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PATHOPHYSIOLOGICAL ANALYSIS OF SYSTEMIC AND RENAL DISREGULATION OF PATHOLOGICAL PROCESSES IN THE DAMAGE OF PROXIMAL TUBULE IN THE NEPHROLITHIASIS

Yurii Rohovyi[1], Oleksandr Ariychuk[2]

[1]**State Educational Establishment of Ukraine "Bukovinian State Medical University",Chernivtsi, Ukraine**
Chief of the department pathological physiology the higher
[2]**Regional Clinical Institution "Hospital of emergency medical care" in "Center of endourology and lithotripsy", st. Fastiv, 2, Chernivtsi, Ukraine**
Doctor-urologist

Abstract

The pathogenesis of urolithiasis in the modern view lies disregulating the pathological process of primary surplus mobilization reactions of protection, which leads to their further transformation in the reaction of damage that is the underlying basis for the formation of vicious circles. 299 patients with nephrolithiasis were examined, 10 patients were in the control group. Found that systemic and renal dysregulation pathological processes of stone the size of stones of 0.6 – 1.0 cm, top, middle cup the upper third of the ureter led to the formation of large and small "vicious circles". Renal and extrarenal dysregulation pathological processes contributed to the increase in damage to the proximal tubule, since the primary damage to the said nephron. Department is not able to mobilize protective adaptive reactions aimed at increasing the excretion of acids and protein reabsorption, since they

require additional energy costs. The use of the drug blemaren in nephrolithiasis reveals protective properties to reduce the manifestations of systemic and renal dysregulation pathological processes and promotes the rupture of formed large and small “vicious circles" with a decrease in proteinuria, the level of tumor necrosis factor-α, improving the transport of sodium ions, fibrinolytic activity of urine and it is advisable to develop guidelines for further use in the clinic of the drug blemaren as a promising method of treatment of urolithiasis.

Key words: nephrolithiasis, systemic and renal dysregulation processes, large and small vicious circles, proximal tubular injury, blemaren.

INTRODUCTION

According to modern concepts, pathogenesis is a mechanism of self-development of the disease as a process of vasa-related and interdependent, successive reactions, each of which arises as an adaptive protective, itself becomes damaging, causing the following protective reaction with similar dynamics, which is the subsequent link of the pathological process, that is, pathogenesis. That is, according to modern concepts, the pathogenesis is based on dysregulation pathological process – the primary excessive mobilization of defense reactions leads to their further transformation in the damage reaction, which is the basic basis for the formation of large and small “vicious circles” [1, 2]. Urolithiasis as the most common urological disease is characterized by frequent early relapses, acquires a social character, since these patients make up 30-45% of all urological patients, and in Europe this disease is detected in 2% of the population. Of interest is the pathophysiological analysis of the study of the role of systemic and renal dysregulation pathological process in the pathogenesis of damage to the proximal tubule by nephrolithiasis in the presence of a concrement of 0.6-1.0 cm in size of the upper, middle cup and the upper third of the ureter, since these patients are subject to the possibility of further treatment using a remote shock wave lithotripsy apparatus lithotripter “Duet Magna” and the drug blemaren [3].

The aim of this study was to find out the role of systemic and renal dysregulation pathological process in the pathogenesis of damage to the proximal tubule for nephrolithiasis and to conduct a pathophysiological analysis of its prevention and treatment.

METHODS

Examination of patients was carried out on the basis of Regional clinical institution “Hospital of emergency medical care” in “Center of endourology and lithotripsy”, st. Fastiv, 2, Chernivtsi and “Central research laboratory” Higher state educational establishment of Ukraine “Bukovinian State Medical University”, Chernivtsi, Teatralnaya square, 2. The

composition of the research group was composed of the doctor of medical Sciences, professor Yurii Rohovyi, doctor-urologist, Oleksandr Ariychuk. 299 patients with nephrolithiasis in the presence of concrements of 0.6-1.0 cm in size of the upper, middle cup and the upper third of the ureter were examined, 10 patients made up the control group. Used: general clinical (diagnosis of urolithiasis), radiological (detection of localization of the concrement and its size), physiological, biochemical, enzyme immunoassay, chemical, statistical methods.

The functional state of the kidneys was studied under water load. Patients consumed tap water heated to a temperature of 37 ° C in an amount of 2% of body weight. The value of diuresis (V) was estimated in 2 h/1.72 m^2 of body surface area. After water loading in order to obtain plasma, blood from the vein was collected in tubes with heparin. In plasma and urine was determined by the concentration of the creatinine reaction with picric acid, of sodium ions - by means of photometry flame on FPL-1, protein by the method of sulfosalicylic acid. Their urinary excretion per 1.72 m^2 of body surface area and 100 ml of glomerular filtrate were calculated. Investigated the glomerular filtration rate by the formula $C_{cr} = U_{cr} \bullet V / P_{cr}$, where U_{cr} is urine creatinine concentration, V - urine output, and P_{cr} is the creatinine concentration in the blood plasma. Control acids renal function was assessed by determination of the concentration of hydrogen ions, acids, which is credited, ammonium ions with the calculations of their excretions, ammonia ratio [4, 5]. Enzymatic fibrinolytic activity of urine was calculated by the formula: FFA = TFA - NFA with preliminary determination of azofibrin lysis with assessment of total (TFA) and non - enzymatic (NFA - incubation of samples in the presence of enzymatic fibrinolysis blocker-aminocaproic acid) fibrinolytic activity [4]. Study the concentration of tumor necrosis factor -α [6] in plasma was performed by enzyme immunoassay with sets of reagents of firm “Diaclone”(France). Blemaren is dosed individually, the average daily dose may be 6-18 g of the active substance (2-6 effervescent tablets per day). Effervescent tablets dissolve in water or fruit juice. The daily dose is divided into 3 equal parts taken during the day (for example, in 7:00, 14:00, 21:00 hours). Control over the effectiveness of blemaren is carried out by determining the pH of fresh urine 3 times a day before the next dose. To do this, use the standard indicator strips embedded in each package. The duration of treatment is not limited. Recommended 2.5-3 months. Up to certain advantages of blemaren over other citrate mixtures include the predominance of citric acid over its salt, as well as the fact that a significant proportion of the buffer component is assumed by the hydrogenated potassium carbonate [3]. All studies were carried out in compliance with the "Rules of ethical principles of scientific medical research with human participation" approved by the Helsinki Declaration (1964-2013), ICH GCP

(1996), EEC Directive No. 609 (dated 24.11.1986), orders of the Ministry of health of Ukraine No. 690 dated 23.09.2009 " No. 944 dated 14.12.2009, No. 616 dated 03.08.2012. Statistical data processing with determination of arithmetic mean, standard error, reliability index was performed using computer programs “Statgrafics”and "Exel 7.0".

RESULTS

The results of our studies have shown an increase in the excretion of acids that are titrated, ammonia and ammonium coefficient for nephrolithiasis in the upper, middle cup and upper third of the ureter with concrement sizes of 0.6 - 1.0 cm (fig. 1). In all these groups inhibition of fibrinolytic activity of urine and growth of tumor necrosis factor- α in blood plasma was revealed. (fig. 2). An increase in glomerular filtration and protein excretion was shown in the presented study groups (fig. 3). The revealed changes contributed to the formation of large and small vicious circle and the possibility of their rupture with the drug blemaren (fig. 4).

DISCUSSION

The results of the study showed that the development of nephrolithiasis in the localization of kidney stones of 0.6-1.0 cm in the upper, middle parts of the calyx and of the upper third of the ureter, respectively, disregulating the increase in the excretion of acids led to the crystallization of urine urates and oxalates in an acidic medium with the formation of kidney stones. The latter caused primary alliteration of kidney tissue, which led to an increase in tumor necrosis factor- α, which caused damage to the proximal tubule [7, 8, 9]. Alteration of the latter led to inhibition of fibrinolytic activity of urine, since the enzyme urokinase is produced by the proximal nephron [4], the lack of activity of which contributes to the deposition of fibrin in the stones. Further precipitation of calcium salts in the rocks led to a build-up of alterations in the kidney tissue and further growth of the tumor necrosis factor- α, which contributed to a further increase in the damage of proximal tubule (large “vicious circle” is closed). However, in the structure of the large vicious circle there are several small “vicious circles”. Thus, the growth of tumor necrosis factor- α led to damage to the proximal tubule, which in turn contributed to the further growth of tumor necrosis factor- α and even greater damage to the proximal tubule (the first small vicious circle was closed). Damage to the proximal tubule caused inhibition of fibrinolytic activity of urine, which contributed to the urothrombosis of the lumen of the proximal tubule [4, 10], and this in turn led to even more damage to the proximal nephron (the second small vicious circle was closed). Systemic and renal dysregulated processes have contributed to increased damage to the proximal tubule as the primary damaged the office of the nephron is unable to mobilize the protective adaptive

response aimed at increasing excretion of acids and reabsorption of the protein [12], because they require additional energy consumption. The use of the drug blemaren in nephrolithiasis shows protective properties [3] with respect to reducing the manifestations of systemic and renal dysregulation of pathological processes and contributes to the rupture of the existing large and small "vicious circles" with a decrease in proteinuria, the level of tumor necrosis factor-α, improving the transport of sodium ions, fibrinolytic activity of urine.

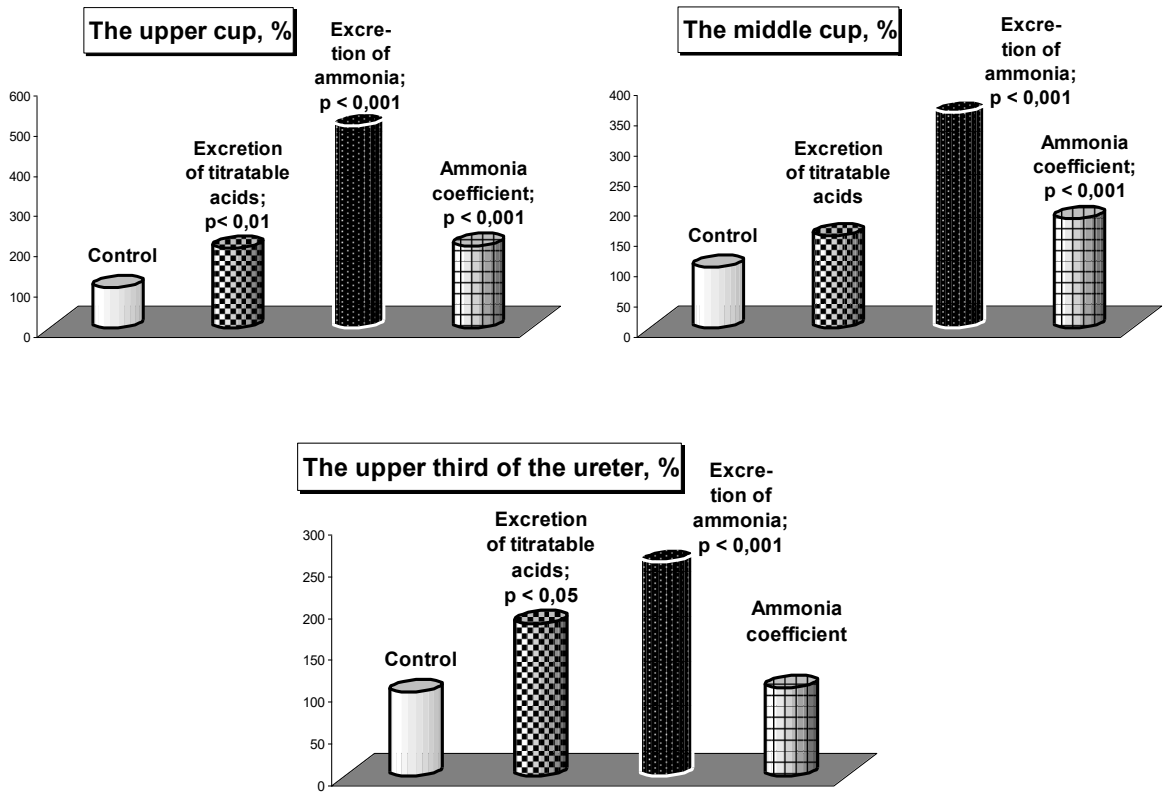

Fig. 1. System dysregulation process for nephrolithiasis. Increased excretion of acids, ammonia and ammonium ratio in patients with kidney stones 0.6-1.0 cm in the upper cup, the middle cup and the upper third of the ureter. p - reliability of differences compared with the control (100%).

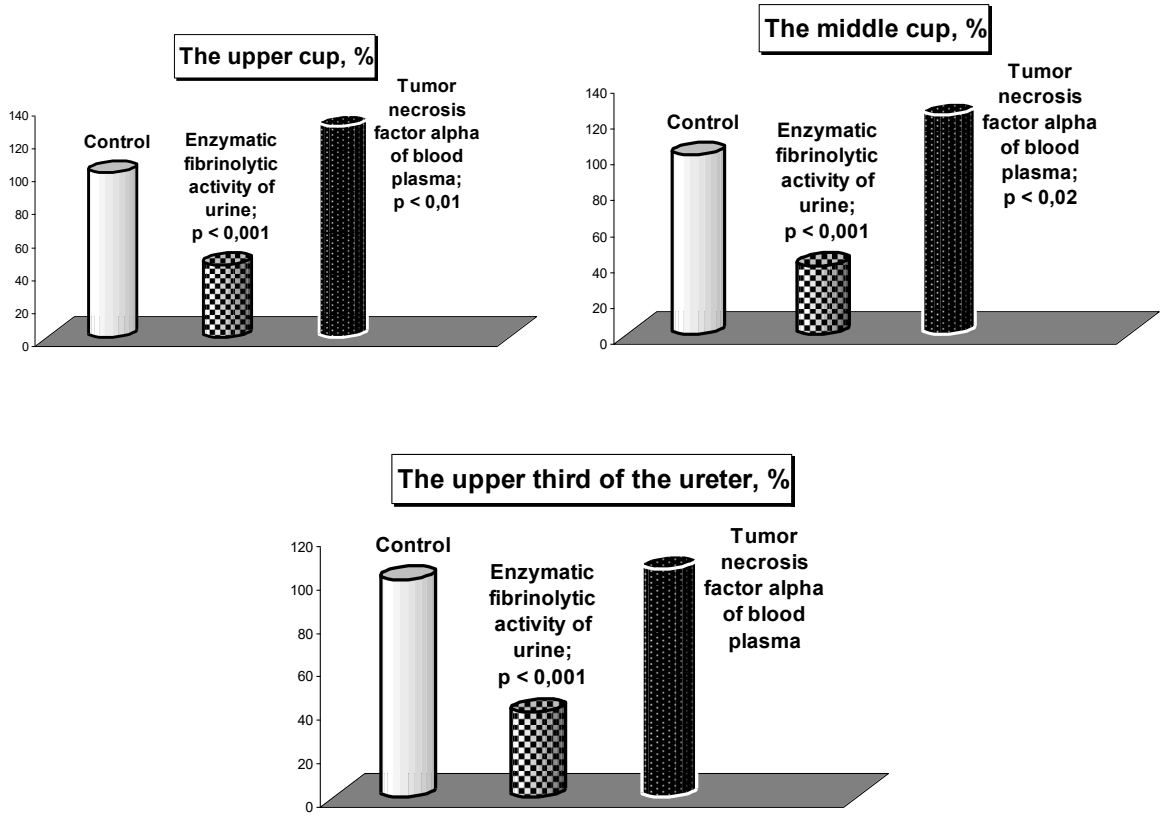

Fig. 2. Damage of the proximal nephron for nephrolithiasis. Reduced enzymatic fibrinolytic activity of urine and increased of the tumor necrosis factor alpha of blood plasma in patients with kidney stones 0.6-1.0 cm in the upper cup, the middle cup and the upper third of the ureter. p - reliability of differences compared with the control (100%).

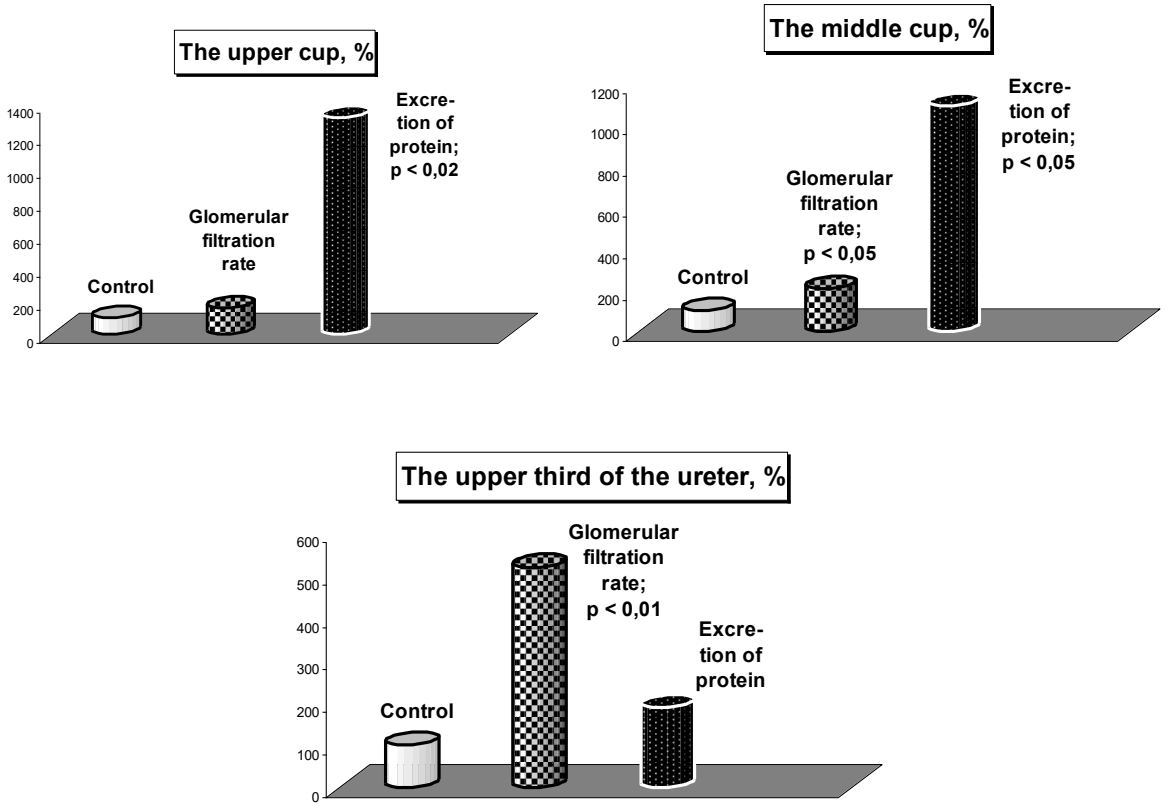

Fig. 3. Renal dysregulation process for nephrolithiasis. Increased glomerular filtration rate and protein excretion in patients with kidney stones 0.6-1.0 cm in the upper cup, the middle cup and the upper third of the ureter. p - reliability of differences compared with the control (100%).

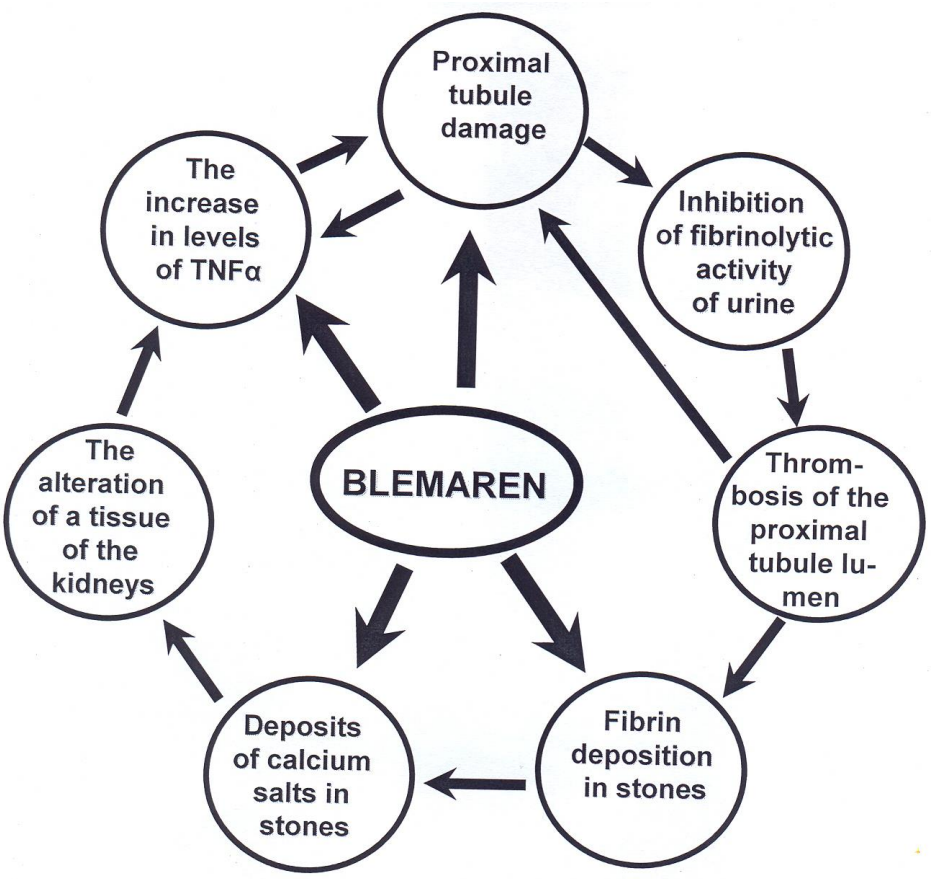

Fig.4. Gap big and small vicious circles using the drug Blemaren.

CONCLUSIONS

1. Systemic and renal dysregulation pathological processes for nephrolithiasis led to the formation of large and small "vicious circles".

2. Renal and extrarenal dysregulation pathological processes contributed to the increase in damage to the proximal tubule, as the primary damage to the part of the nephron is not able to mobilize protective adaptive reactions aimed at increasing the excretion of acids and protein reasorption, as they require additional energy costs.

3. The use of the drug blemaren in nephrolithiasis reveals protective protective protective properties to reduce the manifestations of systemic and renal dysregulation pathological processes and promotes the rupture of formed large and small “vicious circles" with a decrease in proteinuria, the level of tumor necrosis factor-α, improving the transport of sodium ions, fibrinolytic activity of urine and it is advisable to develop guidelines for further use in the clinic of the drug blemaren as a promising method of treatment of urolithiasis.

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