Delayed insulin secretion is associated with rapid kidney function decline

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Background/Aims: Diabetes mellitus and insulin resistance are well known risk factors of chronic kidney disease. However, early metabolic changes, not suitable for DM or insulin resistance, may also affect kidney function. Recently, delayed insulin secretion has been proposed as an early marker of metabolic derangement. Therefore, the relationship between delayed insulin secretion and CKD development was investigated.

Methods: Data were retrieved from a prospective community-based cohort study (Korean Genome and Epidemiology Study). Those with normal kidney function who have undergone oral glucose tolerance test (OGTT) at baseline were enrolled. Participants who were diagnosed with overt DM or insulin resistance were excluded. Delayed insulin secretion was assessed by evaluating the serum insulin level ratio between 60 and 120 minutes after OGTT (120 min: 60 min ratio). Primary outcome was the development of CKD defined as estimated glomerular filtration rate (eGFR)< 60 mL/min/1.73m2 sustained for more than two regular visits, or newly detected proteinuria. A total of 6,967 participants were included in the final analysis.

Results: The mean age was 51.44± 8.66 years, 42.0% were male. Mean eGFR was 78.25 ± 14.75 and 105.47 ± 24.58ml/min/1.73m2 for males and females each. Serum insulin levels at 60 min and 120 min after OGTT were 28.09 ± 25.98 and 21.55 ± 20.36 for males, and 30.00 ± 27.29 and 29.01 ± 25.18 for females. The median 120 min:60 min ratio were 1.59 ± 3.94 for males and 2.31 ± 8.17 for females. During a median follow-up duration of 386 months, incident CKD was observed in 1,308 cases for males and 342 cases for females. When the participants were categorized into quartiles according to120 min:60 min ratio, the risk for CKD development was comparable the 120 min:60 min ratio quartiles in males. However, in females, the risk for incident CKD was significantly higher in the highest quartile compared to the lowest quartile (Hazard ratio 1.53, 95% confidence interval 1.05− 2.25, P=0.028). This relationship remained significant even after adjustments for confounding factors.

Conclusions: A delayed secretion feature of insulin after OGTT may increase the risk of CKD development with normal kidney function

Table1. Baseline characteristics of female participants according to the categories divided by 120/60 ratio

	Total (N=4,024)	Q1 (N=859)	Q2 (N=971)	Q3 (N=1,070)	Q4 (N=1,124)	P
Demographic data						
Age, yr	51.44 ± 8.66	51.59 ± 8.75	51.58 ± 8.62	51.49 ± 8.61	51.10 ± 8.67	0.030
Smoking (%)						0.59
Never	3,822 (95.0)	807 (93.9)	928 (95.6)	1,014 (94.8)	1,073 (95.5)	
Ever	50 (1.2)	14 (1.6)	13 (1.3)	12 (1.1)	11 (1.0)	
Current	152 (3.8)	38 (4.4)	30 (3.1)	44 (4.1)	40 (3.6)	
BMI, kg/m²	24.54 ± 3.17	24.55 ± 3.27	24.52 ± 3.11	24.47 ± 2.99	24.63 ± 3.29	0.66
Comorbidities (%)						
Hypertension	527 (13.1)	114 (13.3)	127 (13.1)	142 (13.3)	144 (12.8)	0.99
Laboratory parameters						
eGFR, ml/min/1.73m²	105.47 ± 24.58	104.10 ± 25.05	105.64 ± 25.33	105.07 ± 23.65	106.75 ± 24.39	0.11
HOMA-IR score	1.49 ± 0.59	1.48 ± 0.60	1.54 ± 0.58	1.49 ± 0.56	1.44 ± 0.60	0.002
Insulin level at 60 minutes during OGTT	30.00 ± 27.29	46.72 ± 35.58	36.68 ± 25.50	28.40 ± 20.30	12.98 ± 14.25	<0.001
Insulin level at 120 minutes during OGTT	29.01 ± 25.18	12.08 ± 10.86	25.36 ± 17.61	33.86 ± 21.62	40.48 ± 30.85	<0.001
Insulin 120/60 ratio	2.31 ± 8.17	0.28 ± 0.13	0.70 ± 0.12	1.21 ± 0.20	6.29 ± 14.73	<0.001

Table2. Event rates according to the categories divided by 120/60 ratio among females

	Total (N=4,024)	Q1 (N=859)	Q2 (N=971)	Q3 (N=1,070)	Q4 (N=1,124)
Person-year	34095.4	7023.8	8538.5	9057.5	9475.6
Events (%)	537 (13.3)	108 (18.3)	135 (13.9)	145 (13.6)	149 (13.3)
Events per 1000 person-yr	15.7	15.4	15.8	16.0	15.7

Table3. Hazard ratios for renal outcome according to the categories divided by 120/60 ratio among females

	Q1 HR (95% CI)	Q2 HR (95% CI)	P	Q3 HR (95% CI)	P	Q4 HR (95% CI)	P
Models							
1		1.25 (0.84 – 1.85)	0.268	1.04 (0.69 – 1.55)	0.867	1.49 (1.02 – 2.19)	0.041
2	Reference	1.26 (0.85 – 1.87)	0.242	1.12 (0.74 – 1.68)	0.591	1.52 (1.04 – 2.23)	0.031
3		1.25 (0.84 – 1.85)	0.267	1.12 (0.75 – 1.68)	0.581	1.53 (1.05 – 2.25)	0.028

Note: Model 1. Adjusted for age, smoking behaviors, medical history of hypertension
Model 2. Model 1 plus baseline estimated glomerular filtration rates
Model 3. Model 2 plus homeostatic model assessment for insulin resistance

Figure1. Kaplan - Meier plot for renal outcome according to the categories divided by 120/60 ratio

P = 0.011
Note: P value is estimated with log-rank test.