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ABOUT COVER

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WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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ORIGINAL ARTICLE

Retrospective Study

Application of urinary N-acetyl-β-D-glucosaminidase combined with serum retinol-binding protein in early detection of diabetic nephropathy

Zhi-Hao Lin, Sheng-Feng Dai, Jian-Nan Zhao, Yue Jiang

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Abstract

BACKGROUND

Diabetic nephropathy (DN) is a microangiopathy of type 2 diabetes mellitus (T2DM), which can damage the kidney through various ways and mechanisms due to the nature of the disease, involving the renal interstitium and glomeruli. However, in the early stage of the disease, patients only showed kidney volume increase and glomerular hyperthyroidism, and typical symptoms that are difficult to arouse individual attention were noticed.

AIM

To observe the expression of serum retinol-binding protein (RBP) and urinary N-acetyl-β-D-glucosaminidase (NAG) in patients with DN, and to analyze their value in disease prediction, so as to provide new targets for early diagnosis and treatment of DN.

METHODS

The baseline data of 50 T2DM patients treated in our hospital between January 2021 and December 2022 were retrospectively reviewed and included in group A. The baseline data of 50 patients with type 2 DN admitted to our hospital during the same period were collected and included in group B. The baseline data and serum RBP and urine NAG expression were compared between the two groups to analyze their value in the early prediction of DN.

RESULTS

There was no significant difference in age, gender, duration of diabetes, combined hyperlipidemia and combined hypertension between the two groups ($P > 0.05$); the expression of urinary NAG and serum RBP in group B was higher than that in group A, and the difference was statistically significant ($P < 0.05$); a multiple logistic regression model was established, and the results showed that urinary NAG and serum RBP were related to the presence or absence of injury in diabetic patients, and overexpression of urinary NAG and serum RBP may be risk factors for renal injury in T2DM patients (OR > 1, $P < 0.05$); receiver operating curve curve was plotted, and the results showed that the area under the curve of urinary NAG and serum RBP expression alone and in combination for predicting DN was > 0.80, and the predictive value was satisfactory; bivariate Spearman linear correlation analysis showed that there was a positive correlation between urinary NAG and serum RBP expression in patients with DN ($r = 0.566$, $P = 0.000$).

CONCLUSION

The increased expression of urinary NAG and serum RBP may be the risk factors leading to the progression of T2DM to DN. The possibility of DN can be considered in patients with urinary NAG and serum RBP overexpression by examining the expression of urinary NAG and serum RBP in patients with T2DM in clinical practice.

Key Words: Diabetic nephropathy; Serum retinol-binding protein; Urinary N-acetyl-β-D-glucosaminidase; Prediction; Type 2 diabetes mellitus

Core Tip: Retinol-binding protein (RBP) can combine with thyroid transporters to form polymer complexes, and activated RBP can free in plasma, pass through glomerular filtration, and be absorbed and decomposed by renal tubules. N-acetyl-β-D-glucosaminidase is a high molecular glycoprotein acidic hydrolase, which is an intracellular lysosomal enzyme mainly present in body fluids, organ tissues and blood cells of the body, and has a high expression especially in the proximal renal tubules, thus being clinically used as an important indicator for the evaluation of renal tubular function.

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INTRODUCTION

Diabetic nephropathy (DN) is a microangiopathy of type 2 diabetes mellitus (T2DM), which is caused by many factors such as hemodynamics, glucose metabolism mechanism, oxidative stress, resulting in relative or absolute lack of insulin in the body. Patients mainly have persistent elevated blood glucose, nutritional metabolism disorders. DN can damage the kidney through various ways and mechanisms due to the nature of the disease, involving the renal interstitium, glomeruli, resulting in pathological changes in the kidney, such as glomerulosclerosis, but the initial manifestations of patients are only increased kidney volume, glomerular hyperfunction, not easy to appear the typical symptoms that attract individual attention, only in patients with edema, proteinuria caused detection, but at this time the disease has progressed to the irreversible stage, the best time of treatment is missed, the prognosis of patients is mostly unsatisfactory[1-3]. Therefore, it is particularly important to find new clinical biochemical factors or examination methods to help the early detection of patients with clinical DN to guide the development of early intervention means and improve the prognosis of patients. It has been reported that tubular injury is earlier than glomerular injury in patients with DN, suggesting that tubular injury-related indicators are more significant for guiding the early detection of DN[4-6]. Urine N-acetyl-β-D-glucosaminidase (NAG) is a hot indicator in the diagnosis and treatment of kidney-related diseases at present, and it has more research value in reflecting kidney injury, especially tubular injury [7-9]. Retinol-binding protein (RBP) is a transporter of retinol in blood and has significant value in the assessment of proximal tubular reabsorption function and glomerular filtration performance[10-12]. Based on the biological mechanism of the above two indicators in the body, consider whether they can be used as early diseases in patients with DN. In view of this, this study will focus on observing the expression of serum RBP and urinary NAG in patients with DN, and analyze the value of the two

indicators in disease prediction, providing a new target for early diagnosis and treatment of patients with DN.

MATERIALS AND METHODS

General data

Retrospective analysis was performed to collect the baseline data of 50 patients with T2DM admitted to our hospital between January 2021 and December 2022, and were included in group A. Within the group, there were 30 males and 20 females; the mean age was (43.12 ± 5.02) years. Baseline data were collected from 50 patients with type 2 DN admitted to our hospital during the same period and included in Group B, Within the group, there were 28 males and 22 females; the mean age was (43.25 ± 5.12) years.

Inclusion and exclusion criteria

Inclusion criteria: (1) The diagnosis of T2DM refers to the contents in the [Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes (2013 Edition)][13], which is clinically confirmed by oral glucose tolerance test; (2) Patients with DN refer to the contents in [the Expert Consensus on the Clinical Diagnosis of Diabetic Kidney Disease in Chinese Adults][14]; (3) No other related diseases of the kidney, such as acute and chronic nephritis; and (4) The relevant treatments involved in this study are properly preserved.

Exclusion criteria: (1) Combined endocrine diseases, such as thyroid disease; (2) Combined tumor, tuberculosis and other cachexia; (3) Patients with kidney damage caused by other reasons, such as long-term drug history; and (4) Patients with low compliance caused by combined psychological or mental disorders, who cannot successfully cooperate with the study.

Baseline data collection method

According to the study objectives and methods, a statistical table of general data was designed, which mainly included duration of diabetes, gender, age, combined hyperlipidemia and combined hypertension. Participants in this study all came from the same region.

Test methods for laboratory indicators

5 mL of fasting venous blood was collected at a rate of 3500 r/min with a radius of 15 cm, and the supernatant was obtained after centrifugation for 5 min. Serum RBP was measured by immunoturbidimetry (Beckman AU5800 automatic biochemical analyzer). Patients were asked to randomly obtain 5 mL of morning midstream urine, centrifuged at 1500 r/min, and the supernatant was obtained after 10 min of centrifugation to detect urinary NAG by colorimetry (kit produced by Beijing Jiuqiang Company). All the above operations were carried out in strict accordance with the instructions of relevant instruments, reagents.

Statistical analysis

Data processing was performed using SPSS 24.0 software, and all measurement data were tested for normality by Shapiro-Wilk test, and data that conformed to the normal distribution were expressed as mean ± SD, and comparisons between groups were performed using the independent samples *t*-test; "%" was used for enumeration data and expressed as χ^2 Test, correlation analysis was performed using bivariate Spearman line, and logistic regression analysis was used to test the relationship between urinary NAG and serum RBP expression and patients with DN; receiver operating curve (ROC) was plotted to test the value of urinary NAG and serum RBP in predicting DN, evaluated by area under the curve (AUC), AUC ≤ 0.50: No predictive value; 0.50 < AUC ≤ 0.70: Low predictive value; 0.70 < AUC ≤ 0.90: Moderate predictive value; AUC > 0.90: High predictive value; $P < 0.05$ was considered statistically significant.

RESULTS

Comparison of data between the two groups

There was no significant difference in age, gender, duration of diabetes, combined hyperlipidemia and combined hypertension between the two groups ($P > 0.05$); urinary NAG and serum RBP expression in group B were higher than those in group A, and the difference was statistically significant ($P < 0.05$, Table 1).

Table 1 Comparison of data between two groups

Indicators	Group A (*n* = 50)	Group B (*n* = 50)	Statistical value	*P* value
Gender, *n* (%)			$\chi^2 = 0.164$	0.685
Male	30 (60.00)	28 (56.00)		
Female	20 (40.00)	22 (44.00)		
Age (mean ± SD, yr)	43.12 ± 5.02	43.25 ± 5.12	$t = 0.128$	0.898
Duration of diabetes (mean ± SD, yr)	2.1 5 ± 0.52	2.23 ± 0.55	$t = 0.747$	0.457
Combined hyperlipidemia, *n* (%)			$\chi^2 = 0.164$	0.685
Yes	20 (40.00)	22 (44.00)		
No	30 (60.00)	28 (56.00)		
Combined hypertension, *n* (%)			$\chi^2 = 0.170$	0.680
Yes	18 (36.00)	20 (40.00)		
No	32 (64.00)	30 (60.00)		
Urine NAG (mean ± SD, U/L)	14.05 ± 2.20	19.45 ± 3.68	$t = 8.906$	< 0.001
Serum RBP (mean ± SD, mg/L)	43.56 ± 5.50	84.98 ± 15.70	$t = 17.606$	< 0.001

NAG: N-acetyl-β-D-glucosaminidase; RBP: Retinol-binding protein.

Logistic regression analysis of relationship between urinary NAG, serum RBP and DN

Serum RBP and urine NAG of the included subjects were used as covariates, and the conditions of the included subjects were used as dependent variables (1 = DN, 0 = T2DM). After binary regression analysis, all the data in 2.1 were included to establish a multiple logistic regression model. The results showed that urine NAG and serum RBP were related to the presence or absence of injury in diabetic patients, and overexpression of urine NAG and serum RBP may be risk factors for renal injury in T2DM patients (OR > 1, $P < 0.05$, Table 2).

Value analysis of urinary NAG and serum RBP expression in predicting patients with DN

Urinary NAG and serum RBP expression of the included subjects were used as test variables, and the conditions of the included subjects were used as state variables (1 = DN, 0 = T2DM) to draw ROC curves (Figure 1), and the results showed that the AUC of urinary NAG and serum RBP expression alone and in combination in predicting DN were > 0.80, with satisfactory predictive value (Table 3).

Correlation analysis between urinary NAG and serum RBP expression in patients with DN

Bivariate Spearman linear correlation analysis showed a positive correlation between urinary NAG and serum RBP expression in patients with DN ($r = 0.566$, $P = 0.000$).

DISCUSSION

DN is a common complication in patients with T2DM. Urinary albumin, creatinine, blood urea nitrogen and other indicators have been used to assess whether diabetic patients have kidney damage. However, since kidney has self-compensation effect, indicators do not show significant changes in early stage renal impairment, the sensitivity of these indicators is low, and the above indicators can detect abnormalities only when the collective kidney has been damaged. However, irreversible damage has occurred in the body kidney at this stage, resulting in difficulty in the early detection of DN[15-17]. In view of this, many clinical reports have pointed out that inflammatory response, polyol metabolic pathway, abnormal changes in renal hemodynamics, oxidative stress and other mechanisms are related to the occurrence and disease progression of patients with DN, in the process of occurrence and progression of DN, there are renal tubular reabsorption dysfunction, glomerular filtration changes, and abnormal changes of multiple molecules in blood and urine. Thus, whether other indicators in serum or urine can be used as early detection of patients with clinical DN[18-20].

RBP is a carrier protein synthesized and secreted by stem cells, which is mainly synthesized by carbohydrates and a polypeptide chain, and has a very short half-life, which is necessary to help vitamin A transport on hepatocytes to epithelial cells. In many plasma, RBP can bind to thyroid transporter to form a polymer complex. Activated RBP can be free in plasma and filtered by glomeruli, where most of

Table 2 Logistic regression analysis of the relationship between urinary N-acetyl-β-D-glucosaminidase, serum retinol-binding protein and diabetic nephropathy

Variable	*B*	SE	Wals	*P* value	OR	95%CI	
						Upper limit	Lower limit
Constant	-9.366	1.808	26.839	0.000	0.000	-	-
Urine NAG (U/L)	0.568	0.111	26.338	0.000	1.765	1.421	2.192
Serum RBP (mg/L)	0.346	0.109	9.996	0.002	1.413	1.141	1.751

NAG: N-acetyl-β-D-glucosaminidase; RBP: Retinol-binding protein.

Table 3 Efficacy analysis of urinary N-acetyl-β-D-glucosaminidase and serum retinol-binding protein expression for predicting diabetic nephropathy

Indicators	AUC	95%CI of AUC	SE	*P* value	Cut-off value	Specificity	Sensitivity	Youden index
Urine NAG	0.867	0.796-0.939	0.036	0.000	11.855 (U/L)	0.980	0.860	0.840
Serum RBP	0.951	0.902-1.000	0.025	0.000	39.620 (mg/L)	0.980	0.780	0.640
Combined diagnosis	0.974	0.936-1.000	0.020	0.000	-	0.980	0.940	

NAG: N-acetyl-β-D-glucosaminidase; RBP: Retinol-binding protein; AUC: Area under the curve.

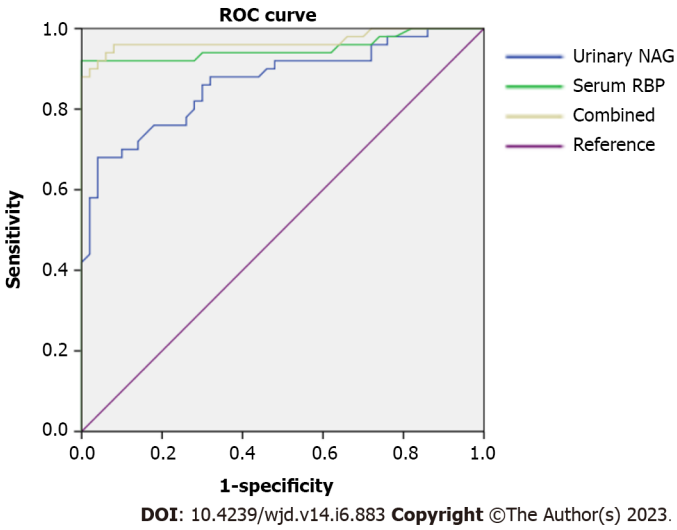

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Figure 1 Receiver operating curve of urinary N-acetyl-β-D-glucosaminidase and serum retinol-binding protein expression for predicting diabetic nephropathy. ROC: Receiver operating curve; NAG: N-acetyl-β-D-glucosaminidase; RBP: Retinol-binding protein.

RBP is absorbed and decomposed by the proximal renal tubules for normal use by tissues, and only a few is excreted in the urine, so the level detected in serum or urine is extremely low under healthy conditions[21-23]. The changes of RBP content suggest the pathological changes of renal tubules and glomeruli. Under the action of induction factors, RBP can stimulate oxidative stress in the body and increase the damage of oxygen free radicals to the vascular endothelium[24-26].

NAG is a large lysosomal molecule present in tubular epithelial cells and does not efficiently pass through the glomerular filtration membrane[27-29]. NAG is a high molecular glycoprotein acid hydrolase, an intracellular lysosomal enzyme mainly present in body fluids, organ tissues and blood cells, especially highly expressed in the proximal renal convoluted tubules, and is clinically used as an important indicator for tubular function assessment[30-32]. In a healthy state, cause NAG has a large molecular weight and cannot normally pass through glomerular filtration, the renal tubules in the early stage of DN can still absorb the excessive proteinuria of glomerular filtration. Urine albumin in this stage is normal, but the expression of NAG increases, which may be due to the strengthening of reabsorption by the renal proximal convoluted tubule, the high protein content in the renal proximal

convoluted tubule stimulating the reabsorption system, activation of mitochondrial lysosomal enzyme, and increased lysosomal enzyme density, the large release of lytic enzyme and the leakage of lysosomal enzyme[33-35]. The results of this study showed that compared with the data of age, gender, duration of diabetes, combined hyperlipidemia and combined hypertension in the two groups, the expression of urinary NAG and serum RBP in group B was higher than that in group A, suggesting that the expression of serum RBP and urinary NAG may be the cause of disease progression to DN in patients with T2DM.

In order to further verify the above conjecture, logistic regression model was used in this study. The results showed that urinary NAG and serum RBP were related to the occurrence of injury in diabetic patients. Urinary NAG and serum RBP overexpression may be risk factors of renal injury in T2DM patients, and ROC curve was drawn, the results showed that the AUC of urinary NAG and serum RBP expression alone and in combination in predicting DN was > 0.80, and the predictive value was satisfactory, suggesting that urinary NAG and serum RBP overexpression are the key to lead to the progression of disease to DN in T2DM patients. The possible reasons for analysis may be: (1) When the renal tubules are damaged, the glomerular filtration decreased, the renal hemodynamics change, when the free RBP passes through the renal tubules, its ability to absorb and decompose the free RBP is limited, resulting in a large number of RBP retention, so the RBP in the serum shows a high expression state[36-38]; and (2) When the renal tubules degenerate, necrosis, damage and fall off, the NAG in the cells enters the urine with the exfoliated and necrotic cells, so a high level of NAG can be measured in the urine[39,40]. In addition, the pathways for obtaining urine NAG and serum RBP were relatively easy, the combination of urine NAG and serum RBP as early evaluation indicators of DN was based on two pathways of urine and blood, which was more reliable than the indicators in pure blood or urine. In this study, bivariate Spearman linear correlation analysis was also used, and the results showed that there was a positive correlation between urinary NAG and serum RBP expression in patients with DN, which may be due to the fact that both indicators are closely related to renal function, so the change of one of the indicators will certainly be cited another indicator changes, but the relationship between the two indicators lacks clinical demonstration support, and the reliability of the study needs to be further explored in the future.

CONCLUSION

In summary, elevated expression of urinary NAG and serum RBP may be risk factors leading to disease progression to DN in patients with T2DM, and the possibility of DN can be considered in patients with urinary NAG and serum RBP overexpression by examining urinary NAG and serum RBP expression in patients with T2DM in clinical practice.

ARTICLE HIGHLIGHTS

Research background

Diabetic nephropathy (DN) is a microangiopathy of type 2 diabetes mellitus (T2DM), which can damage the kidney through various ways and mechanisms due to the nature of the disease, involving the renal interstitium and glomeruli. However, in the early stage of the disease, patients only showed kidney volume increase and glomerular hyperthyroidism, and typical symptoms that are difficult to arouse individual attention were noticed. The symptoms were only noticed when the patients developed edema and proteinuria. At this time, the disease has progressed to an irreversible stage, and the best treatment timing should be taken. Therefore, finding new clinical biochemical factors or examination methods to help early detection of clinical DN patients is particularly important to guide the development of early intervention measures and improve the prognosis of patients.

Research motivation

This study provided new targets for early diagnosis and treatment of DN.

Research objectives

This study aimed to observe the expression of serum retinol-binding protein (RBP) and urinary N-acetyl-β-D-glucosaminidase (NAG) in patients with DN.

Research methods

Total 50 T2DM patients were retrospectively reviewed and included in group A. The baseline data of 50 patients with type 2 DN during the same period were collected and included in group B. The baseline data and serum RBP and urine NAG expression were compared between the two groups to analyze their value in the early prediction of DN.

Research results

The increased expression of urinary NAG and serum RBP may be the risk factors leading to the progression of T2DM to DN.

Research conclusions

The possibility of DN can be considered in patients with urinary NAG and serum RBP overexpression by examining the expression of urinary NAG and serum RBP in patients with T2DM in clinical practice.

Research perspectives

This study showed that urine NAG combined with serum RBP had good application prospects in the early detection of DN. Future studies can further expand the research sample size and improve the diagnostic accuracy of urinary NAG combined with serum RBP.

FOOTNOTES

Author contributions: Lin ZH and Jiang Y concepted the study, supervised the study, contributed to the investigation, the visualization of the study, and originally drafted the manuscript; Dai SF collected the data; Zhao JN contributed to the formal analysis; Dai SF and Zhao JN contributed to the methodology; Jiang Y validated the study; Lin ZH, Dai SF, Zhao JN and Jiang Y reviewed and edited the manuscript.

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