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Observational Study

Role of serum β2-microglobulin, glycosylated hemoglobin, and vascular endothelial growth factor levels in diabetic nephropathy

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Abstract

BACKGROUND

Diabetic nephropathy (DN) is a common complication of type 1 and type 2 diabetes that can lead to kidney damage and high blood pressure. Increasing evidence support the important roles of microproteins and cytokines, such as β2-microglobulin (β2-MG), glycosylated hemoglobin (HbA1c), and vascular endothelial growth factor (VEGF), in the pathogenesis of this disease. In this study, we identified novel therapeutic options for this disease.

AIM

To analyze the guiding significance of β2-MG, HbA1c, and VEGF levels in patients with DN.

METHODS

A total of 107 patients with type 2 diabetes mellitus complicated with nephropathy and treated in our hospital from May 2018 to February 2021 were included in the study. Additionally, 107 healthy individuals and 107 patients with simple diabetes mellitus were selected as the control groups. Changes in β2-MG, HbA1c, and VEGF levels in the three groups as well as the different proteinuria exhibited by the three groups were examined.

RESULTS

Changes in β2-MG, HbA1c, and VEGF levels in the disease, healthy, and simple diabetes groups were significantly different ($P < 0.05$). The expression of these factors from high to low were evaluated in different groups by pairwise comparison. In the disease group, high to low changes in β2-MG, HbA1c, and VEGF levels were noted in the massive proteinuria, microproteinuria, and normal urinary protein groups, respectively. Changes in these factors were positively correlated with disease progression.

CONCLUSION
The expression of serum β2-MG, HbA1c, and VEGF was closely correlated with DN progression, and disease progression could be evaluated by these factors.

Key Words: Type 2 diabetic nephropathy; β2-microglobulin; Glycosylated hemoglobin; Vascular endothelial growth factor; Disease progression

Core Tip: This study investigated the relationship between diabetic nephropathy (DN) and the expression of serum β2-microglobulin (β2-MG), glycosylated hemoglobin (HbA1c), and vascular endothelial growth factor (VEGF). In total, 107 patients with type 2 diabetes mellitus complicated by nephropathy were included in this study. Additionally, 107 healthy individuals were included in the control group. The expression levels of these factors, from high to low, were evaluated in the different groups by pairwise comparison. Serum β2-MG, HbA1c, and VEGF were all closely correlated with DN progression based on all indicators.

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INTRODUCTION

Diabetic nephropathy (DN) is a common clinical diabetic microangiopathy that is known to be an important cause of death in patients with end-stage renal disease[1]. Studies have reported that inflammatory reactions and vascular endothelial cell damage are important factors in the pathogenesis of DN [2]. β2-microglobulin (β2-MG) is a microprotein formed by lymphocytes, polymorphonuclear leukocytes, and platelets, which has a positive effect on the inflammatory response[3]. Glycosylated hemoglobin (HbA1c) levels can reflect the specific control of blood glucose levels in patients in recent months. Excessively elevated HbA1c levels indicate the worsening of hyperglycemic injury in patients, increasing the influence of hyperglycemia on the development of microvascular lesions[4]. Vascular endothelial growth factor (VEGF) reflects the development of capillary malformations caused by pathological changes to a certain extent, and the degree of kidney disease can be determined by analyzing the development of renal microvascular malformations[5]. Considering all of these, this study examined the relationship between the expression of serum β2-MG, HbA1c, and VEGF and the evaluation of DN patients, providing a scientific basis for clinical treatment and analysis of therapeutic effects.

MATERIALS AND METHODS

Study population

A total of 107 patients with type 2 diabetes complicated with nephropathy and treated in our hospital from May 2018 to February 2021 were included in the study. Among them, 59 were male and 48 were female, with a mean age of 49.27 ± 4.26 years old and mean body mass index (BMI) of 24.39 ± 1.54 kg/m^2. These patients were divided into three groups based on urine protein content: normal urinary protein group, < 30 mg/g, 32 patients; microproteinuria group, 30–300 mg/g, 35 patients; and massive proteinuria group, > 300 mg/g, 40 patients. 107 healthy individuals and 107 patients with simple diabetes were recruited, and were established as the two control groups. There were no obvious differences in sex, age, or BMI among the five groups (P > 0.05) (Table 1). All recruited patients provided written informed consent, which was approved by the Ethics Committee.

The inclusion criteria were as follows: (1) diagnosis of DN[6]; (2) blood glomerular filtration rate < 15 mL/min; (3) serum creatinine level > 177 μmol/L; and (4) exhibited normal level of consciousness and ability to communicate.

The exclusion criteria were as follows: (1) tumors; (2) communication disorders; (3) any hormone therapy; (4) abnormal routine blood laboratory findings; and (5) refusal to cooperate with the treatment plan of this study.

Table 1 Comparison of baseline data among the five groups (mean ± SE)

Group	*n*	Age (yr)	BMI (kg/m²)	Sex (male/female)
Normal urinary protein group	32	49.34 ± 4.28	24.33 ± 1.65	15/17
Microproteinuria group	35	49.22 ± 4.34	24.31 ± 1.51	15/20
Massive proteinuria group	40	49.25 ± 4.29	24.52 ± 1.52	29/11
Healthy group	107	49.72 ± 4.11	24.49 ± 1.62	55/52
Simple diabetes group	107	49.88 ± 4.69	24.59 ± 1.97	57/50
χ^2/F value	-	0.281	0.259	8.142
P value	-	0.890	0.904	0.087

BMI: Body mass index.

Enzyme-linked immunosorbent assay

Four milliliters of fasting blood were extracted from all patients and centrifuged at 3500 r/min for 15 min. The supernatant of each sample was then collected, which were used to determine serum β2-MG, HbA1c, and VEGF levels by Enzyme-linked immunosorbent assay. All detection reagents were obtained from Roche Shanghai, and the operating procedures were strictly followed according to the manufacturer's instructions.

Observational index

Changes in β2-MG, HbA1c, and VEGF levels in the disease, healthy, and simple diabetes groups were compared. In the disease group, the same three factors were compared between the normal, microproteinuria, and massive proteinuria groups. Moreover, the correlation between disease progression and β 2-MG, HbA1c, and VEGF levels were also analyzed.

Statistical analysis

SPSS ver. 22.0 was used in the data analysis, and data were expressed as mean ± SE. Analysis of variance was used for multi-group comparisons and the least significant difference-*t* test was used for pairwise comparisons. The count data were expressed as (*n*) %, and the χ^2 test was used. A *P* value < 0.05 indicated a statistically significant difference.

RESULTS

Comparison of changes in β2-MG, HbA1c, and VEGF levels in the disease, healthy, and simple diabetes groups

The changes in β2-MG, HbA1c, and VEGF levels in the disease, healthy, and simple diabetes groups were significantly different ($P < 0.05$). Changes in β2-MG, HbA1c, and VEGF levels, from high to low, were noted in the disease, simple diabetes, and healthy groups, and the differences were statistically significant ($P < 0.05$, Table 2).

Comparison of changes in β2-MG, HbA1c, and VEGF levels among the different disease groups

There were statistically significant differences observed in terms of changes in β2-MG, HbA1c, and VEGF levels among the different disease groups ($P < 0.05$). β2-MG, HbA1c, and VEGF levels, from high to low, were noted in the massive proteinuria, microproteinuria, and normal urinary protein groups (Table 3).

Correlation analysis

Correlation analysis indicated that changes in serum β2-MG, HbA1c, and VEGF levels were positively correlated with disease progression in patients with DN, showing statistically significant differences for all three factors ($P < 0.05$, Table 4).

DISCUSSION

With an aging population in China, the lifestyle of patients with diabetes has changed significantly, resulting an increase in the incidence of diabetes annually[7]. Some studies have reported that diabetes

Table 2 Comparison of changes in β2-microglobulin, glycosylated hemoglobin, and Vascular endothelial growth factor levels in the disease, healthy, and simple diabetes groups (mean ± SE)

Group	*n*	β2-MG (mg/L)	HbA1c (%)	VEGF (ng/L)
Disease group	107	4.34 ± 1.53	10.84 ± 1.81	176.69 ± 11.84
Simple diabetes group	107	2.56 ± 1.14	8.40 ± 1.24	137.84 ± 10.36
Healthy groups	107	1.11 ± 0.82	4.58 ± 0.95	109.32 ± 12.44
F value		195.518	558.284	912.281
P value		0.000	0.000	0.000
LSD-*t* (disease *vs* simple diabetes)		10.862	12.921	24.535
P value		0.000	0.000	0.000
LSD-*t* (disease *vs* healthy)		19.742	33.148	42.548
P value		0.000	0.000	0.000
LSD-*t* (healthy *vs* simple diabetes)		8.879	20.228	18.013
P value		0.000	0.000	0.000

LSD-*t*: Least significant difference; β2-MG: β2-microglobulin; HbA1c: Glycosylated hemoglobin; VEGF: Vascular endothelial growth factor.

Table 3 Comparison of β2-microglobulin, glycosylated hemoglobin, and vascular endothelial growth factor levels among the different disease groups (mean ± SE)

Group	*n*	β2-MG (mg/L)	HbA1c (%)	VEGF (ng/L)
Normal urinary protein group	32	3.37 ± 1.32	9.26 ± 1.33	170.16 ± 10.62
Microproteinuria group	35	4.19 ± 1.39	10.57 ± 1.21	175.45 ± 10.39
Massive proteinuria group	40	5.26 ± 1.29	12.34 ± 1.35	182.99 ± 10.97
F value		18.250	51.067	13.179
P value		0.000	0.000	0.000
LSD-*t* (normal urinary protein *vs* Microproteinuria)		2.516	4.119	2.025
P value		0.013	0.000	0.045
LSD-*t* (normal urinary protein *vs* massive proteinuria)		5.981	9.994	5.066
P value		0.000	0.000	0.000
LSD-*t* (microproteinuria *vs* massive proteinuria)		3.471	5.887	3.051
P value		0.001	0.000	0.003

LSD-*t*: Least significant difference; β2-MG: β2-microglobulin; HbA1c: Glycosylated hemoglobin; VEGF: Vascular endothelial growth factor.

Table 4 Correlation analysis

Index	β2-MG (mg/L)		HbA1c (%)		VEGF (ng/L)	
	r value	*P* value	*r* value	*P* value	*r* value	*P* value
Disease progression	0.705	0.000	0.707	0.000	0.518	0.000

β2-MG: β2-microglobulin; HbA1c: Glycosylated hemoglobin; VEGF: Vascular endothelial growth factor.

is the third most common chronic non-communicable disease. In the disease progression of diabetes mellitus, the risk of DN gradually increases with continuous changes in the patient's microvasculature [8]. Epidemiological investigations show that nearly 37.4% of patients with diabetes mellitus in China have different severities of DN[9]. Currently, the pathogenesis of DN is unclear, but most studies

believe that carbohydrate and lipid metabolism disorders, hemodynamic changes, and abnormal secretion of cytokines lead to the often insidious onset of DN[10]. In most patients, DN manifests as massive proteinuria, which significantly affects patient safety. Considering these, thorough analysis of serological indicators, timely and effective assessment of the patient's condition, and early preventive intervention should therefore have a positive effect on the prognosis of patients.

VEGF has a positive promoting effect on the proliferation of vascular endothelial cells, and is currently clinically considered an important indicator of diabetic retinopathy. It plays a critical role in the effective maintenance of the functional integrity of patients' new blood vessels and endothelial cells [11]. In this study, VEGF levels increased significantly with the progression of the disease, suggesting that with the increase in VEGF levels, the risks of renal malformed vessels as well as vascular permeability changes significantly increase, ultimately resulting in the progression of DN. Through the comparison of VEGF levels in patients with diabetes mellitus, Wang *et al*[12] found that VEGF levels in patients with DN were distinctly higher than those in patients with simple diabetes, which was consistent with this study.

HbA1c has been a common indicator used to evaluate patients' blood glucose control in recent months. The more obvious the increase in HbA1c level, the worse the blood glucose control[13,14]. However, excessive blood glucose levels can damage vascular endothelial cells in patients with DN and easily induce spasms of renal afferent arterioles, thus causing damage to the renal units due to ischemia and hypoxia[15,16]. In the early stages of the disease, kidney injury remains reversible to some extent. However, with gradual enhancement of kidney cell injury, the patient's kidney self-repair ability is eventually lost. By this time, kidney transplantation or dialysis treatment is usually required, which seriously threatens a patient's life[17,18]. Guo *et al*[19] analyzed the HbA1c level of patients with DN, and showed that the determination of HbA1c level in patients has a positive effect on early kidney injury. Yuan *et al*[20] obtained similar results.

β2-MG is a microglobulin protein that can be used as a clinical indicator of chronic kidney disease. During the progression of chronic kidney disease, the glomerular rate of patients significantly decreases as the severity of the disease increases, resulting in a large amount of microglobulin extravasation. In clinical treatment, the therapeutic effect and condition of patients can be determined according to serum β2-MG levels. In this study, β2-MG levels significantly increased as the degree of kidney injury increased, which is consistent with the results of Guo *et al*[19].

There are limitations to this study: (1) The sample size was limited to retrospective studies from a single center; these findings need further multi-institutional validation with a larger sample size[21]; and (2) This was a retrospective study that could not completely avoid missing data and measurement biases. Therefore, further studies must include more candidate biomarkers to develop predictive models in the future[22].

CONCLUSION

Our research shows that the expression of serum β2-MG, HbA1c, and VEGF are closely correlated with DN progression, and the progression of the disease can be evaluated by the expression of these factors in patients in the future.

ARTICLE HIGHLIGHTS

Research background

Diabetic nephropathy (DN) is a common complication of diabetes and is the leading cause of chronic kidney disease. Many identified biomarkers related to DN have been reported in previous studies, but none have been tested at bedside or in clinical trials. Moreover, their validation in larger patient cohorts and longitudinal studies are lacking.

Research motivation

Recent studies have demonstrated that inflammatory reactions and vascular endothelial cell damage are important factors in the pathogenesis of DN. The early detection of changes in renal function is of great benefit for the treatment of DN. Therefore, we aimed to analyze the significance of serum β2 microglobulin (β2-MG), glycosylated hemoglobin (HbA1c), and vascular endothelial growth factor (VEGF) levels in DN.

Research objectives

The objective of this study was to determine whether the expression levels of serum β2-MG, HbA1c, and VEGF are associated with DN.

Research methods

A total of 107 patients with type 2 diabetes mellitus complicated by nephropathy were included in the study, and 107 healthy individuals as well as 107 patients with simple diabetes mellitus were selected as the control groups. Changes in β2-MG, HbA1c, and VEGF levels in the three groups and the different proteinuria groups of the disease group were examined.

Research results

The expression levels of these factors were evaluated in different groups by pairwise comparison. Changes in β2-MG, HbA1c, and VEGF levels in the different disease groups were significantly different. By pairwise comparison, changes in β2-MG, HbA1c, and VEGF levels, from high to low, were noted in the massive proteinuria, microproteinuria, and normal urinary protein groups. Changes in these factors were positively correlated with disease progression.

Research conclusions

The expression of serum β2-MG, HbA1c, and VEGF are closely correlated with DN progression, and the progression of the disease can be evaluated by the expression of these factors in patients in the future.

Research perspectives

Diabetic kidney disease is a major health care challenge that complicates the course of many people living with diabetes. The current study showed that the 22 studied biomarkers had different levels of diagnostic accuracy, ranging from excellent to very good to good, and specificity values. The combined diagnosis of multiple biomarkers may improve the accuracy of early diagnosis of DN. In the future, optimization of biomarkers for clinical situations requires prospective validation in many patients with diabetic nephropathy, and needs to be performed in different critically ill populations.

FOOTNOTES

Author contributions: Yang B contributed to conceptualization, data analysis, and writing; Zhao XH contributed to data analysis and writing; Ma GB revised the manuscript; and all authors have read and approved the manuscript.

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