UNIVERSITATEA DE MEDICINĂ ȘI FARMACIE
GRIGORE T. POPA IAȘI

PhD Thesis Abstract

HYPOPOTASIURIA IN YOUNG LITHIASIC PATIENTS: PROGNOSTIC FACTOR OF KIDNEY STONES RECURRENCE

PhD Supervisor
Prof. Univ. Dr. Cătălin Pricop

PhD Student,
Dr. Dragoş PUIA

2019

Table of contents

Index of abbreviations.. 2
Introduction... 3
I. CURRENT STATE OF KNOWLEDGE
Capitolul 1. Epidemiology....................................... 4
1.1 Incidence and prevalence.................................. 4
1.2 Race dependence.. 6
1.3 Gender distribution... 7
1.3 Age dependence……….. 7
1.4 Employment and work place............................ 8
1.5 Recurrence………... 8
1.6 Treatment costs…….. 9
Capitolul 2. Etiopathogenesis of urinary lithiasis.... 10
2.1. Stages of stone formation................................ 14
2.2. Theories of calculus formation........................ 16
2.3. Genetic factors... 17
2.4. Categories of patients at high risk of recurrent lithiasis.. 18
2.5. Particular types of urinary lithiasis................. 27
2.6. Drug induced kidney stones............................ 29
2.7. Kidney stones induced by anatomic factors...... 30
Capitolul 3. Physiology of potassium excretion...... 31
Capitolul 4. Kidney stones diagnosis...................... 39
II. PERSONAL CONTRIBUTIONS
Capitolul 5. Background and objectives................. 43
Capitolul 6. Material and methods........................... 45
Capitolul 7. Results.. 49
Capitolul 8. Discussion... 72
8.1. Aim of metabolic evaluation............................ 72
8.2. Models of evaluation of the lithiasis patient..... 74
8.3. Imaging diagnosis.. 76
8.4. Serum ionogram... 79

8.5. Urinary volume.. 82
8.6. Urinary oxalate.. 88
8.7. Urinary citrate.. 92
8.8. Urinary calcium... 97
8.9. Urinary phosphate... 107
8.10. Urinary magnesium....................................... 110
8.11. Urinary sodium.. 112
8.12. Urinary potasium.. 113
8.13. The ratio between the various urinary constituents.. 115
8.14. 24 hour urine analysis and the possibility of identifying the stones composition.......................... 117
8.15. Socio-economic aspects of stone disease in Romania.. 121
Capitolul 9. Final conclusions................................. 123
References.. 124

This paper contains 55 figures, 4 tables and 221 bibliographic references. The summary of the paper presents iconography and selective bibliographic references, numbered according to the in extenso thesis.

Key words: kidney stones, 24-hour urine analysis, hipopotasiuria, FTIR

Introduction

Urinary stone disease is a complex condition, relatively common in some areas such as developed countries, where the lifestyle favors the appearance of this condition, but also in areas with a hot climate. Although it has long been considered an organ disease, lately there are increasing clues that we are experiencing a systemic disorder characterized by metabolic changes often manifests itself by acute lithiasic episodes. Epidemiological data indicate an overall increase in incidence and prevalence, which also leads to increased treatment costs. Traditionally, men are considered to be more affected than women.

Background and objectives of the study

Backgroung

The most abundant cation in intracellular fluid, potassium plays an important role in many cellular processes. The increased concentration of potassium in cells and low in the extracellular environment is essential for various cellular processes including the electrical properties of the cell membrane. It plays an important role in maintaining cellular osmolarity and therefore in regulating cell volume.

We aimed to evaluate from the point of view of the 24 hours urine composition in young litiatic patients who were reffered to the Iasi Urological Clinic and were diagnosed with urinary lithiasis.

Objectives

The questions we tried to find answer were:

1. Are there changes in the 24-hour urine composition in young lithiasic patients in our geographical area?
2. If any, these changes are particular or correspond to those described in the literature
3. Can we consider age as an element that influences the 24-hour urine composition?

4. Based on the changes of the chemical composition of the 24-hour urine, can we draw up the metabolic profile of the young lithiasic patient in the northeastern part of Romania?
5. Can we develop personalised recommendations for prophylaxis and metaphylaxis of lithiasis for our patients based on the metabolic changes identified?
6. Is the 24-hour urine analysis sufficient to investigate the etiopathogenesis of urinary lithiasis in young patients in the northeastern part of Romania?

Material and methods

After the "stone-free" status was confirmed, a 24-hour urine analysis was performed. We also evaluated renal function and serum ionogram. After obtaining the consent, patients received a glass container (jar with metal lid) in which they collected urine. This was done to eliminate possible contamination of the urine if the patients had used a personal container. The jar was previously disinfected and rinsed with distilled water to remove any residue or contaminant. Patients were informed on how this procedure should be performed.

General inclusion criteria:

- patients ages between 18 and 40
- first time diagnosed with kidney stones
- patients not receiving chronic treatment for prophylaxis of renal lithiasis (eg potassium citrate, hydrochlorothiazide, methionine, etc.)

Exclusion criteria:

- patients with renal or hepatic impairment

- patients with other pathologies that impede the active presence in the study;
- non-cooperating patients;
- pregnant women

Unfortunately, a complete 24-hour urine analysis could not be performed, some items such as urinary citrate or urinary oxalate were not available.

The biochemical analyzes were performed in the Hospital "CI Parhon" Iaşi laboratory which is RENAR ISO 15189/2013 accredited. For example, the urine ionogram was performed using the COBAS 6000 Roche Diagnostics USA analyzer, while the urine summary examination was performed using the Sysmex UF 1000 analyzer.

The imaging evaluation was performed by the radiologists in the "dr. CI Parhon". hospital The ultrasound examination was performed using the Toshiba Xario 100 and Siemens Acuson X150 devices, and the radiological ones with two Siemens Axiom Iconos MD devices.

An analysis was also carried out between the 24-hour urine composition and the chemical composition of the stones. The number of patients in which the analysis of the chemical composition of the calculations could be performed is much lower than in the ones for which the 24-hour urine analysis was performed for two main reasons: the possibility to perform the analysis by infrared spectroscopy was available only at the end of this work., the second reason was that spontaneously passed stones could not be recovered in all patients.

An Olympus SZ61 microscope was used to take the photographs, and the FTIR spectrophotometer used was Bruker Alpha II.

Statistical data processing was performed using Microsoft Excel programs from Windows 2010 and an online calculator available at https://www.socscistatistics.com/, using the t-Student, Chi-square, Fisher Exact and ANOVA tests. The results were considered statistically significant when $p < 0.05$.

Results and discussion

Results

A total of 118 patients were enrolled, ages between 18 and 40, the mean age was 29.60 years, (SD +/- 6.23 years). Regarding the patients gender, there were 57 women and 61 men. The distribution by gender being represented in figure 2.4.

The mean value of urinary potassium was 33.25 mmol/l (SD = +/- 19.7 mmol/l). We found that hypokaluria was found in a relatively large number of patients 64.40% (n = 76), 33.05% (n = 39) had a normal urinary potassium level and only 2.54% (n = 3) high urinary potassium. Therefore, we divided the patients into two groups: those with hypopotasuria (group A) and with normo- or hyperpotasiuria (group B).

The 24-hour urine potassium values in group A ranged from 7.67 mmol / l to 33.69 mmol / l mean being 22.51 mmol / l (SD = +/- 6.11 mmol / l) , and in the other group between 35.1 and 128 mmol/l with an average of 52.06 mmol/l (SD = +/- 18.62 mmol/l). In the first group we had 40 women and 36 men, and in the second group

17 women and 25 men. Following the statistical analysis the gender distribution was equal ($p = 0.28$; $\chi2 = 1.15$).

Patients had serum creatinine values between 0.55 mg/dl and 1.55 mg/dl, mean serum creatinine values being 0.87 mg/dl in the group of patients with hypopotasiuria, respectively 0.89 mg/dl in the other , the difference was not significant ($p = 0.36$). Serum urea had values between 22 mg/dl and 110 mg/dl, with an average value of 35.59 mg/dl, with no significant differences between the two groups (35.13 mg/dl vs. 36.84 mg/dl, $p=0.41$).

The serum sodium value in the group of patients with hypopotasuria had values between 137 and 142 mEq/l with an average value of 139.35 mEq/l, in the other group between 138 and 143 mEq/l, with an average value of 138.91 mEq/l. We did not find significant differences between groups in terms of serum sodium ($p=0.199$, $t=0.85$). Potassium was in the hypopotasiuria group between 3.65 mEq/l and 4.93 mEq/l with an average of 4.32 mE /l, and in the other group between 3.75 mEq/l and 4.66 mEq / l, the average being 4.34 mEq/l. And from this point of view, we did not find significant differences between groups ($p=0.45$; $t=0.12$). Surprisingly, in the case of chloremia we registered significant differences, in the first group it was between 100 and 107 mEq/l with an average of 103.09 mEq/l, and in the second group it had values between 100 and 103 mEq / l with a mean of 101.63 mEq/l, $p=0.017$; $t=2.183$.

The urinary volume was between 400 and 3400 ml, the average volume being 1654.69 ml (SD = +/- 612.22ml). In patients with hypopotassuria, it was between 550 and 3400 ml, with an average volume of

1783.37 ml (SD = +/- 583.78 ml). In the other group we found a urinary volume between 400 and 3250 ml, the average volume being 1422.43 ml (SD = +/- 590.62 ml).

Following the statistical analysis we noticed that the difference was significantly higher in those with hypopotasiuria ($p = 0.001$; $t = 3.16$).

Urinary density (Fig. 2.10) had values between 1005 and 1030 (SD = +/- 5.02 kg/m^3), with an average value for all patients of 1013.87 kg/m^3. In the group of hypopotasiuria patients the values were between 1005 and 1027 kg/m^3 with an average of 1012.79 kg/m^3 (SD = +/- 4.60 kg/m^3). And in the other group between 1005 and 1030 kg/m^3, with an average value of 1015.80 kg/m^3 (SD = +/- 5.50 kg/m^3). Considering that the urinary density is inversely proportional to the urinary volume, and from this point of view after the statistical processing we found a significant difference ($p = 0.001$; $t = 3.13$).

The urinary pH had values in both groups between 5 and 8, the differences being represented by the standard deviation that those with hypopotassuria was 0.81 and in the others 0.93 and by the average pH value which at those with hypopotassuria was 5.7 and the others 6.1. However, after statistical processing we noticed that the urinary pH (Fig. 2.11) was significantly more acidic than in those without hypopotasiuria, $p=0.03$ ($t = 1.79$).

The 24-hour urine sodium (Fig. 2.12) was in group A between 15 and 151 mmol/l, the average being 67.42 mmol/l (SD = +/- 27.23 mmol/l), and in the other group between 24 and 183 mmol/l with an average of 118.65 mmol/l (SD = +/- 36.84 mmol/l). The difference between the values of urinary sodium between the two groups was found, after statistical analysis, to be significant (p = 0.00001; t = 8.413).

Regarding 24 hour urine chlorine, we noticed that in group A it had values between 14.8 and 140 mmol / l with an average of 62.68 mmol / l (SD = +/- 24.82 mmol / l), and in the other group between 12 and 194 mmol / l the average being 108.85 mmol / l (SD = +/- 47.97 mmol / l). The difference between the chloride values between the two groups was statistically significant (p = 0.00001; t = 6.809).

The 24-hour urine phosphorus (Fig. 2.14) was in group A between 4.41 and 39.8 mmol / l mean 18.79 mmol / l (SD = +/- 8.43 mmol / l) , and in the other group between 36 and 183 mmol / l with an average of 26.50 mmol / l (SD = +/- 10.90 mmol / l). The difference between the values of urinary phosphorus between the two groups was shown, after statistical analysis, to be significant (p = 0.000025; t = -4.219).

Urinary magnesium, considered a powerful inhibitor of crystallization, had in group A values between 0.92 and 9.5 mmol / l the average being 3.40 mmol / l (SD = +/- 1.77 mmol / l) , and in group B between 0.73 and 8.9 mmol / l with an average of 3.83 mmol / l (SD = +/- 1.34 mmol / l). The difference between the values of urinary sodium between the two groups was found, after the statistical analysis, to be not significant (p = 0.094; t = 1.323).

Urinary calcium, considered the main "actor" in lithogenesis, had in group A values between 0.25 and 16 mmol / l the average being 3.96 mmol / l (SD = +/- 3.23 mmol / l), and in group B between 0.16 and 13.7 mmol / l with a mean of 3.92 mmol / l (SD = +/- 2.77 mmol / l).

The difference between the values of urinary sodium between the two groups was found, after statistical analysis, to be not significant ($p = 0.64$; $t = 0.982$). Of all patients, only 14 (11.86%) had hypercalciuria, with no significant difference between groups (10 vs. 4, $p=0.76$).

We also calculated the ratios between the concentrations of the various urinary electrolytes. Thus, the ratio Na / K for the whole studied group was between 1.85 and 5.67, the average ratio being 2.9 (SD = +/- 1.28). In the group of patients with hypokaluria this ratio was between 1.95 and 5.67 with an average ratio of 3.14 (SD = +/- 1.38), and in group B it had values between 1.85 and 3 , 52 with a mean ratio of 2.41 (SD = +/- 0.82), the difference between the urinary Na / K ratios between the two groups being significant ($p = 0.001$; $t = -3.10$).

Regarding the ratio between urinary potassium and urinary calcium, we noticed that in group A it was between 1.31 and 93.14 with an average ratio of 13.25 (SD = +/- 16.66). In group B it was between 1.21 and 312, the average of the reports being 31.83 (SD = +/- 63.38) (Fig. 2.19). Following the statistical analysis we found that this difference between reports was also statistically significant ($p = 0.009$; $t = 2.38$).

The ratio of the main urinary ions with magnesium antagonist role - known as crystallogenesis inhibitor and urinary calcium - the main constituent of most calculations was in group A between 0.51 and 11.4 with a mean of 1.70 (SD = +/ - 2.01), and in group B between 0.2 and 13.18 with an average ratio of 1.57 (SD = +/- 2.00), the difference between groups being not statistically significant ($p = 0.36$; $t = 0.34$) (Fig. 2.20).

The ratio between the main ions favoring the occurrence of sodium / calcium renal lithiasis was in group A between 5.6 and 224, the average ratio being 37.99 (SD = +/- 46.88), and in group B between 2, 72 and 586 with a mean of 58.85 (SD = 91.25). From a statistical point of view, this difference is significant ($p = 0.0084$; $t = 1.38$).

We also evaluated the ratio of urinary potassium to urinary magnesium. Thus in group A between 2.21 and 22 with an average of 8.53 (SD = +/- 5.76), and in group B between 4.5 and 29.60 with an average ratio of 16.11 (SD = +/- 11.55), the difference between groups being statistically significant ($p = 0.00001$; $t = 4.69$).

The ratio between urinary phosphorus and magnesium had values in group A between 6.8 and 27.2; the average ratio was 6.34 (SD = +/- 3.93), and in group B between 1.4 and 23, the average value was 7.61 (SD = +/- 3.92). The difference in this case between the groups was significant ($p = 0.049$; $t = -1.66$).

Estimated salt intake (sodium chloride) in patients with hypopotassuria was between 1.27 and 15.02 g / 24 hours, mean value was 6.92 g / 24 hours (SD = +/- 3.3), and in group B between 3.67 and 18.88 g / 24 hours, the mean value was 9.66 g / 24 hours (SD = +/- 4.29). The difference between the groups was significant ($p=0.00011$; $t = 3.81$).

The FTIR spectroscopic analysis of the stones was also performed in conjunction with the 24-hour urine analysis in 14 patients. Given that the chemical composition of the core of calculation is often different from that of the outer shell, and this is complex, as shown in the figures below, we have considered the predominant substances.

The chemical composition of the calculations of the patients undergoing FTIR spectroscopy was very heterogeneous, as shown in the figure below. Of the 14 patients (8 women and 6 men), 5 (35.71%) patients had hypopotassuria.

The 24-hour urine sodium was found in those with hypopotasiuria between 44 and 88 mmol / l, the average being 65.2 mmol / l (SD = +/- 27.55 mmol / l), and in the other group between 24 and 163 mmol / l with an average of 116 mmol / l (SD = +/- 41.60 mmol / l). The difference between the values of urinary sodium between the two groups was found, after statistical analysis, to be significant (p = 0.015; t = -2,42814).

Calciuria, one of the "main characters" of lithogenesis, had in patients with hypopotassuria in which to perform the spectroscopic analysis of the calculation values between 4.6 and 11.53 mmol / l the average being 9.49 mmol / l (SD = +/- 4.19 mmol / l), and in others between 7.5 and 14 mmol / l with an average of 8.24 mmol / l (SD = +/- 3.14 mmol / l). The difference between the values of the urinary sodium between the two groups was found, after the statistical analysis, to be not significant (p = 0.28). Urinary magnesium, in patients with hypopotassuria, performed spectroscopic analysis of the calculation between 3.4 and 16.4 mmol / l mean 7.34 mmol / l (SD = +/- 2.89 mmol / l), and in others between 2.23 and 7.34 mmol / l with an average of 5.7 mmol / l (SD = +/- 1.94 mmol / l). The difference between the values of the urinary sodium between the two groups was proved, after the statistical analysis, to be not significant ($p = 0.211$). A similar thing I noticed also regarding the average value of the urinary pH which had values of 5.8 and 5.88 respectively, the difference being significant in terms of statistical deviation ($p = 0.43$). Surprisingly, despite the small sublot, there were significant differences in natriuria. Thus, 24-hour urine sodium was included in patients with hypopotassuria in whom the spectroscopic analysis of the calculation between 28 and 88 mmol / l was performed, the average being 65.2 mmol / l (SD = +/- 27.23 mmol / l), and in the other group between 24 and 163 mmol / l with an average of 116 mmol / l (SD = +/- 27.53 mmol/l). The difference between the values of urinary sodium between the two groups was found, after statistical analysis, to be significant ($p = 0.015$; $t = 2.42814$). Another element that was significantly different between the two sublots was chloride. It had values between 33 and 84 mmol / l with an average of 61.6 mmol / l (SD = +/- 28.07 mmol / l), respectively 87 and 181 mmol / l with an average of 61.6 mmol / l (SD = +/- 28.07 mmol / l). The difference was statistically significant ($p = 0.022$; $t = -2,24097$). Although the number of patients in whom the spectroscopic analysis of the calculation composition could be performed was too small to be statistically correlated with the 24-hour urine composition, however, we found that there were frequently significant differences between the chemical composition of the nucleus and that of the outer layer. This makes us think that, at least in the case of lithiasis patients in northeastern Romania, a single 24-hour urine analysis may not be sufficient for a correct and complete metabolic evaluation.

Discussion

Although enrolled patients have a history of at least one lithiasis episode, we noted that they do not take into account the main recommendation for prophylaxis of lithiasis: increased fluid intake. The subjects in our study had a daily diuresis of between 400 and 3400 ml, the average volume being 1654.69 ml (+/- 612.22ml). In patients with hypopotasiuria, it was between 550 and 3400 ml, with an average volume of 1783.37 ml (+/- 583.78 ml). In the other group we found a urinary volume between 400 and 3250 ml, the average volume being 1422.43 ml (+/- 590.62 ml). On the other hand, it seems that a diuresis below that recommended is a relatively common change in lithiasis patients. Thus Jawalekar *et al*. noticed an average urinary volume of 1671 ± 646 ml / 24 hours and Amaro *et al*. reported an average urinary volume of 1475.35 (+/- 559.31) ml / day in men and 1471.99 (+/- 560.01) ml / day in women. Therefore Chandhoke *et al.* estimates that 62% of patients with lithiasis have a urinary volume below 2000 ml / day [76].

Although hypercalciuria is considered by many authors to be one of the major changes in the composition of 24-hour urine, this was not valid in our group. Its incidence in litiatic patients according to literature data varies widely, Chandhoke *et al.* encountered it in 65% of the cases, in the patients of Wu *et al.* in only 26%. In our group the incidence was even lower, of all patients only 14 (11.86%) had hypercalciuria, without significant difference between groups (10 vs. 4, p = 0.76) [82,168]. This aspect leads us to believe that hypercalciuria is not the main cause of the formation of calculations in young patients in the northeastern part of Romania.

In our patients, magnesium had values between 0.92 and 9.5 mmol / l mean 3.40 mmol / l (SD = +/- 1.77 mmol / l) in group A, and in group B between 0 , 73 and 8.9 mmol / l with a mean of 3.83 mmol / l (SD = +/- 1.34 mmol / l). These values are comparable to those reported by other authors. Thus the patients of Wu *et al*. had an average magnesium magnification of 3.29 +/- 2.67 mmol / l and in the case of Jawalekar *et al*. 3.82 +/- 1.3 mmol / l [168,190]. Although there were no patients with hypomagnesuria in our group, this change has a very variable incidence. Wu *et al.* they reached it in only 11.8% of patients with CaP lithiasis, while Hussein *et al.* showed it in 59.3% of the patients with lithiasis [168,191].

In our patients, natriuria was on average 67.42 mmol/l in those in group A, significantly lower ($p < 0.05$) compared to those with normo/hyperpotasiuria, whose average was 118.65 mmol/l. This can be explained by the fact that those with hypopotassuria had a significantly lower salt consumption (6.92 +/- 3.3 g/day vs. 9.66 +/- 4.29 g/day; $p=0.00011$). Although from the data obtained by us, the young patients from the northeastern part of Romania have a lower salt intake than the one reported by the European Commission, it should be mentioned that even so the salt consumption is much higher than the one recommended by the Organization. World Health of up to 2 grams per day [152].

Sriboonlue *et al.* were among the first to associate hypopotasiuria with renal lithiasis [197]. The results of the authors are similar to ours, considering that almost

65% of patients had urinary potassium values below normal, with potassium being on average 22.51 mmol/l (SD = +/- 6.11 mmol / l).

According to Hesse *et al.,* in patients with calcium oxalate lithiasis, in the urine for 24 hours we should have hypercalciuria (≥8mmol/24h), hyperoxaluria (≥0.5 mmol/24h), hyperuricosuria (≥4 mmol/24h), hypocitraturia (≤2.5 mmol/24h) and hypomagnesuria (≤3 mmol/24h). Usually the urinary pH should be above 6, if the urinary pH value is below 5.8, the existence of renal tubular acidosis should be suspected. In patients with hyperuricosis (≥4.0 mmol/24h or 672 mg/24h) and with a constant urinary pH below 6 we should suspect the presence of uric lithiasis. According to the authors, calcium phosphate lithiasis is suggested by the presence of hypercalciuria, hyperphosphaturia (≥35 mmol/24h), hypocitraturia and a urinary pH above 6.8. When the calculations are obstructive, 24-hour urine should show hyperammonuria (≥50 mmol/24h), hyperphosphaturia and pH> 7 [215].

Conclusions

Urinary lithiasis is a disease with an increasing incidence and prevalence not only in Romania but throughout the world and has a high potential for recurrence. Due to this aspect, affecting young individuals leads to significant expenditures on the part of the medical systems but it also has indirect economic consequences because it can make people unfit for work. Moreover, the suffering endured by the patient from the renal colic to the secondary one of the endourological interventions is difficult to quantify but not neglected. In this light, all young lithiasis patients should benefit from metabolic evaluation as a first step in initiating prophylaxis and metaphylaxis of urinary lithiasis.

This paper has highlighted the following aspects in young litiatic patients:

- Hypopotasiuria is a peculiarity of young litiatic patients from northeastern Romania.
- Hypoplasiasuria is accompanied by significant changes in the ratios between the urinary concentrations of ions such as phosphorus/magnesium, sodium/calcium, potassium/calcium or potassium /magnesium, without the etiopathogenic mechanism of these changes being yet elucidated.
- Although they have been through a liturgical episode, the young people from the northeastern part of Romania seem to disregard the recommendation to have a lucid contribution that would bring a diuresis of over 2000 ml.
- The 24-hour urine analysis in conjunction with the spectroscopic analysis of the calculations could open new perspectives for clarifying the etiopathogenesis of urinary lithiasis and consequently the adoption of individualized prophylaxis and metaphylaxis measures.

In summary:

- hypokaliuria is an alarm signal

- the questionnaire - informational and educational factor
- the treatment of urinary lithiasis should be customized in relation to the 24-hour urine changes and the chemical composition of the calculation.

References

76. Chandhoke PS. When is medical prophylaxis cost-effective for recurrent calcium stones? *J Urol.* 2002 ;168(3):937-40.
82. Chandhoke PS. Evaluation of the recurrent stone former. *Urol Clin North Am*. 2007;34(3):315-22.
152. EU Salt Reduction Framework disponibil pe: https://ec.europa.eu/health/sites/health/files/nutrition_physical_activity/docs/salt_report1_en.pdf
168. Wu W, Yang D, Tiselius HG, et al. The characteristics of the stone and urine composition in Chinese stone formers: primary report of a single-center results. *Urology*. 2014;83(4):732-7.
191. Hussein NS, Sadiq SM, Kamaliah MD, et al. Twenty-four-hour urine constituents in stone formers: a study from the northeast part of Peninsular Malaysia. *Saudi J Kidney Dis Transpl.* 2013;24(3):630-7.
197. Sriboonlue P, Prasongwattana V, Tungsanga K, et al. Blood and urinary aggregator and inhibitor composition in controls and renal-stone patients from northeastern Thailand. *Nephron.* 1991;59(4):591-6
215. Hesse A, Tiselius HG, Jahnen A. Urinary stones diagnosis, treatment, and prevention of recurrence. S. Karger; 3rd, revised and enlarged edition edition (August 4, 2009)