Correlation between glomerular filtration rate and insulin resistance index in patients with type 2 diabetes mellitus and chronic kidney disease

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Abstract

Objective: To investigate the changes of insulin resistance index[Homa-IR (CP)] in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) at different stages of glomerular filtration rate (eGFR), and to analyze the relationship between them. **Methods:** From January 2015 to June 2019, 1013 patients with T2DM and CKD were admitted to Mudanjiang Cardiovascular Disease Hospital Diabetes Branch Hospital (grade three grade a hospital). The general conditions of the patients were collected, and the biochemical indexes were measured by the laboratory department of our hospital. After calculating the HOMA IR (CP) and EGFR values according to the obtained data, the patients were divided into five groups according to the CKD grouping criteria: 0 ~ 15 ml·(min·1. 73m^2)$^{-1}$ for group A, 15 ~ 30 ml·(min·1. 73m^2)$^{-1}$ for group B, 30 ~ 45 ml·(min·1. 73m^2)$^{-1}$ for group C, 45 ~ 60 ml·(min·1. 73m^2)$^{-1}$ for group D and 60 ~ 90 mL·(min·1. 73m^2)$^{-1}$ for group E. The relevant data were statistically analyzed by SPSS software. **Results:** (1) There was a negative correlation between EGFR and HOMA IR (CP) in T2DM patients with CKD (r = - 0.25, P = 0.000). (2) The comparison results between HOMA IR (CP) groups showed that there was significant difference between group A and group B and other groups, and there was significant difference between group C and group D and other groups (P0.05). (3) The pairwise comparison between fasting blood glucose groups showed that there was significant difference between group A and group B (LSD-t = -1.74, P = 0.034). There was significant difference in insulin dosage between group A and other groups (P0.05), and there was significant difference between group D and group E (LSD-t = 0.06, P = 0.005). (4) Logistic analysis of EGFR showed that age, serum creatinine and HOMA IR (CP) were the main influencing factors of EGFR (P0.05). Conclusion: there is a significant negative correlation between EGFR and HOMA IR (CP) in T2DM patients with CKD. In the process of aggravating insulin resistance, EGFR increased more significantly in the two stages of 45 ~ 60 ml·(min·1. 73m^2)$^{-1}$ and 15 ~ 30 ml·(min·1. 73m^2)$^{-1}$.

Keywords: type 2 diabetes mellitus; chronic kidney disease. glomerular filtration rate. insulin resistance index

1.Introduction

According to statistics, the total prevalence rate of diabetes is 11.6% in China over 20 years old, and the number of cases is as high as 114 million. Among them, the undiagnosed diabetes accounted for 63%[1] of the total. High incidence rate and low diagnostic rate are easy to cause diabetic complications. Diabetic nephropathy is one of the unique microvascular complications of diabetes. It is also the leading cause of end-stage renal disease (ESRD). The onset of diabetic nephropathy is hidden. Once entering a large amount of proteinuria stage, the rate of progression to ESRD is 14 times[2] of other renal diseases. When the glomerular filtration rate (eGFR) decreases in diabetic patients with chronic kidney disease, the metabolic clearance rate of both the insulin secreted by the islet itself and the insulin injected outside the body slows down, resulting in the decrease of insulin accumulation and blood glucose level. However, it is found in clinical work that when the EGFR of patients is 45 ~ 60ml·(min·1.73m^2)$^{-1}$, even if a large amount of exogenous insulin is injected, it is still difficult to regulate blood glucose. When EGFR drops below 15ml·(min·1.73m^2)$^{-1}$, especially in uremic patients, low-dose insulin treatment is still prone to hypoglycemia. Therefore, this study reflects the relationship between insulin resistance and renal function injury by exploring the correlation between EGFR and HOMA IR (CP), so as to provide a theoretical basis for accurate clinical treatment.

2. Materials and methods

The object of this study was to screen 1013 patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) who were admitted to the diabetes branch of Mudanjiang Cardiovascular Disease Hospital from January 2015 to June 2019. There were 529 males and 484 females, with an average age of (62.93 ± 10.35) years. According to the CKD grouping criteria, the subjects were divided into 5 groups: 126 cases in group A with 0 ~ 15ml·(min·1.73m^2)$^{-1}$. 15 ~ 30ml·(min·1.73m^2)$^{-1}$ was 110 cases in group B. 158 cases in group C were 30 ~ 45ml·(min·1.73m^2)$^{-1}$. 45 ~ 60ml·(min·1.73m^2)$^{-1}$ was 213 cases in group D. 60 ~ 90ml·(min·1.73m^2)$^{-1}$ was 406 cases in group E.

The diagnostic criteria were used to diagnose diabetes according to the 1999 WHO standard. The criteria for the diagnosis and grouping of chronic kidney disease refer to the 2007 American Diabetes and chronic kidney disease clinical guideline (K/DOQI).

Exclusion criteria: a. Suffering from pancreatitis or other pancreatic diseases. b. Acute metabolic disorders such as diabetic ketoacidosis and hyperosmolar coma. c. Suffering from hypertension. d. There are kidney related diseases such as acute renal function injury and renal malignant tumor. e. There are acute active infection, surgery and other stress states. There are infectious diseases, such as hepatitis B, tuberculosis, etc.

Medical history collection collect gender, age, height, weight and treatment plan through the inpatient medical records of patients, and calculate their BMI (BMI = weight kg / height m^2).

Biochemical index test: ask the patient to collect fasting blood samples in the morning of the next day and send them to the laboratory department of our hospital to measure fasting blood glucose, fasting C-peptide,

glycosylated hemoglobin, blood creatinine and blood lipid spectrum. Fasting blood glucose was measured by hexokinase method, blood creatinine and blood lipid spectrum by enzyme method, which were all placed in the au680 automatic biochemical analyzer of Beckman Coulter company in Japan. Serum C-peptide was measured by magnetic particle chemiluminescence method and placed in Autobio auto LUMO a2000 automatic chemiluminescence analyzer.

The calculation formula of HOMA IR (CP) and EGFR HOMA IR (CP) is HOMA IR (CP) = 1.5 + FPG ($mmol \cdot L^{-1}$) × FCP($pmol \cdot L^{-1}$)/2800。 EGFR is calculated as EGFR = 175 × Cr($mg \cdot dL^{-1}$)-1.234 × Age -0.179 (female) × 0.79).

The statistical method is spss20 0 software for statistical analysis. The counting data are expressed in frequency and percentage, and are used χ 2 inspection. The measurement data were expressed by mean ± standard deviation, and the analysis of variance was used for comparison among multiple groups. Pearson correlation coefficient was used for two variable correlation analysis. Logistic regression analysis was used to screen the influencing factors of EGFR. $P < 0.05$ was statistically significant.

3. Results

Comparison of general data there were significant differences in BMI, fasting C-peptide, glycosylated hemoglobin, serum creatinine, HOMA IR (CP) and insulin dosage among the five groups ($P < 0.05$). See **Table 1**.

Table 1. Statistics of baseline data and clinical characteristics of 5 groups of subjects

EGFR grouping	n	Age / year	BMI	Fasting blood glucose / $mmol \cdot L^{-1}$	Fasting C-peptide / $pmol \cdot L^{-1}$
Group A	126	60.55±11.00	24.24±5.14	11.69±7.15	1757.13±1292.24
Group B	110	63.26±9.47	25.12±5.29	13.42±7.19	1358.43±843.49
Group C	158	64.35±10.63	27.27±17.93	13.78±6.37	1044.12±634.29
Group D	213	64.73±10.46	26.02±3.94	12.78±6.22	1031.28±530.48
Group E	406	62.09±10.00	25.74±3.89	12.61±5.62	887.50±567.43
F value		-1.47	-3.39	-1.50	10.66
P value		0.142	0.001	0.134	0.000

EGFR grouping	n	HbA1C/%	Triglyceride / $mmol \cdot L^{-1}$	Total cholesterol / $mmol \cdot L^{-1}$	HDL-C/$mmol \cdot L^{-1}$
Group A	126	7.15±1.66	3.36±19.25	5.38±1.74	1.16±0.43
Group B	110	8.16±2.22	2.49±1.78	5.70±2.18	1.18±0.43
Group C	158	8.85±2.14	2.77±2.08	5.51±1.88	1.07±0.35
Group D	213	8.56±1.88	2.67±1.99	5.57±1.68	1.11±0.32
Group E	406	8.81±2.01	2.67±2.215	5.52±1.65	1.15±0.38
F value		-8.16	0.96	-0.78	0.16
P value		0.000	0.338	0.435	0.875

EGFR grouping	n	LDL-C/$mmol \cdot L^{-1}$	Serum creatinine / $ng \cdot DL^{-1}$	Homa-IR(CP)	Insulin dosage / u	Average body weight insulin dosage / u
Group A	126	3.27±1.35	6.46±2.64	8.62±8.42	15.75±11.44	0.23±0.18
Group B	110	3.30±1.57	2.70±0.51	8.02±5.60	27.50±14.97	0.41±0.24
Group C	158	3.10±1.34	1.72±0.24	6.58±4.02	28.35±16.72	0.41±0.24

Group D	213	3.22±1.31	1.33±0.16	6.11±2.99	30.28±15.40	0.44±0.23
Group E	406	3.43±4.90	1.02±0.14	5.37±2.92	26.12±16.01	0.39±0.25
F value		-0.36	41.47	6.62	-6.75	-6.29
P value		0.721	0.000	0.000	0.000	0.000

Note: BMI: body mass index. HbA1c: glycosylated hemoglobin. HDL-C: high density lipoprotein. LDL-C: low density lipoprotein. HOMA IR (CP): homeostatic model index of insulin resistance.

Correlation analysis between EGFR and various indexes Pearson correlation analysis showed that fasting C-peptide, serum creatinine and HOMA IR (CP) were negatively correlated with EGFR. The dosage of HbA1c and insulin was positively correlated with EGFR ($P < 0.05$). The results showed that HOMA IR (CP) increased with the decrease of EGFR. See **Table 2**.

The fasting blood glucose, HOMA IR (CP) and insulin dosage in group 5 were compared between the two groups. The results showed that there were significant differences between HOMA IR (CP) group A and group B and other groups, and between group C and group D and other groups. There was significant difference in fasting blood glucose between group A, group B and group C. There was significant difference in insulin dosage between group A and other groups, and there was significant difference between group D and group E. That is, when EGFR was in two stages of 45 ~ 60ml·(min·1.73m^2)$^{-1}$ and 15 ~ 30ml·(min·1.73m^2)$^{-1}$, the degree of insulin resistance was significantly worse than that in the previous stage. Fasting blood glucose decreased significantly when EGFR < 15ml·(min·1.73m^2)$^{-1}$. The insulin dosage of patients increased significantly when EGFR was in the stage of 45 ~ 60ml·(min·1.73m^2)$^{-1}$, but decreased significantly when EGFR was less than 15ml·(min·1.73m^2)$^{-1}$. See **Table 3**.

Table 2. Correlation Analysis between various indicators and EGFR

index	eGFR	
	Pearson correlation coefficient (R)	P value
BMI	0.026	0.413
Fasting C-peptide	-0.34**	0.000
HbA1C	0.23**	0.000
Serum creatinine	-0.25**	0.000
Homa-IR（CP）	-0.25**	0.000
Insulin dosage	0.12**	0.000
Average body weight and insulin dosage	0.12**	0.000

Note: * * the correlation is significant when the confidence (bilateral) is 0.01. HbA1c: glycosylated hemoglobin. HOMA IR (CP): homeostatic model index of insulin resistance.

Analysis of influencing factors of EGFR take EGFR grouping as dependent variable and statistically different indicators between groups as independent variable for multi classification logistic regression analysis. The results showed that age and serum creatinine were the main influencing factors of EGFR in 0 ~ 90ml·(min·1.73m^2)$^{-1}$ stage, while HOMA IR (CP) was only the influencing factors of EGFR in group A and group B. See **Table 4**.

Table 3. Comparison results of fasting blood glucose, HOMA IR (CP) and insulin dosage between groups

group	Number of cases	Homa-IR(CP)	Fasting blood	Insulin	Average body weight

			glucose	dosage	and insulin dosage
Group A	126	8.62±8.42	11.69±7.15	15.75±11.44	0.23±0.18
Group B	110	8.02±5.60	13.42±7.19	27.50±14.97	0.41±0.24
Group C	158	6.58±4.02	13.78±6.37	28.35±16.72	0.41±0.24
Group D	213	6.11±2.99	12.78±6.22	30.28±15.40	0.44±0.23
Group E	406	5.37±2.92	12.61±5.62	26.12±16.01	0.39±0.25
Overall comparison: F, P		17.08,0.000	2.33,0.054	19.23,0.000	16.65，0.000
Multiple comparisons:	Group a vs group B	0.61,0.299	-1.74,0.034	-11.75,0.000	-0.18，0.000
LSD-t, P	Group a vs group C	2.04,0.000	-2.09,0.005	-12.60,0.000	-0.18，0.000
	Group a vs group D	2.15,0.000	-1.09,0.121	-14.53,0.000	-0.21，0.000
	Group a vs group e	3.26,0.000	-0.92,0.149	-10.37,0.000	-0.16，0.000
	Group B vs group C	1.44,0.010	-0.35,0.649	-0.85,0.655	I 0.01, 0.876
	Group B vs group D	1.90,0.000	0.65,0.379	-2.78,0.124	-0.03，0.258
	Group B vs group e	2.65,0.000	0.82,0.224	1.38,0.405	0.02，0.409
	Group C vs group D	0.47,0.322	1.00,0.128	-1.93,0.233	-0.03，0.238
	Group C vs group e	1.21,0.004	1.17,0.046	2.23,0.122	0.03，0.229
	Group D vs group e	0.75,0.049	0.17,0.747	4.16,0.001	0.06，0.005

Table 4. Logistic regression analysis of influencing factors of EGFR

Grouping a		B	S.E.	Wald	P	Or (lower limit, upper limit)
Group A	intercept	-121.530	12.172	99. 691	0. 000	
	Age	0.393	0.070	31. 762	0. 000	1.481（1.292，1.697）
	BMI	-0.003	0.117	0. 001	0. 980	0.997（0.792，1.255）
	Fasting C-peptide	-0.002	0.001	2. 532	0. 112	0.998（0.996，1.000）
	HbA1C	-9.283	32.997	0. 079	0. 778	9.296×10-（57.160×10-33，1.136×1024）
	Serum creatinine	47.819	3.240	217. 817	0. 000	5.854×102（01.022×1018，3.353×1023）
	Homa-IR（CP）	0.528	0.178	8. 750	0. 003	1.695（1.195，2.404）
Group B	intercept	-89.508	8.431	112. 697	0. 000	
	Age	0.299	0.051	34. 620	0. 000	1. 349（1. 221，1. 490）
	BMI	0.016	0.064	0. 066	0. 797	1. 017（0. 897，1. 153）
	Fasting C-peptide	-0.002	0.001	3. 120	0. 077	0. 998（0. 997，1. 000）
	HbA1C	-33.629	23.225	2. 097	0. 148	2. 483×10-1（5 4. 225×10-35，145 957. 464）
	Serum creatinine	41.652	2.958	198. 325	0. 000	1. 228×101（8 3. 730×1015，4. 045×1020
	Homa-IR（CP）	0.538	0.164	10. 760	0. 001	1. 713（1. 242，2. 362）
Group C	intercept	-50.431	4.160	146. 999	0. 000	

Continued Table 4. Logistic regression analysis of influencing factors of EGFR

Grouping a	B	S.E.	Wald	P	Or (lower limit, upper limit)
Age	0. 146	0. 023	40. 115	0. 000	1. 158（1. 106，1. 211）
IBMI	0.038	0. 059	0. 416	0. 519	1. 069（0. 926，1. 165）
Fasting C-peptide	-0. 001	0. 001	3. 150	0. 076	0. 999（0. 998，1. 000）
HbA1C	-7.628	12. 019	0. 403	0. 526	0. 000（2. 860×10-14，8 281 615. 191）
Serum creatinine	28. 105	1. 879	223. 649	0. 000	1. 606×101（2 40 382 736 270，6. 391×1013）
Homa-IR(CP)	0. 198	0. 101	3. 795	0. 051	1. 219（0. 999，1. 487）
Group D intercept	-26. 339	2. 591	103. 328	0. 000	
Age	0. 092	0. 015	36. 547	0. 000	1. 096（1. 064，1. 129）

IBMI	0. 011	0. 033	0. 102	0. 750	1. 011（0. 947，1. 078）
Fasting C-peptide	0. 000	0. 000	0. 192	0. 661	1. 000（0. 999，1. 001）
HbA1C	-7. 775	8. 475	0. 842	0. 359	0. 000（2. 566×10-11，6879. 171）
Serum creatinine	15.925	1. 324	144. 747	0. 000	8 243 637. 200（615 777. 472，110 360 572. 500）
Homa-IR(CP)	0. 027	0. 078	0. 123	0. 726	1. 028（0. 883，1. 196）

Note: A: the reference category is egfr60 ~ 90ml·(min·1.73m^2)$^{-1}$ group. HbA1c: glycosylated hemoglobin. HOMA IR (CP): homeostatic model index of insulin resistance.

5. Discussion

Insulin resistance is an initiating factor in the occurrence of diabetes and chronic kidney disease, and it is also an independent risk factor throughout the disease. Studies have shown that[3-5], there is a negative correlation between insulin resistance and renal function injury, and it can be used as an independent predictor of end-stage renal disease. This study found that HOMA IR (CP) increased gradually with the decrease of EGFR, and was one of the main influencing factors of EGFR level. Decosmo and other experiments show that podocytes are the main component of glomerular filtration membrane and insulin sensitive cells. The increase of NOD2 expression in podocytes was Glucose dependent, accompanied by the increase of proinflammatory factors and the activation of MAPKs and NF KB signaling pathway. The level of insulin signaling pathway, GLUT4 translocation and the decrease of glucose intake after NOD2 activation all lead to the production of podocyte insulin resistance[6,7]. Under the action of insulin resistance, insulin mediated vasodilation is weakened and vasomotor function is dysregulated, resulting in high perfusion, high pressure and high filtration in glomerular capillaries[8]. The long-term "three highs" phenomenon causes endothelial cell damage, extensive glomerular sclerosis and further damage to podocytes, resulting in aggravation of renal damage. Therefore, reducing the degree of insulin resistance is of great significance to delay the progression of the disease.

The study showed that the degree of insulin resistance in patients with EGFR in the stage of 45 ~ 60ml·(min·1.73m^2)$^{-1}$ was significantly worse than that in the group with EGFR > 60ml·(min·1.73m^2)$^{-1}$, and the fasting blood glucose showed an upward trend, and the amount of insulin treatment also increased. This is consistent with the phenomena observed in the real world. At this time, with the decline of renal function, the patient's insulin resistance increases and insulin sensitivity decreases, resulting in the inability to make full use of exogenous insulin and the difficulty in regulating blood glucose level. The study found that[9], fluctuating hyperglycemia can cause acute damage to the arterial wall, or the direct toxic effect of oxidative stress can destroy endothelial cells, thus affecting the level of a variety of cytokines and leading to further damage to the kidney. Therefore, patients at this stage can effectively avoid the adverse effects of blood glucose fluctuation by giving appropriate amount of insulin and combining appropriate oral drugs to increase insulin sensitivity and reduce the degree of insulin resistance.

In this study, patients with EGFR <

15ml·(min·1.73m^2)$^{-1}$, although the degree of insulin resistance continued to increase, their blood glucose level decreased and the amount of insulin decreased. The occurrence of hypoglycemic symptoms can be seen in the real world. Some scholars analyze the causes of hypoglycemia in patients with diabetic nephropathy[10]: Except for elderly factors, stress, irregular diet and drug factors, hypoglycemia caused by renal factors is more common. In patients with renal failure, the clearance of insulin in the kidney is reduced and the half-life is prolonged, resulting in an increase in the level of free insulin in the blood. At the same time, uremic toxic substances reduce the activity of hepatic glycogen synthase and hepatic glycogen synthesis, resulting in hypoglycemia. It can be seen that patients at this stage should give blood glucose monitoring for many times and reduce the dose of exogenous insulin in time to prevent the harm caused by hypoglycemia.

In conclusion, there was a significant negative correlation between EGFR and HOMA IR (CP) in T2DM patients with CKD. At different stages of EGFR, the degree of insulin resistance, blood glucose and water of patients are different, and the treatment plan should be changed. Pay attention to the change of EGFR level, and the degree of insulin resistance is also changing, which has a certain clinical significance to avoid the adverse effects of blood glucose fluctuations.

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