

# Urolithiasis in adults

## Clinical and biochemical aspects

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### ABSTRACT

Urolithiasis is a multifactorial recurrent disease of world-wide distribution in rural, urban, industrial and non-industrial regions. Changes in urinary pH is a risk factor especially with hyperuricosuria, hypercalciuria or hyperoxaluria. With recurrence, hypercalciuria and higher urinary oxalate levels are more frequent. Hypercalciuria and hyperuricosuria showed correlation with family history of stones. The ionic relations between various stone forming salts in urine of patients are opposite to that in controls and are well represented in stone composition. Obesity is a risk factor in both genders. Over eating a diet rich in all nutrients was associated with hyperuricosuria while a diet high only in fat was associated with other urinary disturbances. High protein and fat intake are risk factors. High or low calcium diet was associated with urolithiasis and supplemental calcium is not a risk factor. Potassium and magnesium citrate are potent in inhibiting the growth of stone fragments after extracorporeal shock wave lithotripsy. Whether in patients or normal subjects, drinking hard water should be avoided; tap water or low calcium content water is preferable. Seasonal variations in temperature affected urinary volume, pH and relative saturation of uric acid. To prevent recurrence, patients should maintain high fluid intake achieving a urine volume of 2 liters per day.

Saudi Med J 2005; Vol. 26 (5): 705-713

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**C**linical aspect. Urolithiasis in adults is a rapidly increasing universal problem which has an important effect on the health care system and leads to a high economic impact reaching up to \$1.83 billion a year in the United States.<sup>1</sup>

**1. Incidence.** According to hospital statistics, urolithiasis in adults is the most common urological problem in different regions worldwide.<sup>2-12</sup> However, in any community, especially screening a population<sup>13</sup> and studies of well-defined samples of unselected population<sup>14</sup> are of major importance for the proper identification of prevalence and regional variation in the incidence of stones with its possible etiological implications. Therefore, urolithiasis certainly reached epidemic proportions in Western Europe and North American as the early available population studies,<sup>15-19</sup> revealed much higher figures

of stone incidence than what has been generally appreciated, as 25% of all stone formers in 17,000 individuals had never been admitted for hospital care.<sup>15</sup> Furthermore, in clinico-epidemiological studies, the crude prevalence rate in a rural Caribbean region was similar to that estimated worldwide,<sup>20</sup> while in Saudi Arabia,<sup>21</sup> it was either close to<sup>9,22,23</sup> or even higher than<sup>20,24,25</sup> current reports. Therefore, the prevalence of urolithiasis seems to be correlated to factors other than industrial development.<sup>26</sup>

**2. Age, sex and pattern.** According to hospital statistics, in Saudi Arabia,<sup>4,9,27-30</sup> Abu-Dhabi,<sup>10</sup> Sudan,<sup>31</sup> Southern Iraq,<sup>32</sup> Jordan<sup>33</sup> and Tanzania,<sup>12</sup> the peak age of presentation (22-44 years), male preponderance (3.9-5:1) and the pattern of the disease in children and adults is in accordance with

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the current data.<sup>34-39</sup> Meanwhile, in the current epidemiological studies,<sup>15,16,21,24,40-43</sup> the male preponderance ratio was close to previous hospital statistics, while the results of univariate analysis for age<sup>21,24</sup> showed a continuous increase in the age specific prevalence rates with a peak at the age group 55-64 years and the risk of having stone disease in the age group 25-35 become more than double (2.6:1).<sup>21</sup> Alternatively, the male to female ratio was lower than that reported previously in; Leeds, Melbourne, Sydney, South Carolina, Singapore, Portugal, Uppsala and Osaka.<sup>44-51</sup> Thus denoting higher prevalence rate of urolithiasis in the females of these regions.

**Biochemical aspect.** The likelihood of an individual to form a urinary calculus may be predicted from the following risk factors; 24 hour urinary pH, amount of calcium (Ca), oxalate and uric acid excreted and level of urinary inhibitors,<sup>52</sup> in addition to the possible role of diet, drinking water and seasonal variations on the previous risk factors.

**1. Urinary pH.** In controls, the 24 hour urinary pH is higher than patients with urolithiasis<sup>21,53,54</sup> though the difference may be insignificant.<sup>55,56</sup> Therefore, low urinary pH is considered as a risk factor,<sup>52</sup> particularly below the dissociation constant of uric acid (5.48). It is a major factor in uric acid lithiasis as because the urine is considered in a state of supersaturation with uric acid,<sup>57</sup> in addition to being below the increase of the inhibition index for Ca oxalate crystal growth.<sup>58</sup> Accordingly, precipitation of uric acid becomes a function of pH rather than concentration.<sup>59</sup> Therefore, in gouty diathesis (uric acid stone formation in primary gout), the 24 hour urinary pH is less than 5.5 (5.38±0.31) and the uric acid content is within the normal range of 750 mg/day in women and 800 mg/day in men.<sup>60</sup> Alternatively, at higher pH values (>5.5), the urine is in a state of fairly constant urinary inhibition and mean while at the lower range of the inhibition index for Ca oxalate crystal growth.<sup>58</sup> Therefore, in hyperuricosuric Ca oxalate urolithiasis the 24 hour urinary pH (6.09±0.36) is higher than that in gouty diathesis and the urinary uric acid level is high.<sup>60</sup> Meanwhile, in the siblings (sisters) of Ca stone formers, urinary pH (usually higher, 6.31±0.55 versus 5.98±0.48,  $p=0.01$ ) is one of the reasonable identifiers of those who are at risk of stone formation.<sup>61</sup> However, in controls, a low 24 hour urinary pH of 5.2 was reported.<sup>21</sup> Therefore, as urolithiasis is a multifactorial process with many unknown aspects, the change in urinary pH is a risk factor in the presence of other urinary disturbances.

**2. Hypercalcaemia.** Hypercalcaemia is considered when the 24 hour urinary Ca content is above the upper limit of normal which is 300 mg in males and

250 mg in females.<sup>21,62-64</sup> Meanwhile, a lower upper limit of normal was also stated.<sup>65</sup> Hypercalcaemia is a multifactorial metabolic abnormality frequently found in patients with urolithiasis and a strong correlation between hypercalcaemia and predominantly Ca oxalate dihydrate stones was reported.<sup>66</sup> Meanwhile, 3 types of hypercalcaemia have been recognized and each is associated with Ca nephrolithiasis,<sup>60,63,67,68</sup> as the relative risk of stone formation increased with increasing urine Ca level and concentration.<sup>61,69</sup> Therefore, in patients with stone recurrence, strong enhancement of Ca excretion,<sup>70</sup> and hypercalcaemia is markedly more frequent than in first stone formers.<sup>71</sup> It is reported that more than half of both men and women with recurrent stone formation have hypercalcaemia.<sup>68</sup> In Saudi Arabia and Abu-Dhabi, hypercalcaemia accounts for 9-29% of patients with urolithiasis.<sup>7,10,21,63</sup> However, a higher percentage than that and up to 81% of patients with urolithiasis is stated in current western reports.<sup>14,54,64,69,72-75,80</sup> However, in controls, hypercalcaemia is less commonly reported and at a lower relative frequency percent than in patients.<sup>21,54,69</sup> Therefore, it seems that hypercalcaemia is a risk factor in the presence of other urinary disturbances<sup>21,76</sup> as change in urinary pH,<sup>60,61</sup> low urinary volume as a specific abnormality<sup>68</sup> or hyperuricosuria.<sup>60</sup>

**3. Hyperuricosuria.** Hyperuricosuria is considered when the 24 hour urinary uric acid content is 5000 μmol or more<sup>21,62</sup> and a lower level was also reported.<sup>63,77</sup> More frequently, uric acid is evaluated in mg and hyperuricosuria then will be considered when the 24 hour urinary uric acid content exceeds 800 mg in men and 750 mg in women.<sup>60</sup> In patients with urolithiasis, hyperuricosuria is the second metabolic urinary disturbance after hypercalcaemia.<sup>75</sup> Therefore, it is frequently reported in these patients.<sup>7,21,54,56,60,63,71</sup> Meanwhile, in patients with uric acid lithiasis, uric acid concentration and 12 hour urinary excretion were found to be significantly greater in patients than controls.<sup>56</sup> However, unlike Ca, there was no difference in the urinary uric acid excretion between first and recurrent stone formers.<sup>56,70,71</sup> Alternatively, hyperuricosuria is one of the biochemical presentations which differentiate between gouty diathesis (uric acid stones in primary gout) and hyperuricosuric Ca oxalate urolithiasis.<sup>60</sup> Furthermore, it is one of the most common medical diagnoses predicted by stone composition (specially non-calcareous stones) which has some predictive value in diagnosing the underlying medical condition.<sup>78</sup> However, in controls, hyperuricosuria was reported only in Saudi Arabia<sup>21,63</sup> where the mean 24 hour urinary uric acid content was higher than that reported for controls or patients with urolithiasis in some current reports.<sup>53,55,79-81</sup> Therefore, hyperuricosuria seems a high risk factor

for urolithiasis in the presence of other urinary disturbances as hypercalcaemia and higher urinary pH.<sup>60</sup>

**4. Hyperoxaluria.** Hyperoxaluria is considered when the 24 hour urinary oxalate content exceeds the upper limit of normal which is 40 mg.<sup>21,64</sup> Also an upper limit of normal higher<sup>82</sup> or lower<sup>60</sup> than that was considered. Idiopathic Ca oxalate urolithiasis is a frequent and recurrent multifactorial disease. In patients with Ca oxalate stones (monohydrate or mixed mono and dihydrate), hyperoxaluria in 24 hour urine was the most common abnormality after hypocitraturia.<sup>71</sup> Furthermore, in patients with Ca nephrolithiasis oxaluria was frequently reported<sup>21,64,84</sup> and the mean 24 hour urinary oxalate content was either significantly higher<sup>21,54,71,79,80,84</sup> or similar;<sup>3,85</sup> to controls. Meanwhile, in recurrent stone formers, the difference between patients and controls in the 24 hour urinary oxalate content was even significantly greater ( $p=0.002$ ).<sup>86,70</sup> In addition, urinary oxalate has emerged as the most important determinant of Ca oxalate crystallization.<sup>86,87</sup> Furthermore, it is 23 times more potent than Ca in its effect on supersaturation of Ca oxalate.<sup>88</sup> Accordingly, the relative supersaturation of Ca oxalate increased significantly in patients with recurrence.<sup>70</sup> Therefore, in Ca nephrolithiasis, hyperoxaluria seems to play a more critical role than hypercalcaemia. On the other hand, in controls, hyperoxaluria was not frequently identified<sup>83,80,85</sup> and rarely reported.<sup>21,79</sup> In Saudi Arabia, in patients with urolithiasis the mean 24 hour urinary oxalate content was higher in males than females and in either patients or controls<sup>21,81,89</sup> it was higher than some current reports.<sup>53,72,79,82,90</sup> Therefore, this risk factor seems to be prevalent in Saudi Arabia where an overall probability of stone formation is 20%.<sup>91</sup>

**Some Ionic Correlations.** **A. Magnesium, calcium, potassium.** In controls, in the 24 hour urine, magnesium (Mg) shows prominent direct correlation with uric acid, oxalate and phosphate.<sup>21</sup> Meanwhile, Ca shows no correlation with Mg<sup>21</sup> and an obvious direct correlation with uric acid.<sup>21,85</sup> Thus leading to a low urinary Ca/Mg ratio in the controls.<sup>21,92</sup> Furthermore, in the controls, the 24 hour urinary potassium (K), shows direct correlation with phosphate, uric acid and Ca but not oxalate.<sup>21</sup> On the other hand, in patients with urolithiasis, the 24 hour urinary Ca shows prominent direct correlation with uric acid<sup>21,54,85</sup> and oxalate.<sup>21,93,94</sup> However, phosphate show prominent correlation with Mg more than Ca.<sup>21</sup> Thus leading to an increase in the Ca/Mg ratio in these patients<sup>92</sup> especially in those with hyperoxaluria, hyperuricosuria, or both.<sup>21</sup> In addition, the direct correlations between Ca and oxalate in the 24 hour urine of stone formers is well represented in the Ca stone composition.<sup>21</sup> Meanwhile, it may be attributed to the presence of malondialdehyde

(MDA, one of the urinary lipid peroxides) in the urine of patients which show correlations with both oxalate (significantly linear correlation) and Ca (negative linear correlation).<sup>84</sup> Furthermore, in patients with urolithiasis, the 24 hour urinary K shows more correlations with phosphates than oxalate or uric acid and no correlation with Ca.<sup>21</sup> Therefore, it was reported that the 24 hour urinary Mg level is lower in patients with urolithiasis than controls although the difference is statistically insignificant.<sup>61,71,84</sup> On the other hand, higher ranges of 24 hour urinary K, were reported in controls more than in patients with urolithiasis.<sup>21</sup> In addition, after extracorporeal shock wave lithotripsy (ESWL), the mean 24 hour urinary K was lower in patients with stone growth than in those without stone growth.<sup>95</sup>

**B. Uric acid, oxalate, phosphate.** In controls, in the 24 hour urine, uric acid shows a direct correlation with phosphate<sup>21</sup> and oxalate.<sup>21,85</sup> However, its correlation with phosphate is far more than that with oxalate. However, in patients with urolithiasis, the 24 hour urinary uric acid shows prominent direct correlation with oxalate far more than with phosphate. This correlation is presented in the uric acid stone composition by the presence of variable amounts of oxalate (<40%) and only trace amount of phosphate.<sup>21</sup> Meanwhile, in the 24 hour urine of stone formers, there is a mutual direct correlation between oxalate and phosphate.<sup>21</sup> This correlation is well presented in the composition of phosphate stones by the presence of variable amount of oxalate (<40%).<sup>21</sup>

**Correlations with family history of stones.** Family history of stones is frequently reported in patients with urolithiasis.<sup>21,48,49,50,54,61,96,97</sup> Therefore, it is denoted that a family history of stones substantially increases the risk of stone formation in their siblings.<sup>61,96</sup> Furthermore, patients with urolithiasis, hypercalcaemia and hyperuricosuria show prominent correlations with family history of stones.<sup>21,61</sup> Meanwhile, in the siblings of patients with Ca renal stones, hypercalcaemia is considered as one of the reasonable predictors for those who are at risk of stone formation in both genders.<sup>61</sup> In addition, in patients with urolithiasis and family history of stones, the incidence of recurrence is higher than in those without a family history of stones.<sup>21,27,50</sup> Therefore, family history of stones is considered as one of the 8 items in the stone recurrence predictive score.<sup>88</sup>

**5. Dietary factors.** The large geographical variation in the incidence of renal stone disease was correlated with social and economic conditions.<sup>90,99</sup> In Europe, North America, Australia, Japan and Saudi Arabia, affluence has spread to all social classes and people have tendency to eat a large quantity of rich food particularly the Saudi diet is

over rich in protein and fat.<sup>21,89</sup> Meanwhile, upper urinary tract stones are more frequent among affluent people with high animal protein consumption.<sup>91,99</sup> Furthermore, the risk of stone formation increased significantly with increasing body mass index among both men and women with urolithiasis.<sup>91,100-102</sup> Accordingly, the mean body mass index in patients with urolithiasis was significantly higher than that of controls.<sup>21,75,102,103</sup> Although in Japan obesity is a risk factor for stone formation only in males,<sup>102</sup> in Saudi Arabia, it is a risk factor more common in females than males.<sup>21</sup> Meanwhile, as the dietary and nutritional elements are important risk factors to the etiology of urinary calculi,<sup>104</sup> we will consider them as follows:

**A. Dietary animal protein.** In patients with urolithiasis, the mean daily intake of dietary animal protein was significantly higher than that in controls.<sup>21,54,75</sup> Less commonly, the difference in the mean protein intake between patients and controls is insignificant<sup>105</sup> and the mean protein intake in patients is low or even lower than that in controls.<sup>21</sup> Mostly the high intake of dietary animal protein was directly associated with the risk of stone formation.<sup>20,91,99,106,107</sup>

**B. Dietary fat.** In patients with urolithiasis, the mean daily intake of fat was significantly higher than that in controls.<sup>21,109</sup> Meanwhile, in patients, it is reported that the daily intake of fat was higher in men than women and the difference was statistically highly significant.<sup>108</sup>

**C. Energy.** In patients with urolithiasis, the mean of total daily intake of energy was commonly significantly higher,<sup>21,105</sup> less commonly lower than that of controls.<sup>21,79</sup> Furthermore, in young women, sucrose intake showed relative risk of stone formation.<sup>107,109</sup> In accordance with this, in animals, the deposition of Ca oxalate in the kidney was the greatest with sucrose, fructose, sorbitol and the least with glucose.<sup>110</sup>

**D. Dairy products and calcium supplements.**

The dietary Ca intake is inversely associated with the risk of kidney stones.<sup>96,106,107,109,111-114</sup> Meanwhile, there is no evidence of any rise in the risk of stone formation in relation to dietary Ca intake.<sup>91</sup> Accordingly, in patients with urolithiasis, the mean dietary Ca intake was commonly lower,<sup>21,54,75,105</sup> less commonly significantly higher than that of controls.<sup>21</sup> However, the intake of supplemental Ca was positively associated with risk of stone formation in women when consumed without meals.<sup>109</sup> Otherwise, in patients with urolithiasis, it is recommended in a daily dose of at least 800 mg/day to prevent negative Ca balance with bone mineral loss and the increased intestinal absorption of oxalate.<sup>96,107,113,114</sup> As the intestinal absorption of oxalate depended linearly on the Ca intake,<sup>112,113</sup> it is reported that Ca is the most effective in reducing the urinary excretion of oxalate.<sup>88,115</sup> However, rise in

urinary oxalate with drinking water high (370 mg) or low (<20 mg) in Ca content was observed in normal volunteers.<sup>116</sup> Meanwhile, univariate linear regression analysis revealed a non-significant association between dietary Ca and urinary oxalate in patients with urolithiasis of both genders.<sup>108</sup>

**E. Magnesium and potassium.** In patients with urolithiasis and hyperabsorptive hypercalciuria, oral supplementation of Mg is favorable as it decreases Ca absorption and increases Mg absorption which as an inhibitor reduces risk factors of the disease.<sup>117</sup> However, K intake was found to be inversely related to the risk of stone formation.<sup>106</sup> Meanwhile, multiple linear regression analysis demonstrated that for each 10 mmol decrease in dietetic K intake, there was a corresponding 0.2 mm increase in stone growth.<sup>93</sup>

**F. Vitamins.** It was found that, in both men and women, there are no correlations between the risk of stone formation and the intake vitamins B6 or C even when taken in large doses.<sup>118,119</sup>

**G. Dietary habits as risk factors.**

Hyperuricosuria and other multiple urinary disturbances were common in patients with the highest; body mass index, daily intake of protein, fat, energy, Ca, fibres and vitamins.<sup>21,120</sup> In accordance with this is the results of multiple linear regression analysis which revealed significant positive relationship between body mass index and uric acid, sodium, ammonium and phosphate excretion together with an inverse correlation with urinary pH in both gender and urinary excretion of Ca only in men and oxalate only in women.<sup>101</sup> However, hypercalciuria and urinary disturbances other than hyperuricosuria were common in patients with body mass index higher than that of controls but significantly lower than that of previously mentioned patients.<sup>21,114</sup> Meanwhile, their daily intake of protein, energy, fibres, Ca and vitamins were significantly lower than that of controls.<sup>21,114</sup> However, their daily intake of fat was significantly higher than that in controls.<sup>21</sup> Therefore, as partial regression analysis revealed a weak but statistically significant relation between fat intake and urinary uric acid only in women,<sup>108</sup> it is possible that dietary fat has a more important role in stone formation than has been previously recognized. Accordingly, quantitative as well as qualitative dietary modifications especially for Ca, animal protein, fat and minerals may play an important role in reducing the likelihood of recurrent stone formation.<sup>121</sup>

**6. Drinking water.** The possible correlation between the drinking water and prevalence of urolithiasis was considerably investigated.<sup>21,91,115,116,122-126</sup> There is no evidence of any rise in the risk of stone formation in relation to tap water hardness<sup>21,91</sup> and underground water in the Western Region of Saudi Arabia.<sup>21</sup> Meanwhile, drinking of soft water

alone or with an additional factor was associated with high prevalence of urolithiasis.<sup>21,122,123</sup> However, it was reported that in patients with urolithiasis, drinking soft water was not associated with any changes in the urinary parameters.<sup>125</sup> In addition, whether in patients with urolithiasis<sup>115,125</sup> or normal subjects<sup>116</sup> drinking bicarbonate alkaline water with a high content of Ca (370-380 mg/L) leads to an increase in the urinary Ca by 50% in patients<sup>124</sup> and approximately 80 mg/day in normal subjects.<sup>116</sup> Furthermore, in patients with urolithiasis, drinking mineral water with high sulphate and intermediate Ca content (123.9 mg/L)<sup>115</sup> or the replacement of one litre of the usual fluid intake with mineral water in normal subjects,<sup>126</sup> elevated the urinary Ca as well. Meanwhile, the presence of bicarbonate radicle in drinking water leads to an increase in the urinary citrate level whether in normal subjects or patients with urolithiasis.<sup>115,116,125</sup> In the former group the Ca/citrate ratio was constant<sup>116</sup> while in the latter it was increased.<sup>125</sup> In addition, drinking water with high or intermediate Ca content, raised urinary oxalate, increased osmolar excretion and significantly changed the urinary saturation in normal subjects<sup>116</sup> while in patients with urolithiasis, the urinary excretion of oxalate either remained unchanged<sup>125</sup> or significantly decreased with tendency of an increase in the urinary uric acid excretion.<sup>115</sup> However, drinking low Ca content water (<20 mg/L) in patients with urolithiasis no changes in any of the urinary parameters were observed,<sup>115</sup> while in normal subjects, a rise in urinary oxalate and significant decrease in urine osmolality were reported.<sup>116</sup> Accordingly, contrary to what was suggested,<sup>124</sup> there is a possible correlation between the drinking water types and prevalence of urolithiasis. Therefore, whether in patients with urolithiasis or normal subjects, drinking hard water should be avoided due to its effects on the urinary risk factors.<sup>115,116,125</sup> Meanwhile, in patients, for increasing urinary volume to prevent stone recurrence the use of low Ca content water or tap water is recommended.<sup>116,125</sup>

**7. Urinary inhibitors.** Since normal urine is supersaturated with various stone forming salts, it must contain potent inhibitors for controlling crystal formation, aggregation and subsequent stone formation.<sup>127</sup> These inhibitors are the low molecular weight molecules; Mg, K, citrate and the macromolecules; glycoproteins, glyco-saminoglycans (GAGs) and bikunin.

**A. Citrate, magnesium, potassium.** In the in-vitro experiments, Mg and citrate reduced the growth and nucleation kinetics as well as the supersaturation.<sup>88</sup> In combination, these 2 components were more effective in reducing the growth and supersaturation.<sup>88</sup> Meanwhile in patients with residual stone fragments after ESWL, K citrate therapy significantly alleviated Ca oxalate stone

activity and ameliorated the outcome of these fragments by decreasing its growth or agglomeration.<sup>128</sup> In addition, in patients with urolithiasis, treatment with K Mg citrate was efficiently potent in prophylaxis against recurrence of stone formation.<sup>129</sup> Accordingly, urinary citrate seems to provide an effective inhibitory activity to Ca oxalate crystallization, aggregation and agglomeration. Therefore, hypocitraturia was found in 88% of the first and 76% of the recurrent stone formers.<sup>71</sup> Meanwhile, in women, the frequency of hypocitraturia was significantly higher in recurrent than first stone-formers.<sup>68</sup> In patients with urolithiasis, the mean urinary citrate level in 24 hour urine is lower than that of controls and the difference is even greater in recurrent cases.<sup>21,68,71,84</sup> Furthermore, in patients with urolithiasis, urinary citrate level had no statistically significant correlations with urinary oxalate, Ca or the free radicle MDA, frequently present in the urine of patients.<sup>84</sup> Meanwhile, the citrate levels had significantly negative linear correlations with the tubular enzymes glutathione s-transferase (GST) and galactoside (GAL) found frequently in the urine of patients.<sup>84</sup>

**B. Mucopolysaccharides. i. Glycosaminoglycans.** The inhibitory role of the urinary glycoproteins and GAGs in Ca oxalate urolithiasis has been established.<sup>130</sup> Therefore, a subject with a mean GAG level of 29 µg/mg has a risk of nephrolithiasis about 1.47 times that of a subject with mean GAGs level of 36 µg/mg.<sup>56</sup> Accordingly, the mean GAGs level was significantly higher in controls than in patients with urolithiasis.<sup>21,56,131-133</sup> Meanwhile, the difference was even more prominent between controls and patients with urinary disturbances other than hyperuricosuria<sup>21,132</sup> as in patients with hyper-uricosuria levels of GAGs were significantly higher.<sup>21,133</sup> Therefore, a correlation between the urinary level of GAGs and dietary intake of protein was suggested.<sup>134,135</sup> In accordance with this, in patients with uric acid lithiasis, a statistically significant negative correlation between the uric acid concentration and GAG/creatinine level was observed.<sup>56</sup> ii Bikunin: Bikunin is a glycoprotein that has been shown in vitro, to be a potent inhibitor of Ca oxalate crystallization. In healthy individuals, its rate of excretion showed no regular diurnal variations and is not affected by age or sex. Its deglycosylated form is less inhibitory to Ca oxalate crystallization.<sup>130,136</sup> Meanwhile, correlation of bikunin levels with active stone disease is still a controversial matter.

**8. Seasonal variations.** Urolithiasis and renal colic showed seasonal variations reaching the maximum rate in the summer months of June, July and August.<sup>11,20,137-139</sup> This was correlated with the rise of temperature, increased physical activities and

sweating with subsequent dehydration.<sup>137,139,140</sup> Furthermore, in patients with urolithiasis, it is reported that urinary: volume, sodium and pH were significantly lower and the relative saturation of uric acid is higher during the summer (June, July, August) than winter (December, January, February).<sup>139,141</sup> These seasonal variations are risk factors for crystal precipitation and subsequent nephrolithiasis. Therefore, due to the close relation between dehydration,<sup>140</sup> urine volume and changes in pH,<sup>141</sup> patients with urolithiasis are always advised to increase their fluid intake to achieve urine volume of 2 liters per day.<sup>86,113,142</sup> as water intake is inversely related to the risk of stone formation.<sup>20,106</sup>

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