

Prognostic significance of biomarkers in the early diagnosis of nephropathy in diabetes mellitus II type

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Abstract. Clinical and laboratory markers evaluating the development of nephropathy were studied in 62 patients in the compensation period of type II diabetes. A comparative analysis of the relationship between the results of laboratory biomarkers and the duration of the disease was carried out. 62 patients (including 30 men, 32 women) in the compensation stage of type II diabetes were involved in the research work. Their average age is 48.4 ± 1.2 . Systolic and diastolic blood pressures were 154.1 ± 1.8 and 99.8 ± 1.5 mmHg, respectively. Above average blood sugar, glycosylated hemoglobin values were 8.4 ± 1.6 mmol/l and $8.0 \pm 1.5\%$, respectively. All patients had an average GFR of 71.8 mL/min or more per 1 minute per 1.73 m² body surface area. The results of the analysis showed that in the early years of diabetes, patients had a clear nephrinuria, without the appearance of clinical symptoms of nephropathy. Currently, MAU is detected in the 3-4th year of the disease. Hyperfiltration was observed in 30.6% of patients, and 24.1% of these patients had no renal functional reserve at all during the 4-5 years of the disease.

1 Introduction

Despite the positive results achieved in the diagnosis and treatment of diabetes mellitus (DM) in recent years, even today this disease remains one of the important problems facing the world medicine and is becoming a pandemic in terms of its spread. Diabetic nephropathy is of special importance, considering the changes occurring in vessels as a serious complication of DM that threatens human life. According to some data, 30-40% of patients with DM experience this complication and take a leading place in the development of chronic kidney disease (CKD). The fact that the number of deaths due to DM is the second highest in the world after cardiovascular diseases indicates how urgent this problem is today [1, 2].

Therefore, it is important to study the mechanisms of development of DM nephropathy and to identify kidney damage in the early stages.

A few years ago, a mesangialcentric idea was put forward in the development of nephropathy in DM, which was believed to be caused by the early accumulation of mesangial matrix in the renal glomeruli. Currently, this morphological sign, as well as glomerular hypertrophy and thickening of the glomerular basement membrane, are considered

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characteristic changes in the kidney that occur in DM. In recent years, the existence of an organic connection between albuminuria and ultrastructural and functional changes in podocytes has been proven in a number of experimental and clinical investigations [3,4]. These changes have been shown to occur early in DM before urinary albuminuria occurs.

The state of hyperglycemia in diabetes induces the synthesis of AT II through the expression of angiotensin in podocytes [5]. In addition, due to the expression of prorenin receptors by podocytes under the influence of hyperglycemia, they have a direct modulating effect on renin-angiotensin-aldosterone system (RAAS) [6]. The additive nephroprotective effect of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) may be explained by this pathway. In addition, podocytes express mineralocorticoid receptors, which bind to aldosterone, another component of RAAS. Therefore, it is possible to slow down negative processes in podocytes under the influence of aldosterone antagonists. But it is necessary to continue studying these changes [7].

AT II directly or through transforming growth factor $\beta 1$ (tgf- $\beta 1$) activates the process of apoptosis of podocytes, which increases the production of inflammatory cytokines. Cytokines, in turn, increase the production of matrix proteins by podocytes and lead to the formation of glomerulosclerosis [8]. In addition to the above, AT II suppresses the production of nephrin, an important protein of podocytes [9].

RAAS activation in hyperglycemia induces oxidative stress and increases the production of free radicals. In the experiment, under the influence of free oxidation radicals, podocytes call for the polymerization of actin fibers, and as a result, its cytoskeleton is damaged, the podocytes begin to fuse and separate from the basement membrane [10].

Glycation end products are biomarkers of metabolic stress. They accumulate in blood vessels and kidney structures (mesangia, endothelium, glomerular basement membrane, podocytes) and have a toxic effect, participating in the formation of diabetic nephropathy. Among those listed, podocytes are the main target [11]. AT II AT2 - receptors activate the production of end products of glycation by podocytes. In addition, the final products of glycation activate podocyte apoptosis [11].

2 Materials and methods

The research group consisted of 62 patients (including 30 men and 32 women) in the compensation stage of type II diabetes. Their average age is 48.4 ± 1.2 . Systolic and diastolic blood pressures were 154.1 ± 1.8 and 99.8 ± 1.5 mmHg, respectively. Above average blood sugar, glycosylated hemoglobin values were 8.4 ± 1.6 mmol/l and $8.0 \pm 1.5\%$, respectively. All patients had an average CFT of 71.8 mL/min or more per 1 minute per 1.73 m² body surface area.

Assessment of the diagnostic value of markers evaluating kidney damage in the early stages of the disease in patients with type II diabetes was carried out in several stages. First, glomerular filtration rate (GFR) and renal functional reserve (RFR) were determined using traditional (creatinine) and modern (cystatin C) markers, and the correlation of indicators with AU levels was evaluated. At the next stage, a comparative analysis of MAU manifestations with indicators of nephrinuria was conducted. Then, the GFR and RFR indicators determined on the basis of cystatin S were compared with several markers (TGF $\beta 1$, VEGF A and Coll IV type) that evaluate nephron sclerosis, and their correlations were studied.

3 Results of research analysis

Assessment of the diagnostic value of markers identified in the early stages of kidney failure in patients with type II diabetes was carried out in several stages. First, GFR and RFR were determined using traditional (creatinine) and modern (cystatin S) markers, and the correlation of indicators with AU level was studied. At the next stage, a comparative analysis of MAU manifestations with indicators of nephrinuria was conducted. After that, the comparative analysis and correlation of GFR and RFR indicators determined on the basis of cystatin S with several markers (TGF β 1, VEGF A and Coll IV type) evaluating nephron sclerosis were studied.

Table 1 presents a general classification of clinical and laboratory markers studied in patients diagnosed with type II diabetes.

Table 1. Overview of studies conducted in patients with type II diabetes.

	Indicators	Control group	Type II diabetes
1	Number of patients	30	62
2	Gender (Male/Female)	12/13	30/32
3	Age (M \pm m)	44, 7	48.4 \pm 1.2
4	Disease duration (years)	-	4.8
5	BMI kg/m ²	24.4	29.3
7	BP systolic, mm.Hg	118.1	154.1 \pm 1.8
8	BP diastolic, mm.HG	75.7	99.8 \pm 1.5
9	Pain behind the sternum, %	-	12.3
10	Headache (%)	-	30.6
11	Dizziness, %	-	21.8
12	Smoking (tobacco), %	-	11.3
13	Glucose, μ mol/l	3.6	6.9
14	HbA1c, %	4.2	8.3

Note: BP-arterial blood pressure, BMI- body mass index

Based on the study plan, basal GFR and protein load-stimulated GFR were determined using the CKD-EPI formula based on creatinine and cystatin C, and BFZ was calculated. In all patients, indicators of AU/PU and nephrinuria were detected in overnight urine (Table 2).

2 type of diabetes mellitus, when FRK was determined using creatinine and cystatin C, the average index, reserve, respectively, was 10.3% and 8.8%, and it can be seen that it was reduced in both groups. But as can be seen from the table, there are those with no reserve and those with sufficient reserve in both verification methods. In RFR (Cr) reserves were 29.1%, reduced reserves were 33.8% and non-reserves were 37.1%, respectively 27.5% in RFR (Sys C); It was 41.9% and 30.6% ($p < 0, 01$).

The lowest rate was -14.8% when determined by creatinine and -18% when determined by cystatin C.

Table 2. Comparative analysis of glomerular filtration rate and indicators of renal functional reserve in patients with type II diabetes.

Indicators	Control group n = 30	Type II diabetes n = 62
Creatinine, mmol/l	58.2 [41.8; 64.5]	89.3 [68.4; 138.7]
GFR (Cr), ml/min/1.73m ²	147.4 [129.4; 141.2]	118.4 [58.4; 136.2]

Continuation of Table 2.

RFR (Cr), %	43.7 [15.4 ; 51.3]	10.3 [- 14.8;17.1]
Cystatin C, mg/l	0.94 [0.57; 0.98]	1.68 [1.07; 1.91]
GFR (Cys C), ml/min/1.73m.2	134.1 [116.3; 142.4]	104.3 [52.1;83.3]
RFR (Cys C), %	41.1 [22.4; 47.3]	8.8 [-18;15, 7]
MAU/PU mg/day	4.7 [0.3;5.7]	88.2 [51.3;100.2]
Nephriuria, pg/ml	77.4 [57.6-103.8]	238.6 [197.6;288.7]

Note: RFR -Renal functional reserve; GFR- glomerular filtration rate; MAU-microalbuminuria; PU-proteinuria

A comparative analysis between the degree of hyperfiltration in GFR and the manifestation of RFR was also conducted in the group of patients with type II diabetes in the early stages. The results of the analysis are presented in Figure 1.

As can be seen from the diagram, the percentage of patients with hyperfiltration in the compensation period of type II diabetes is 30.6±2.4%, which is 1.4 times higher than those with high blood pressure, and 1.7 times higher than patients with AH 1 level. times less. Among patients in 2 groups, the percentage of patients without RFR was 26.4±2.3%.

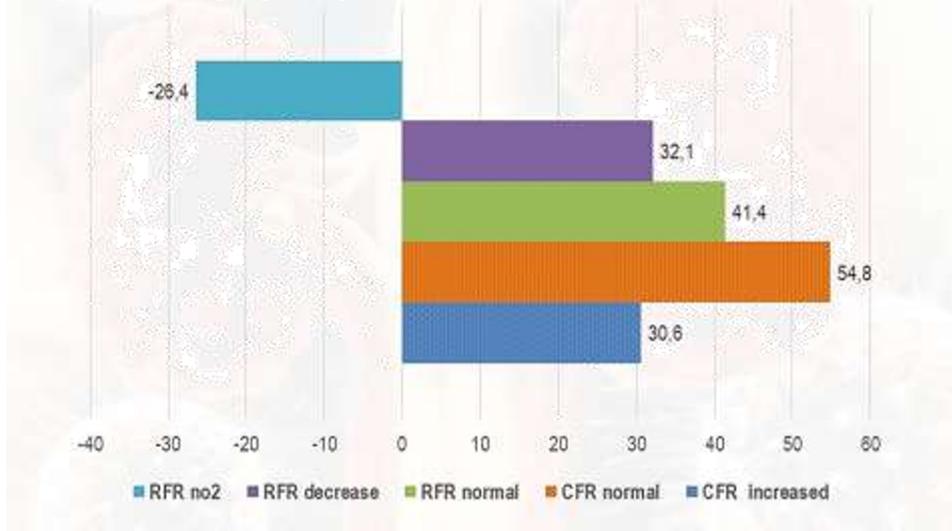


Fig. 1. Comparative analysis (%) of indicators of hyperfiltration and renal functional reserve in patients with type II diabetes.

The results of laboratory markers evaluating the development of nephrosclerosis were analyzed in 2 groups of patients included in the study. They are listed in Table 3.

As can be seen from the data presented in the table, laboratory markers evaluating the development of glomerulosclerosis in patients with type II diabetes were more pronounced than in patients with hypertension. It was noted that TGF β1 indicator was 1.7 times higher, VEGF A 1.5 times, Coll IV type 1.24 times and nephriuria indicator 2.2 times higher than the control group.

Table 3. Classification of laboratory tests performed in patients with type II diabetes.

Indicators	Control group n = 30	Type II diabetes n = 62	r
TGF β1 (pg/ml)	59.8 [44.2-96.5]	162.9 [128.7 ; 175.5]	0, 213
VEGF A (pg/ml)	88.7 [76.4;110.6]	165,3 [11 5, 6; 1 89, 7]	0, 117
Coll IV type μg/l	21.2 [17.4;26.2]	32.7 [18.3 ; 34.2]	0.0 53
Nephrin (in urine) ng/ml	59.8 [44.2-96.5]	238.6 [1 9 7, 6 ; 288, 7]	0.07 9

A comparative analysis of the dependence of the markers evaluating the functional and structural impairment of the kidney on the duration of the disease is presented in Figure 3.6.

As shown in the diagram, it was observed that in patients with type II diabetes, almost all indicators increase depending on the duration of the disease. A strong positive correlation between indicators was found in nephrinuria ($r=1.31$), VEGF A ($r=0.97$) and MAU ($r=0.73$) ($r<0.001$).

When comparing the indicators of MAU and nephrinuria, the reliability of nephrinuria was 95%, the specificity was 85%, the reliability of MAU was 80%, the specificity was 75%. Normoalbuminuria was detected in 23 patients (37.1%) and 17 (27.4%) patients in the 1st year of the disease duration, and nephrinuria was detected in all of these patients in the first years of the disease.

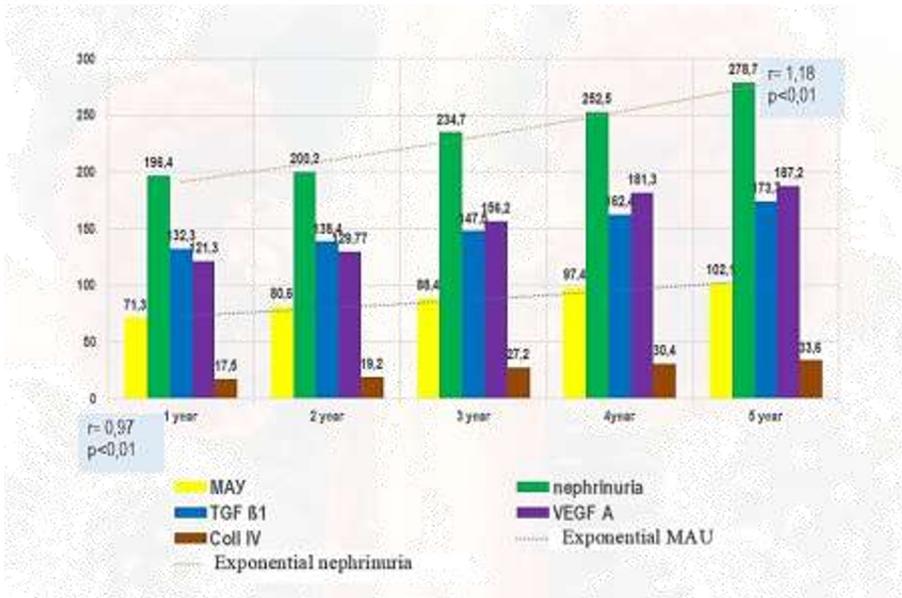


Fig. 2. Correlation of the appearance of nephropathy markers with the duration of the disease in patients with type II diabetes.

4 Conclusions

In patients with type II diabetes mellitus, when RFR was determined using creatinine and cystatin C, the average reserve index was 10.3% and 8.8%, respectively, and it was found to be reduced in both groups. But there are patients who do not have a reserve in both methods of examination, and it is sufficient. RFR in patients with type II diabetes, it was observed that

almost all indicators increase depending on the duration of the disease. A strong positive correlation between indicators was found in nephrinuria ($r=1.31$), VEGF A ($r=0.97$) and MAU ($r=0.73$) ($r<0.001$).

When MAU and nephrinuria indicators were compared, the reliability of the last marker was 95%, and the specificity was 85%. MAU reliability was 80%, specificity was 75%. Normoalbuminuria was detected in 23 patients (37.1%) in 1 year of the disease duration and in 17 (27.4%) patients in 2 years, nephrinuria was noted in all of them in the first years of the disease.

In its early stages type II diabetes mellitus, in the compensation stage, GFR (Cr) 59.2% and GFR (Cys C) 76.6%, sensitivity of PU/AU 54.1%; nephrinuria 82.3%; the sensitivity of TGF β 1 is equal to 73.8%, and it has been proved that the calculation of GFR and RFR by using cystatin C and the determination of nephrinuria are important in the early diagnosis of nephropathy;

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