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Research Article

Predictors of Kidney Damage in Patients with Metabolic Syndrome

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Abstract
Metabolic syndrome is an epidemic of XXI century. Each of the components of metabolic syndrome (arterial hypertension, hyperglycemia or dyslipidemia) can be a risk factor for chronic kidney disease. However, it remains unknown what plays a key role in the progression of the disease.
The objective of the research was to identify early detectors of kidney damage in patients with metabolic syndrome.
Materials and methods. The study involved 70 patients with metabolic syndrome. In addition to standard examination methods, markers of endothelial disfunction (hydrogen sulfide and nitrogen monooxide) were measured in venous blood samples and the urine was tested for microalbuminuria. All the patients were divided into 3 groups according to the degree of albuminuria: normoalbuminuria, microalbuminuria and macroalbuminuria. To compare the indices between the groups, the Student's t-test was used; to determine the relationship between the individual values, the Pearson correlation coefficient (r) was applied.
Results. The indicator of systolic blood pressure was higher in patients with microalbuminuria compared to those with normoalbuminuria (163.4±14.4 mmHg, versus 153.0±17.7 mmHg; $p<0.01$). Hydrogen sulfide level was higher in patients with normoalbuminuria (66.8±7.2 μmol). There was a moderate positive correlation between systolic blood pressure and microalbuminuria ($r=0.3804$; $p<0.01$) and a moderate negative correlation between hydrogen sulfide and microalbuminuria ($r=0.3404$; $p<0.01$).
Conclusions. We revealed a decrease in hydrogen sulfide level to 57.4±7.9 μmol in patients with metabolic syndrome. This may be an early predictor of kidney damage.

Keywords
metabolic syndrome; kidney damage; hydrogen sulfide; microalbuminuria

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Problem statement and analysis of the recent research

Metabolic syndrome (MS) is an epidemic of XXI century. Its prevalence in highly industrialized countries constitutes 20-30%. The main components of MS including abdominal obesity, glucose intolerance or type 2 diabetes mellitus (T2DM), arterial hypertension (AH), dyslipidemia lead to the development of severe cardiovascular complications [6, 8, 13].

These risk factors play a significant role in the development of chronic kidney disease (CKD) as well. The number of patients requiring dialysis is growing every year [1, 6, 8, 9, 11, 12]. Many epidemiological studies confirmed that MS is an independent predictor of the occurrence of proteinuria and CKD as well as its progression till the terminal stage [6, 8, 11-13]. This is evidenced by a correlation between MS and known CKD markers, namely proteinuria, microalbuminuria and glomerular filtration rate (GFR). Chronic inflammation and insulin resistance being the main signs of MS result in the activation of renin-angiotensin-aldosteron system, hyperfiltration and albuminuria [13-15].

Abdominal obesity is considered as the main cause of insulin resistance, hyperglycemia, AH and dyslipidemia [5]. The increase in visceral fat from 0.5 kg to 1.8 kg leads to the reduction in tissue sensitivity to insulin by 60% [8]. Due to obesity, hyperfiltration and hypertrophy of podocytes further contributing to CKD occurrence develop [5].

Kidney damage in patients with cardiovascular risk factors is associated with oxidative stress and chronic systemic inflammation [11-13]. Hydrogen sulfide (H2S) and nitrogen monoxide (NO) play a significant role in these processes [2, 4, 10]. Together with carbon monoxide (CO), they belong to the family of gasotransmitters which are involved in the regulation of the physiological functions of the cardiovascular, nervous and digestive systems [10].

Endothelial cells release H_2S and NO in response to different stimuli including insulin, estradiol, acetylcholine, bradykinin, endothelium growth factor (EGF) [2-4]. In 2008, there was found that that H_2S is released not only by smooth muscle cells of the vascular wall, but also by the endothelium [10].

Abdominal obesity, AH, DM are accompanied by oxidative stress [6, 8, 11, 12]. In hypoxia, the accumulation of H_2S in the medulla helps restore oxygen balance through the increase in the renal circulation, the reduction in energy requirements for Na ions transport and the inhibition of mitochondrial respiration. Hydrogen sulfide deficiency can lead to progression of kidney damage in patients with comorbidities [3]. The decrease in endogenous H_2S is known to inhibit protective vasodilatation in response to high blood pressure (BP) as well as to provoke kidney damage [2-4, 7]. The results of the study carried out in 2016 including 1,004 patients with T2DM showed that high concentration of H_2S correlated with low degree of proteinuria [14]. The results of study conducted in 2015 demonstrated that the use of hydrogen sulfide donors in mice accelerated the recovery of the kidneys after ischemic injury [7].

Renal dysfunction in patients with MS probably appears long before the onset of DM and AH. Its pathogenesis has not been studied well yet and is quite disputable. MS component which plays the most important role in the disease progression is still unknown.

The objective of the research was to identify early detectors of kidney damage in patients with MS.

1. Materials and methods

The study involved 70 (20 men and 50 women) patients with MS. The diagnosis of MS was made according to the International Diabetes Federation Criteria (2015). Patients with type 1 diabetes mellitus (T1DM), left ventricular systolic dysfunction (EF<45%), renovascular hypertension, disorders of the hypothalamic-hypophyseal system, thyroid disorders, parathyroid and adrenal diseases, systemic connective tissue disorders, urinary and oncologic diseases were excluded from the study. All the patients underwent clinical examinations – their complaints were recorded, a medical history was taken, basic laboratory tests (complete blood count, urine analysis, blood glucose test, biochemical blood assay, lipid profile) as well as instrumental ones (electrocardiography, chest X-ray, echocardiography and ultrasound examination of the internal organs) were performed.

In addition, blood sample was taken from the vein for the determination of the level of uric acid, NO (method of Sumbaeva VV, Yasinska IM.) and H_2S [15]; the urine was tested for microalbuminuria (MAU). GFR was calculated according to the Cockcroft–Gault (CG) and Modification of Diet in Renal Disease (MDRD) formulas.

Kidney damage was assessed by the degree of albuminuria. All the patients were divided into 3 groups according to the degree of albuminuria (the American Diabetes Association, 2016): Group I included patients with normoalbuminuria (<0.03 g/l), Group II included patients with microalbuminuria (0.03 – 0.3 g/l), Group III included patients with macroalbuminuria (<0.3 g/l).

To compare the indices between the groups, the Student's t-test was used; to determine the relationship between the individual values, the Pearson correlation coefficient (r) was applied.

2. Results and discussion

The average age of all patients was 62.3±10.4 years. Normoalbuminuria was detected in 18 (25.7%) patients, microalbuminuria was found in 35 (50.1%) patients, macroalbuminuria was observed in 17 (24.2%) patients. All parameters are presented in Table 1.

In patients with macroalbuminuria, body mass index (BMI) was higher compared to patients with microalbuminuria (35.0±3.5 kg/m$_2$; 30.5±3.8 kg/m$_2$; $p< 0.05$). There was no difference in BMI between Group I and Group II. The average waist circumference (WC) was higher in Group II (103.3 ± 9.1 cm) as compared to Group I (95.3±5.1 cm), $p<0.001$. There was no difference in WC between Group II and Group III.

The average value of systolic blood pressure (SBP) was higher in patients with microalbuminuria as compared to those with normoalbuminuria (163.4±17.5 mm Hg; 153.0±14.4 mmHg; $p<0.001$). The average value of diastolic blood pressure (DBP) was higher in Group III as compared to Group II (105.1±10.5 mm Hg; 97.2±8.9 mmHg; $p<0.001$).

The level of triglycerides (TG) was higher in Group III as compared to Group I (2.8±0.8 mmol/l; 2.2±0.7 mmol/l; $p<0.05$). The concentration of H_2S was higher in Group I as compared to Group III and Group III (66.3±5.7 μmol; 62.2±7.9 μmol; 57.4 ±7.9 μmol; $p<0.05$, $p<0.01$).

There was no difference in the indicators of lipid profile, GFR and NO between groups.

There was a moderate positive correlation between SBP and MAU ($r=0.3804$; $p<0.01$) and a moderate negative correlation between H_2S and MAU ($r= -0.34042$; $p<0.01$); the same correlation was observed between SBP and MAU ($r=-0.4443$; $p <0.01$) (Fig.1).

Thus, a decrease in H_2S level leads to the increase in SBP which in turn increases the degree of MAU.

Having analyzed the aforementioned results, we can state that among all the components of MS, increased BP is the most harmful for the kidneys. The difference in this indicator between patients with normoalbuminuria and those with microalbuminuria indicates that even slight BP fluctuations lead to impaired renal function. Correlation between H_2S, MAU and SBP proves that endothelial dysfunction is involved in its pathogenesis. The obtained results are consisted with the results of other authors, who indicated that low H_2S concentration correlated with high degree of proteinuria [14].

Conclusions

We revealed a decrease in hydrogen sulfide level to 57.4±7.9 μmol in patients with metabolic syndrome. This may be an early predictor of kidney damage.

Table 1. General characteristics of all patients

	Normoalbuminuria, n=18	Microalbuminuria, n=35	Macroalbuminuria, n=17
Age (years)	63.1±9.1	61.0±10.8	65.0±11.0
BMI (kg/m$_2$)	30.5±3.8*	33.5±6.5	35.0±3.5*
WC (cm)	95.3±5.1**	103.3±9.1**	106.1±9.5
SBP (mmHg)	153.0±14.4**	163.4±17.5**	171.7±19.6**
DBP (mmHg)	93.1±11.2	97.2±8.9**	105.1±10.5**
Total cholesterol (mmol/l)	5.9±1.3	5.4±1.4	5.3±1.2
HDL (mmol/l)	1.1± 0.2	1.0±0.3	1.0±0.3
LDL (mmol/l)	3.4±1.3	2.8±1.2	2.9±0.9
TG (mmol/l)	2.2±0.7 *	2.7±1.9	2.8±0.8*
TG/HDL index	2.2±0.1 *	3.2±0.9*	2.8±0.6
Glucose (mmol/l)	7.5±2.7	8.0±2.6	6.7±2.1
HbA1c, %	6.0±2.1	6.8±2.1	6.0±1.1
GFR (MDRD), ml/min/1,73m2	64.9±20.5	65.4±14.5	61.7±15.3
GFR (CG), ml/min	89.1±19.6	87.1±26.1	78.9±24.1
NO, μmol	26.6±4.4	28.0±3.0	26.4±2.5
H_2S, μmol	66.3±5.7*	62.2±7.9**	57.4±7.9**

Notes. *p<0.05; **p<0.01.

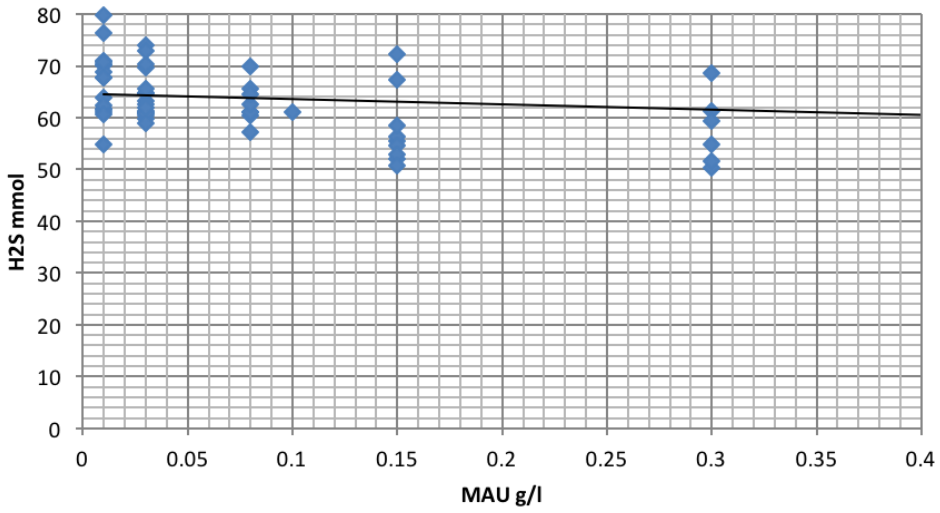

Figure 1. Correlation between H_2S and MAU

Prospects for further research

Our works will be aimed at the development of preventive measures for early kidney damage, decrease in MAU and BP through the administration of hydrogen sulfide donors or drugs elevating the level of endogenous H_2S in patients with MS.

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