Ref: Ro J Med Pract. 2023;18(1)
DOI: 10.37897/RJMP.2023.1.3

Metabolic disorders and preventive measures against stones in the urinary tract

Petrit NURAJ, Agron BEQIRI

Department of Urology, University Clinical Center of Kosovo, Prishtina, Republic of Kosovo

ABSTRACT

Introduction. *Urolithiasis is not a simple disease, but it is a group of metabolic and endocrine disorders in the organism, coupled with changes in the urinary tract.*

Objectives. *Research on the etiopathogenesis of urolithiasis; to analyze parathyroid hormones, to determine citrates in urine; their influence on the occurrence of urolithiasis. Research and the role of infection in the occurrence of urolithiasis, clinical symptoms, diagnostic methods, prevention methods and as well as preventive measures.*

Materials and methods. *The research was conducted on our patients at the Urology Clinic, University Clinical Center of Kosovo, in Pristina. The work was prospective; in our research, we included 102 patients.*

Results. *Our research has increased Parathormone in 5, 88% of cases. We had hypocitraturia in 57, 84% of cases. Hypocyturia then affects the creation of conditions for the crystallization and aggregation of stone-forming substances. Urolithiasis includes both sexes, primarily men 66, 7%, and women 33.3%. With X2-test we obtained a significant difference with statistical significance in the number of cases by gender (X2 = 11.3, P = 0.001). The most attacked age group was 40-49 years old. Symptoms are dominated by colic, nephralgia, dysuria, and hematuria. In this research, we have 22.5% of positive results of urine cultures.*

Conclusion. *Therefore, there is still no explanation about the pathogenesis of urolithiasis, and with the knowledge of the etiopathogenesis of urolithiasis, symptoms, clinic, metabolic disorders and pathomorphology of urolithiasis, prophylactic measures can be taken, and urolith recurrence can be prevented.*

Keywords: stones, parathormone, hypocitraturia

INTRODUCTION

Urolithiasis is a disease with multifactorial etiology. Urolithiasis is as old as humanity itself. The incidence of urolithiasis depends on geographical, climatic, ethnic, dietary, and genetic factors. The risk of recurrence of urolithiasis is determined based on diseases or disorders caused by stone formations. The prevalence of urolithiasis in the urinary tract ranges from 1% to 20%. In countries with high standards, such as Sweden, Canada, USA, the prevalence of urinary tract stones is not high (> 10%). However, for some countries, it ranges up to 37% [1,2,8]. Urolithiasis is not a simple disease, but it is a group of metabolic and endocrine disorders in the body, which, accompanied by changes in the urinary tract (whether congenital or acquired), lead to the formation of stones in the renal parenchyma or urinary tract. Lithogenesis is a multifactorial disorder. The formation of renal stones is related to the risk factors entering urolithiasis; crystalline supersaturation, low citrate excretion, metabolic disorders, and genetic predisposition [3,6].

Thus, with the interaction of exogenous factors, endogenous ones of the organism, and general ones, with the active participation of local factors and causal factors of the urinary tract, the conditions for the formation of conditions that lead to the formation of stones can be completed [2,7]. In most European countries

Corresponding author:
Petrit Nuraj
E-mail: petrit.nuraj@uni-pr.edu

Article History:
Received: 6 February 2023
Accepted: 14 February 2023

and the USA, upper urinary tract stones are found in 2-3% of the population. About 90% of stones are found in the upper parts of the urinary tract (calyx, pyelone, and ureter), and only 10% are found in the urinary bladder. Also, metabolic disorders hyperparathyroidism, hyperthyroidism, obesity, sarcoidosis, hypercalcemia, and hyperuricosuria affect the occurrence of urolithiasis. Infections also affect the appearance of stones, especially infectious stones: urease-producing bacteria, Proteus, E. coli, and Klebsiella [1,3,4].

Urolithiasis can cause kidney damage up to the loss of kidney function, renal failure, and dialysis. The number of patients on dialysis due to renal insufficiency caused by obstructive and infectious urolithiasis is not small. Therefore, detecting etiological factors, clinical examinations, and adequate treatment of urolithiasis would prevent kidney damage and treat patients with urolithiasis.

OBJECTIVES

We have researched the etiopathogenesis of urolithiasis: the influence of hyperparathyroidism on urolithiasis to analyze parathyroid hormones, their role in the influence of urolithiasis in our patients. In addition, we have determined citrates in urine; their influence on the occurrence of urolithiasis. Also, we researched the role of infection in the occurrence of urolithiasis by gender, age group, clinical symptoms, diagnostic methods, treatment and prevention methods, and preventive measures.

MATERIAL AND METHODS

The research was conducted on our patients at the Urology Clinic, University Clinical Centre of Kosovo, in Pristine. The study was prospective, with patients of different sexes and ages. Before participating in the study, all patients were informed about our research, and those who agreed with this study, participated in our research. Tests were performed: hemogram, urea, creatinine, glycemia, urine, urine culture with antibiogram. From the radiological examinations, we performed: Natural X-ray ultrasonography, Intravenous Urography and CT without contrast and in some cases even with contrast. Parathyroid hormone (PTH) analysis was also done in the blood. A urine citrate study has been done. Hypocyturia was observed when the excretion was less than 320 mg/day. Citrates are crystallization inhibitors that inhibit the formation of crystallization and aggregates in urine. Hypocyturia then affects the creation of conditions for the crystallization and aggregation of stone-forming substances. The most attacked age group and gender will be determined. The most common symptoms in our patient's diagnostic methods will be analyzed. In the occurrence of urolithiasis, the infection will be investigated through urine culture with an antibiogram at the Institute of Microbiology, Pristina.

Ethical issues

This study was approved by the Faculty of Medicine, University of Prishtina's ethics committee, and was conducted under the Declaration of Helsinki guidelines. Written informed consent was obtained from the patient prior to inclusion in the study.

Statistical analysis

Data processing is done with the statistical package InStat 3. The obtained data were presented through tables and graphs. The structure index, arithmetic mean, and standard deviation were calculated based on the statistical parameters. Qualitative data testing was done with X2-test or Fisher test, while quantitative data testing was done with T-test. Test verification was done with a reliability rate of 99.7% (P <0.01) and a reliability of 95% (P <0.05).

RESULTS

According to the age group, out of 102 patients included in the research, 4 or 3.9% are in the age group 0-9 years and 10-19 years, 12 or 11.8% are in the age group 20-29 years, 26 or 25.5% are of age group 30-39

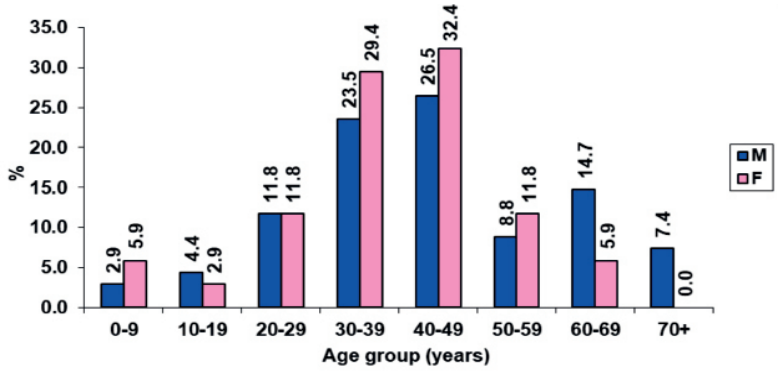

FIGURE 1. *The structure of patients with urolithiasis by age group and gender*

years; 29 or 28.4% are in the age group 40-49 years; 10 or 9.8% are in the age group 50-59 years, 12 or 11.8% are in the age group 60-69 years, and 5 or 4.9% are in the age group 70 and more years (**Figure 1**).

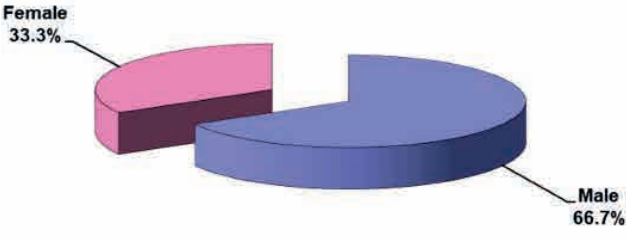

FIGURE 2. *The structure of patients with urolithiasis by gender*

The study included 102 patients with urolithiasis, of which 68, or 66.7% were male and 34, or 33.3%, female. With X^2-test, we obtained a statistically significant difference in the number of cases by gender (X^2 = 11.3, P = 0.001) (Figure 2).

TABLE 1. *Urolithiasis by place of residence and gender*

	Gender				Total	
	M		F			
Residence	**N**	**%**	**N**	**%**	**N**	**%**
Rural	23	33.8	22	64.7	45	44.1
Urban	45	66.2	12	35.3	57	55.9
Total	**68**	**100.0**	**34**	**100.0**	**102**	**100.0**
X^2-test, P-value	X^2=7.56, P=0.006					

According to the place of residence, out of the 102 patients included in the research, 45 or 44.1% live in the countryside, while 57 or 55.9% live in the city. With the distribution of cases by gender and place of residence from a total of 68 men of which 23 (33.8%) live in rural areas and 45 (66.2%) live in cities. Of 34 women, 22, or 64.7%, live in the countryside, and 12, or 35.3%, live in the city. With X^2-test, we obtained a statistically significant difference in the number of cases by place of residence and sex; women with urolithiasis with punctures lived in the village compared to men (X^2 = 7.56, P = 0.006) (Table 1).

According to the localization, in 53 cases, we have kidney stones; in 30 cases, we have stones in the ureter; and in 19 cases, we have stones in the urinary bladder (Table 2).

In cases where the stones were in the bladder, the patients had dysuria and dysuria with hematuria. Of the 60 patients with nephralgia, 46.7% of the stone was in the ureter and 53.3% in the kidney. Of the 23 patients with colic, in 95.6% of cases, the stones were in the kidney, and in 4.3%, in the ureter (Table 3).

As seen in the graph from the 102 patients included in study 23 or 22.5% of the urine culture results were positive. In 9 (8.82%) cases with urine culture Proteus was isolated; in 6 (5.88%) cases, E. coli; in 4 (3.92%) cases of Klebsiella; in 3 cases (2.94%) Pseudomonas and Staphylococcus aurous 1 case (0.98%), (Figures 3 and 4).

Urine citrate research has been performed. Hypocyturia is observed when the excretion is less than 320 mg/day. In our research, we found that in 59 cases, or 57.84%, we have hypocyturia. The citrates in our research are mostly reduced in stones with Calcium oxalate and calcium phosphate composition.

Citrates are crystallization inhibitors that inhibit the formation of crystallization and aggregates in urine. Hypocyturia then affects the creation of conditions for the crystallization and aggregation of stone-forming substances.

Parathyroid hormone (PTH) analysis has also been performed. We found that in 6 cases, or 5.88%, we had an increase in parathormone. Primary hyperparathyroidism is found in the adenoma of the hyperparathyroid gland in one lobe in 92%, while 4% in both lobes of the hyperparathyroid gland, and carcinoma is rare. The production of PTH depends directly on the level of cal-

TABLE 2. *Urolithiasis by localization and gender*

		M		F		Total	
Localization		**N**	**%**	**N**	**%**	**N**	**%**
Right Kidney (RK) Left Kidney (LK)	RK	17	51.5	11	55.0	28	52.8
	LK	15	45.5	8	40.0	23	43.4
	RK+LK	1	3.0	1	5.0	2	3.8
	Total	**33**	**100.0**	**20**	**100.0**	**53**	**100.0**
X^2-test, P-value		**X^2=0.001, P=0.980**				**X^2=0.45, P=0.50**	
Right Ureter (RU) Left Ureter (LU)	RU	11	57.9	6	54.5	17	56.7
	LU	7	36.8	5	45.5	12	40.0
	RU+LU	1	5.3	0	0.0	1	3.3
	Total	**19**	**100.0**	**11**	**100.0**	**30**	**100.0**
X^2-test, P-value		**X^2=0.007, P=0.932**				**X^2=0.81, P=0.269**	
Urinary Bladder		16	23.5	3	8.8	19	18.6
X^2-test, P-value		**X^2=8.89, P=0.003**					
Total		**68**	**100.0**	**34**	**100.0**	**102**	**100.0**

TABLE 3. *Clinical symptoms by localization*

Localization		Clinical symptoms								Total	
		Dysuria		Dysuria + Hematuria		Colic		Nephralgia			
		N	%	N	%	N	%	N	%	N	%
KIDNEY	RK	-	-	-	-	16	26.7	12	52.2	28	27.5
	LK	-	-	-	-	14	23.3	9	39.1	23	22.5
	RK+LK	-	-	-	-	2	3.3	1	4.3	3	2.9
URETER	RU	-	-	-	-	16	26.7	1	4.3	17	16.7
	LU	-	-	-	-	12	20.0	0	0.0	12	11.8
BLADDER		11	100.0	8	100.0	-	-	-	-	19	18.6
Total		**11**	**100.0**	**8**	**100.0**	**60**	**100.0**	**23**	**100.0**	**102**	**100.0**

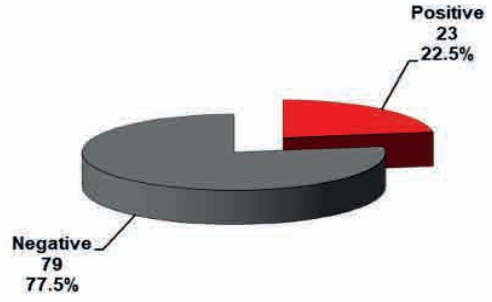

FIGURE 3. *Urine culture results*

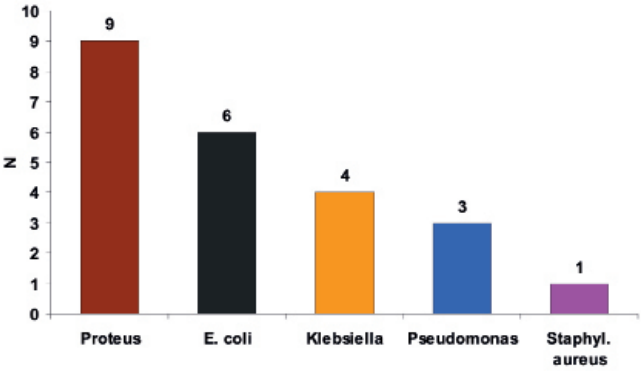

FIGURE 4. *Bacteria isolated in urine culture*

cium in the blood. Hypocalcemia stimulates, whereas hypercalcemia reduces PTH production. The action of phosphates is indirect. Hyperphosphatemia causes hypocalcemia, then it affects the production of PTH, PTH then affects the regulation of calcium metabolism, so it acts on the kidneys and bones. PTH in nephron tubules affects calcium reabsorption and inhibits phosphate reabsorption.

PTH analysis has been performed several times in the same patient due to intermittent hypersecretion. Afterward, after the treatment by us, patients were instructed by the Endocrinologist and the surgeon for the eventual intervention of the adenoma of the hyperparathyroid gland. After treatment by the endocrinologist and surgeon, we had no recurrence of urolithiasis in these cases.

DISCUSSIONS

Urolithiasis can cause kidney damage to the point of loss of renal function — renal failure and dialysis. The number of patients on dialysis due to renal insufficiency caused by obstructive and infectious urolithiasis is not small. Therefore, detecting etiological factors, clinical examinations, and adequate treatment of urolithiasis would prevent kidney damage and treat patients with urolithiasis.

All forms of urolithiasis can be divided into primary and secondary. Primary or aseptic calculus begins unrelated to the etiological causes of urinary tract infection. These may include enzymatic disorders or tubular cell dysfunction, chronic gastrointestinal disorders, surgical diseases of the intestinal tract, disorders of food reabsorption, and so on. Secondary or septic calculus is associated with chronic urinary tract infection disorders, isolated or combined with urinary stasis. Epidemiology of urinary tract infection, which is the cause of this type of calculus, "Infection stones", is an infection caused by urease-forming microorganisms, and alkalization of urine that leads to the formation of concretions composed of magnesium ammonium phosphate and apatite carbonate. Treatment of urease-producing microorganisms, uric acidification, may prevent urolithiasis recurrence [9-11].

The study included 102 patients with urolithiasis, of whom 68, or 66.7%, were male and 34 or 33.3%, female. With X^2-test, we have obtained a statistically significant difference in the number of cases by gender ($X^2 = 11.3$, $P = 0.001$). In terms of age, 40-49 years old has dominated.

According to the place of residence, out of the 102 patients included in the research, 45 or 44.1% live in the village, while 57 or 55.9% live in the city. With the distribution of cases by gender and place of residence from a total of 68 men, of which 23 or 33.8% live in rural areas and 45 or 66.2% live in cities. Out of 34 women, 22 or 64.7% live in the countryside and 12 or 35.3% live in the city. With X^2-test we have obtained a statistically significant difference in the number of cases by

place of residence and gender; women with urolithiasis with punctures lived in the village compared to men (X^2=7.56, P = 0.006). According to the localization, in 53 cases, we have kidney stones; in 30 cases, we have stones in the ureter; and in 19 cases, we have stones in the bladder.

Among the symptoms in our research were nephralgias and colic stones in the upper urinary tract. In the stones in the lower urinary tract, dysuria dominated, most often, but in some cases, was accompanied by dysuria with hematuria. In cases where the stones were in the bladder, the patients had dysuria and dysuria with hematuria. Of the 60 patients with nephralgia of the 46.7% the stone was found in the ureter and in 53.3% in the kidney. Of the 23 patients with colic in 95.6% of cases, the stones were in the kidneys and in 4.3% in the ureter.

In some study had positive histories of the presence of urea-producing bacteria dominated by *Proteus Mirabilis* and *Escherichia Coli* over 50%. So infection is one of the causes that affect the formation of stones, especially infectious ones. Infectious stones are common. This group includes about 15-20% of the total concretions. For the pathogenesis of this group, it is important that bacteria such as *Proteus, Klebsiela, Pseodomonas, Staphylococcus* affect that urea through urease form ammonia (NH3), which then passes to the ammonium ion (NH4) and affects the pH of the urine, affecting the alkalization of urine, and creates the conditions for crystallization and formation of infectious stones such as magnesium ammonium phosphate; and this in the form of tripelphosphatite or as ostrich, and calcium stones phosphatapate [5,10,13].

In our study, out of 102 patients included in the study of 23 or 22.5% the urine culture results were positive. In 9 cases with urine culture Proteus was isolated, in 6 cases *E. coli,* in 4 cases *Klebsiella,* in 3 cases *Pseudomonas* and *Staphylococcus aureus* 1 case. In our research, bacteria that affect the passage of urea under the influence of urease production in ammonia ion and then ammonium ion and alkalization of urine dominate. These bacteria in our research were isolated through urine culture: *Proteus* 8.82%, *E. coli* at 5.88%, *Klebsiella* 3.92%, *Pseudomonas* 2.94%, and *Staphylococcus aureus* in 1 case.

According to Celiksoy et al., hypocitraturia in children often occurs with calculi and that with calcium content. In 30-60% of children with stones have hypocyturia, according to Celiksoy. The test for hypercalciuria is when more than 4 mg/kg/day or (0.1mmol/kg/day) is excreted in the urine within 24 hours, thus confirming that we have hypercalciuria in the patient. Supersaturation with calcium (hypercalciuria) and oxalate (hyperoxaluria) or the breakdown of crystallization inhibitors such as citrates (hypocitraturia) or magnesium (hypomagnesemia) play an important role in stone formation [11]. Stone formation is a complex outcome involving metabolic disorders, anatomical factors, and the presence of infections [12].

Urine citrate research has been done. Hypocyturia was observed when the excretion was less than 320 mg/day. In our research, we found that in 59 cases or 57.84% we have hypocyturia. The citrates in our research have mostly been reduced in stones with Calcium oxalate and calcium phosphate composition. Citrates are crystallization inhibitors that inhibit the formation of crystallization and aggregates in urine. Hypocyturia then affects the creation of conditions for the crystallization and aggregation of stone-forming substances.

Parathyroid hormone (PTH) analysis has also been performed. We found that in 6 cases or 5.88% we had an increase in parathormone. Primary hyperparathyroidism is found in adenoma of the hyperparathyroid gland in one lobe in 92%, while 4% in both lobes of the hyperparathyroid gland, and carcinoma is rare. The production of PTH depends directly on the level of calcium in the blood. Hypocalcaemia stimulates, whereas hypercalcemia reduces PTH production. The actions of phosphates are indirect. Hyperphosphatemia causes hypocalcaemia, then it affects the production of PTH, PTH then affects the regulation of calcium metabolism, so it acts on the kidneys and bones. The parathyroid hormones in nephron tubules affect calcium reabsorption and inhibit phosphate reabsorption.

PTH analysis has been performed several times in the same patient due to intermittent hypersecretion. Then the patients after our treatment were referred to the Endocrinologist and the surgeon for eventual intervention of the adenoma of the hyper parathyroid gland. After treatment by the endocrinologist and surgeon, we had no recurrence of urolithiasis in these cases.

Therefore, with the knowledge of the etiopathogenesis of urolithiasis, symptoms, clinic, metabolic disorders and path morphology of urolithiasis, prophylactic measures can be taken and the recurrence of stones in our patients can be hindered. In this way we enable patients to have a better life and prevent kidney damage from stones - chronic insufficiency to renal dysfunction.

CONCLUSION

In our research, we have increased Parathormone in 5.88% of cases. In these cases, we also had hypercalcemia. Therefore, hyperparathyroidism has influenced the formation of uroliths. We had hypocyturia in 57.84% of cases. Citrates are inhibitors of crystallization that inhibit the formation of crystallization and aggregates in urine. Symptoms are dominated by colic, nephralgia,

colic, nephralgia dominates in kidney stones, while in bladder stones we have dysuria, and sometimes accompanied by hematuria. We have a positive urine culture in 22.5% of cases. Infections were with the following bacteria: *Proteus, E. coli, Staphylococcus aureus, Klebsiella* and *Pseudomonas.*

Therefore, there is still no explanation for the pathogenesis of urolithiasis, and by knowing the etiopathogenesis of urolithiasis, symptoms, clinic, metabolic disorders and pathomorphology of urolithiasis, prophylactic measures can be taken, and urolith recurrence can be prevented.

Conflict of interest: none declared
Financial support: none declared

REFERENCES

1. Bonkat G et al. EAU Guidelines on Urological Infections, in EAU Guidelines, Edn. published as the 37th EAU Annual Meeting, Amsterdam, E.A.o.U.G Office, Editor. 2022, European Association of Urology Guidelines Office: Arnhem, The Netherlands.
2. Dissayabutra T, Kalpongkul N, Rattanaphan J, Boonla C, Srisa-Art M, Ungjaroenwathana W et al. Urinary stone risk factors in the descendants of patients with kidney stone disease. *Pediatr Nephrol.* 2018 Jul;33(7):1173-1181.
3. Skolarikos A, Straub M, Knoll T, Sarica K, Seitz C, Petřík A et al. Metabolic evaluation and recurrence prevention for urinary stone patients: EAU guidelines. *Eur Urol.* 2015 Apr;67(4):750-63.
4. Jenkins AD. Calculous formation. In: Gillenwater JY, Grayhack JT, Howards SS et al. editors. 4th edition Adult and pediatric urology, vol. 1. Philadelphia: Lippincott Williams and Wilkins; 2002. p. 356- 92.
5. Arnett TR. Extracellular pH regulates bone cell function. *J Nutr.* 2008 Feb;138(2):415S-418S.
6. Asplin JR, Parks JH, Nakagawa Y et al. Reduced crystallization inhibition by urine from women with nephrolithiasis. *Kidney Int.* 2002 May;61(5):1821-9.
7. Lee SC. Impact of obesity in patients with urolithiasis and its prognostic Usefulness in stone recurrence. *J Urol.* 2008 Feb;179(2):570-4.
8. Hesse A. Reliable data from diverse regions of the world exists to show that here has been a steady increase in the prevalence of urolithiasis. *World J Urol.* 2005 Nov;23(5):302-3.
9. Ronald AR, Nicolle LE, Stamm E et al. Urinary tract infection in adults: research priorities and strategies. *Int J Antimicrob Agents.* 2001 Apr;17(4):343-8.
10. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. *Nat Rev Microbiol.* 2015;13(5):269-84.
11. Celiksoy M , Yilmaz A , Aydogan G, Kiyak A , Topal E, Sander S. Metabolic disorders in Turkish children with urolithiasis. 2015 Apr;85(4):909-13.
12. Srivastava T, Alon US. Urolithiasis in adolescent children. *Adolesc Med Clin.* 2005 Feb;16(1):87-109.
13. Nicoletta JA, Lande MB. Medical evaluation and treatment of Urolithiasis. *Pediatr Clin North Am.* 2006 Jun;53(3):479-91, vii.