)	CKD (<i>n</i> = 144)	<i>p</i>
Gender	Men	1,961 (42.9)	78 (51.7)	0.037
Smoking	Current smoker	790 (17.3)	17 (11.3)	0.007
Alcohol drinking	Yes	2,445 (53.5)	48 (31.8)	< 0.001
Regular exercise	Yes	457 (10.0)	8 (5.3)	0.057
Metabolic syndrome	Yes	1,283 (29.1)	74 (51.4)	< 0.001
Age (years)		50.28 $\pm$ 16.04	70.42 $\pm$ 9.7	< 0.001
eGFR (mL/min/1.73 m ²)		94.17 $\pm$ 17.27	49.72 $\pm$ 11.52	< 0.001
BMI (kg/m ²)		23.80 $\pm$ 3.40	24.80 $\pm$ 3.55	< 0.001
WM (cm)		82.20 $\pm$ 9.69	87.61 $\pm$ 10.01	< 0.001
SBP (mmHg)		119.43 $\pm$ 16.96	127.71 $\pm$ 17.46	< 0.001
DBP (mmHg)		75.25 $\pm$ 10.07	73.08 $\pm$ 12.46	0.030
TC (mg/dL)		190.89 $\pm$ 35.14	184.28 $\pm$ 43.87	0.069
TGs (mg/dL)		132.06 $\pm$ 101.42	147.75 $\pm$ 104.38	0.062
HDL-C (mg/dL)		51.51 $\pm$ 12.91	44.53 $\pm$ 12.11	< 0.001
FBG (mg/dL)		95.41 $\pm$ 10.20	99.55 $\pm$ 11.33	< 0.001
Insulin (μ U/mL)		7.99 $\pm$ 1.86	9.91 $\pm$ 6.93	0.001
HOMA-IR		1.93 $\pm$ 1.86	2.50 $\pm$ 1.92	< 0.001
HOMA-B		91.47 $\pm$ 74.51	100.63 $\pm$ 63.80	0.135
BUN (mg/dL)		14.28 $\pm$ 4.09	22.63 $\pm$ 12.36	< 0.001
Crea (mg/dL)		0.82 $\pm$ 0.17	1.59 $\pm$ 1.54	< 0.001
hs CRP (mg/L)		1.18 $\pm$ 2.20	2.18 $\pm$ 3.81	0.002

non-CKD, eGFR $\geq$ 60 mL/min/1.73 m²; CKD, eGFR < 60 mL/min/1.73 m²; eGFR, estimated glomerular filtration rate; BMI, body mass index; WM, waist measurement; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TGs, triglycerides; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood glucose; HOMA-IR, Homeostasis model assessment of insulin resistance; HOMA-B, Homeostasis model assessment of beta cell function; BUN, blood urea nitrogen; Crea, serum creatinine; hs CRP, high sensitivity C reactive protein.

Table 3 Clinical characteristics according to non-CKD and CKD in subjects with T2DM

<i>n</i> (%), Mean $\pm$ SD (<i>n</i> = 463)				
Variables	Category	non-CKD (<i>n</i> = 432)	CKD (<i>n</i> = 31)	<i>p</i>
Gender	Men	235 (54.4)	14 (45.2)	0.319
Smoking	Current smoker	86 (19.9)	3 (9.7)	0.235
Alcohol drinking	Yes	225 (52.1)	6 (19.4)	< 0.001
Regular exercise	Yes	31 (7.2)	1 (3.2)	0.106
Metabolic syndrome	Yes	299 (69.2)	21 (67.7)	0.271
Age (years)		60.71 $\pm$ 12.29	72.35 $\pm$ 7.35	< 0.001
eGFR (mL/min/1.73 m ²)		91.59 $\pm$ 17.44	46.68 $\pm$ 13.17	< 0.001
BMI (kg/m ²)		25.58 $\pm$ 17.44	24.65 $\pm$ 3.13	0.198
WM (cm)		89.17 $\pm$ 9.95	88.24 $\pm$ 8.69	0.610
SBP (mmHg)		126.35 $\pm$ 16.84	126.71 $\pm$ 18.74	0.910
DBP (mmHg)		75.35 $\pm$ 11.41	66.23 $\pm$ 11.47	< 0.001
TC (mg/dL)		185.02 $\pm$ 41.10	175.65 $\pm$ 36.79	0.218
TGs (mg/dL)		189.08 $\pm$ 175.05	210.00 $\pm$ 205.62	0.526
HDL-C (mg/dL)		45.85 $\pm$ 11.23	42.32 $\pm$ 10.52	0.135
FBG (mg/dL)		166.33 $\pm$ 47.48	176.62 $\pm$ 54.22	0.249
Insulin (μ U/mL)		14.29 $\pm$ 15.87	20.05 $\pm$ 15.72	0.051
HOMA-IR		6.08 $\pm$ 7.97	9.30 $\pm$ 8.21	0.031
HOMA-B		54.59 $\pm$ 57.20	65.17 $\pm$ 46.87	0.315
BUN (mg/dL)		15.56 $\pm$ 4.41	26.71 $\pm$ 12.49	< 0.001
Crea (mg/dL)		0.83 $\pm$ 0.16	1.66 $\pm$ 1.50	0.004
hs CRP (mg/L)		1.90 $\pm$ 2.89	2.08 $\pm$ 3.65	0.750

non-CKD, eGFR $\geq$ 60 mL/min/1.73 m²; CKD, eGFR < 60 mL/min/1.73 m²; eGFR, estimated glomerular filtration rate; BMI, body mass index; WM, waist measurement; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TGs, triglycerides; HDL-C, high density lipoprotein cholesterol; FBG, fasting blood glucose; HOMA-IR, Homeostasis model assessment of insulin resistance; HOMA-B, Homeostasis model assessment of beta cell function; BUN, blood urea nitrogen; Crea, serum creatinine; hs CRP, high sensitivity C reactive protein.

Table 4 Comparisons of HOMA-IR and HOMA-B levels according to non-CKD and CKD in subjects without T2DM

(n = 4,725)

Category		non-CKD (eGFR $\geq$ 60 mL/min/1.73 m ²)	CKD (eGFR < 60 mL/min/1.73 m ²)	<i>p</i>
HOMA-IR	Model 1	1.93 $\pm$ 0.03 (1.88–1.99)	2.45 $\pm$ 0.15 (2.15–2.75)	0.001
	Model 2	1.93 $\pm$ 0.03 (1.88–1.98)	2.16 $\pm$ 0.14 (1.89–2.44)	0.100
	Model 3	1.93 $\pm$ 0.03 (1.88–1.98)	2.13 $\pm$ 0.14 (1.86–2.40)	0.163
	Model 4	1.93 $\pm$ 0.03 (1.88–1.98)	2.26 $\pm$ 0.14 (1.98–2.53)	0.020
HOMA-B	Model 1	91.50 $\pm$ 1.10 (89.35–93.65)	99.66 $\pm$ 6.06 (87.78–111.55)	0.185
	Model 2	91.28 $\pm$ 1.03 (89.25–93.30)	95.44 $\pm$ 5.78 (84.11–106.77)	0.479
	Model 3	91.33 $\pm$ 1.03 (89.32–93.34)	93.92 $\pm$ 5.75 (82.64–105.20)	0.658
	Model 4	90.91 $\pm$ 1.00 (88.95–92.86)	106.71 $\pm$ 5.65 (95.63–117.78)	0.006

Model 1, adjusted for gender, smoking, drinking, and regular exercising; Model 2, Model 1 further adjusted for SBP, DBP, BMI, and WM; Model 3, Model 2 further adjusted for hs CRP, TC, and TGs; Model 4, Model 3 further adjusted for age.

Table 5 Comparisons of HOMA-IR and HOMA-B levels according to non-CKD and CKD in subjects with T2DM

(n = 463)

Category		non-CKD (eGFR $\geq$ 60 mL/min/1.73 m ²)	CKD (eGFR < 60 mL/min/1.73 m ²)	<i>p</i>
HOMA-IR	Model 1	6.11 $\pm$ 0.38 (5.35–6.86)	9.00 $\pm$ 1.45 (6.15–11.86)	0.055
	Model 2	6.08 $\pm$ 0.38 (5.34–6.82)	9.45 $\pm$ 1.44 (6.61–12.28)	0.025
	Model 3	6.10 $\pm$ 0.38 (5.36–6.83)	9.19 $\pm$ 1.45 (6.35–12.03)	0.040
	Model 4	6.09 $\pm$ 0.38 (5.35–6.83)	9.29 $\pm$ 1.46 (6.43–12.16)	0.035
HOMA-B	Model 1	54.70 $\pm$ 2.71 (49.37–60.02)	63.63 $\pm$ 10.26 (43.47–83.79)	0.401
	Model 2	54.39 $\pm$ 2.62 (49.24–59.55)	68.42 $\pm$ 10.07 (48.64–88.21)	0.180
	Model 3	54.37 $\pm$ 2.62 (49.22–59.53)	68.73 $\pm$ 10.11 (48.86–88.60)	0.172
	Model 4	54.29 $\pm$ 2.63 (49.13–59.45)	69.91 $\pm$ 10.20 (49.86–89.95)	0.141

Model 1, adjusted for gender, smoking, drinking, and regular exercising; Model 2, Model 1 further adjusted for SBP, DBP, BMI, and WM; Model 3, Model 2 further adjusted for hs CRP, TC, and TGs; Model 4, Model 3 further adjusted for age.

beta cell function altering the course of the disease such as T2DM and MetS [36, 37]. Defronzo *et al.* reported that beta cell dysfunction is a common pathogenetic feature of both type 1 and type 2 DM and that T2DM never develops without beta cell dysfunction [38]. In addition, they suggested that the preferential treatment of T2DM should aim to restore beta cell function.

We examined the relationship between CKD and beta cell function in non-T2DM and T2DM, and our findings were interesting. In non-T2DM or non-MetS, HOMA-IR in the CKD group was higher than those in the non-CKD group, but HOMA-B in the CKD group was also higher than those in the non-CKD group (Table 4 and Supplement table 2). In non-T2DM or non-MetS populations with CKD, it may be a possibility that it is presented a compensatory action that beta cell function is activated by corresponding of IR increases. In T2DM or MetS populations with CKD, the function and mass of beta cells have already been reduced [39–41], and it is possible that no compensatory mechanism appears. Some studies reported that

decreases in beta cell mass were mainly seen in subjects with IR [42, 43]. They suggested that this is caused by an increase in pancreatic beta cell apoptosis and necrosis in the state of insulin resistance. Our results were similar to the results of Pham *et al.* [44]. They reported that a lower eGFR was associated with higher IR ($p = 0.004$) in non-diabetic adults. However, beta cell function ($p < 0.001$) was also augmented, and the risks of impaired glucose tolerance were not increased. They suggested that this phenomenon in these results was caused by a compensatory action in non-diabetic adults. The prevalence of CKD in populations with T2DM is higher than those in populations without T2DM. As one of the reason for these results, we are thought a possibility that a compensatory action in populations without T2DM. Therefore, the restoration of beta cell function in diabetic patients is thought to be helpful in the prevention of CKD or slow the progression of CKD. The present study assessed the IR and beta cell function using HOMA-IR and HOMA-B. In the measurements of IR and beta cell function, the

“gold-standard” method (*e.g.*, hyperinsulinemic-euglycemic clamp and the hyperglycemic clamp test) is known to be more accurate than HOMA indices. Some studies suggested that HOMA-IR is imperfect to estimate insulin resistance in CKD due to its several limitations [45, 46]. Therefore, in future studies, it is necessary to study the relationship between CKD and IR and beta cell function using the “gold-standard” method.

In conclusion, the present study was conducted to assess the relationship between CKD and the insulin resistance and beta cell function in Korean adults with or without type 2 diabetes mellitus (T2DM). Insulin resistance was positively associated with CKD in Korean adults with or without T2DM. Beta cell function was positively associated with CKD in Korean adults without T2DM but not in Korean adults with T2DM.

The present study has some limitations; first, KNHANES data are representative national data in Korea. However, considering the sample size and study population, this study has limited capacity for generalization. Second, the glomerular filtration cannot be measured directly in humans; therefore, the true GFR cannot be known with certainty. In current guidelines, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation that uses serum creatinine and cystatin C are recommended [15, 47]. However, both methods may be biased compared to the true GFR [48]. In clinical and research studies, results may differ for the CKD-EPI equation using serum creatinine and cystatin C. In addition to these two methods, it is creatinine clearance or inulin clearance method as the method of estimating the glomerular filtration. Therefore, standardization across eGFR methods, including the devel-

opment of more accurate eGFR equations, could help achieve consistent results in clinical and research studies. Third, the present study assessed the IR and beta cell function using HOMA indices. In the measurements of IR and beta cell function, the “gold-standard” method is more accurate than HOMA indices. Although HOMA indices are not the “gold-standard” method, they may be more appropriate for use in large epidemiological studies [49]. In addition, one of the difficulties in conducting the extensive research required to determine the clinical utility of measures of insulin resistance, sensitivity, and secretion is the lack of standardized insulin assays. Results reported from one study to the next are not comparable, which makes only qualitative comparisons between studies possible. Fourth, albuminuria is associated with glomerular inflammation, oxidative stress, CKD, and T2DM. However, we were not known to difference in albuminuria between two groups since urine microalbumin and creatinine levels were not conducted in the 2015 Korea National Health and Nutrition Examination Survey (KNHANES) data. Fifth, because this study was cross-sectional, it has only a limited ability to establish a causal relationship between CKD and IR and beta cell function. Nevertheless, this is the first reported study to determine the relationship between CKD and IR and beta cell function in Korean adults with or without T2DM. Therefore, more accurate results might be obtained by performing a cohort study.

Disclosure

The authors declare that there is no conflict of interest associated with this manuscript.

Supplement table 1 Comparisons of insulin levels according to non-CKD and CKD in subjects with or without T2DM

		(n = 5,188)		
Category		non-CKD (eGFR ≥ 60 mL/min/1.73 m ²)	CKD (eGFR < 60 mL/min/1.73 m ²)	P
Non-T2DM (n = 4,725)				
Insulin (μU/mL)	Model 1	8.00 ± 0.10 (7.79–8.20)	9.74 ± 0.57 (8.62–10.86)	0.003
	Model 2	7.99 ± 0.09 (7.81–8.17)	8.78 ± 0.52 (7.75–9.80)	0.141
	Model 3	8.00 ± 0.09 (7.81–8.18)	8.64 ± 0.52 (7.62–9.66)	0.225
	Model 4	7.97 ± 0.09 (7.79–8.15)	9.31 ± 0.52 (8.29–10.34)	0.012
T2DM (n = 463)				
Insulin (μU/mL)	Model 1	14.32 ± 0.76 (12.83–15.82)	19.57 ± 2.88 (13.91–25.23)	0.080
	Model 2	14.25 ± 0.74 (12.80–15.70)	20.78 ± 2.83 (15.22–26.34)	0.027
	Model 3	14.27 ± 0.74 (12.82–15.72)	20.54 ± 2.84 (14.96–26.12)	0.034
	Model 4	14.25 ± 0.74 (12.80–15.70)	20.82 ± 2.87 (15.19–26.46)	0.028

Model 1, adjusted for gender, smoking, drinking, and regular exercising; Model 2, Model 1 further adjusted for SBP, DBP, BMI, and WM; Model 3, Model 2 further adjusted for hs CRP, TC, and TGs; Model 4, Model 3 further adjusted for age.

Supplement table 2 Comparisons of HOMA-IR and HOMA-B levels according to non-CKD and CKD in subjects with or without MetS (*n* = 5,188)

Category	Variables	non-CKD (eGFR $\geq$ 60 mL/min/1.73 m ²)	CKD (eGFR < 60 mL/min/1.73 m ²)	<i>P</i>
Non-MetS (<i>n</i> = 3,511)				
	HOMA-IR	1.62 $\pm$ 0.02 (1.57–1.67)	2.09 $\pm$ 0.16 (1.78–2.40)	0.004
	HOMA-B	81.79 $\pm$ 0.94 (79.95–83.62)	99.47 $\pm$ 6.12 (87.48–111.46)	0.004
MetS (<i>n</i> = 1,677)				
	HOMA-IR	3.16 $\pm$ 0.07 (3.02–3.31)	3.59 $\pm$ 0.30 (2.99–4.18)	0.177
	HOMA-B	90.95 $\pm$ 1.67 (87.67–94.23)	104.42 $\pm$ 7.03 (90.63–118.20)	0.063

Adjusted for age, gender, smoking, drinking, regular exercising, DBP, BMI, WM, hs CRP, TC, and TGs.

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