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WEIGHT GAIN AS A POTENTIAL RISK FACTOR IN KIDNEY STONES FORMERS

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ABSTRACT: *The prevalence of kidney stones is increasing and obesity has reaching epidemic proportions. The aim was to investigate whether obesity influences the kidney stone forming. 421 patients, 31.6% women and 41.6% men were overweight (OV), and 25% and 9.6% were obese (OB), respectively. Serum uric acid increased significantly OB women($p<0.001$), differences between gender($p<0.001$). Creatinine increased in OB men($p<0.05$), and men respect to women($p < 0.001$), urea between OB women and men($p<0.05$). PTH increased in OB women($p<0.05$). Urinary excretion phosphorus($p<0.05$), uric acid($p<0.01$) increased in OB women. Creatinine clearance was higher in OB both sexes($p<0.05$), and differences compared women to men($p<0.001$). BMI was positively correlated with serum uric acid, sodium, potassium and PTH in both sexes and urinary uric acid excretion, calcium, sodium, phosphate in women and oxalic acid in both sexes. Glomerular filtration rate, urine specific gravity and pH were inversely related to BMI. Uric acid is main stone constituent in obese women(86.36%) and overweight men(86.66%). In conclusion, higher body weight could be associated with an increased risk of renal stone forming and some metabolic gender differences were found.*

KEYWORDS: Nephrolithiasis, Obesity, Metabolic Studies, Uric Acid Stones

INTRODUCTION

Previous study suggests that the incidence and prevalence of kidney stones is increasing globally. These increases are seen across sex, race, and age. Reported about kidney stone disease affects one in 1000 American adults, the average prevalence for 1 year only was 5.14% in adult population from Buenos Aires Argentina (Romero et al., 2010).

Previous observations appear to suggest the existence of different lithogenic metabolic profiles in men and in women that could explain the different clinical presentations. There is a clinical predominance of urolithiasis in men compared to women (Johnson et al., 1979). Currently, the incidence of nephrolithiasis is rising especially in women according with increasing age (Frassetto and Kohlstadt, 2011). The pathogenic mechanism leading to this higher morbidity from urinary stone disease is still not fully understood.

Obesity is one of the main public health challenges the next years. Currently, the most of the population is overweight or obese. Over 300 million people are estimated to be obese in the world (DeMaria E.J., 2007). Obesity has reached epidemic proportions, 30-40% of adults being already obese and the incidence in children and adolescent is increasing (James P.T., 2004, Health, United States, 2010)

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The obesity has been reported in the general population 10% to 50%, the most acceptable standard definition used by World Health Organization (WHO) and IOTF, it is in terms of body mass index (BMI) (Cole et al., 2000, Deurenberg et al., 1991). BMI is a useful epidemiologic tool and it has been defined as a BMI normal-weight individuals ($18.5 \geq BMI < 25$), overweight individuals ($25 \geq BMI < 30$), obese greater than 30 kg/m^2, with extreme obesity defined as a BMI greater than 40 kg/m^2.

Recently, obesity is associated with a higher incidence of a number of diseases such as obesity, hypertension, hyperlipidemia, hypercholesterolemia, diabetes mellitus, cardiovascular disease and cancer (Taylor et al., 2005, Kuroczycka-Saniutycz et al., 2015). The prevalence and incidence of stone disease have been reported to be associated with body weight and BMI (Kuroczycka-Saniutycz et al., 2015, Curhan et al., 1998). Previous studies have identified metabolic differences associated with nephrolithiasis in obese patients (Powell et al., 2000)

Obesity is considered as a possibly cause for increasing nephrolithiasis, there is a temporal relationship between obesity epidemic and increase incidence of kidney stones. However, epidemiologic controversial data could be doubt about this relationship. Apparently, there is a metabolic predisposition in obese patients to development urinary stone disease. Therefore, we wanted to determine if obesity increase the metabolic risk to renal stone forming. Up to now, few studies reported metabolic alterations in urinary stone disease have taken gender into account.

The aims of this study were to investigate the lithogenic metabolic risk factors in adults with urolithiasis and to determine whether obesity influences the kidney stone forming in both sexes.

MATERIALS AND METHODS

The observational and cross-sectional retrospective study was undertaken. The data base utilized for this study represents data collection from a private Chemical Laboratory (San Luis, Argentine) dedicated to performing metabolic evaluations collected from outpatients. The population chosen for our study included patients with suspicion of urolithiasis who submitted outpatient 24-hour urine samples and questionnaires; no specific inclusion or exclusion criteria were used. Total metabolic variables were assessed in the data base, including serum and urine chemistries. A metabolic evaluation has been carried out on a total of 421 patients (2010-2013). The studied individuals included in the analysis had 20 years of age or older.

Body weight and height were measured and BMI was calculated. This is a measure derived from dividing body weight in kilograms by the square of height in meters. Body mass index (BMI) values were stratified as normal (BMI <25 kg/m^2), overweight (BMI 25–29.9 kg/m^2) or obese ($BMI \geq 30$ kg/m^2). Screening evaluation consisting of serum chemistries and urinalysis on a patient diagnosed with suspicion of kidney or urethral stones. Patients collected 24-hour urine samples and later were taken 2 hours. Patients with suspicion of renal stones and relatively high urinary calcium could be to limit milk products and sodium intake, and consume 1,000-1,200 mg per day of calcium during 7 days. Metabolic testing should consist of two 24-hour and 2 hours urine collections obtained on a restricted diet and

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analyzed at minimum for total volume, pH, calcium, oxalate, uric acid, citrate, sodium, potassium and creatinine. Serum parathyroid hormone (PTH) level was determined as part of the screening evaluation if primary hyperparathyroidism is suspected.

The patients were evaluated using the same standard protocol. The samples of 24-h urine were collected, stored and closed containers at 4°C until the chemistries measurements were conducted.

Serum creatinine concentration, calcium, magnesium, phosphorus, urea, uric acid were determined by Metrolab 4000 Analyzer Apparatus (Quality Control: Wiener y BioRad and PEEC-Fundación Bioquímica Argentina, matrícula D00001). Urine citrate concentrations were determined by an enzymatic method using a commercial system (Boehringer Mannheim/RBiopharm, Darmstadt, Germany). Urine oxalate levels were examined using standard Sigma enzymatic–spectrophotometer methodology (Spectrophotometer Metrolab 1600). Urinary pH was determined using a pH meter. PTH was determined using the PTH Kit (IRMA) and sodium and potassium by flame emission spectrometry (Metrolab 315). The estimated glomerular filtration rate (GFR) was calculated from MDRD equation: GFR (mL/min/1.73 m^2) $= 175 \times (S_{cr})^{-1.154} \times (Age)^{-0.203} \times$ (0.742 if female) × (1.212 if African American).

The data were analyzed using Statistical Package for the Social Sciences (SPSS) version 12.0 for Windows (SPSS Inc., Chicago, IL). Descriptive statistical, frequencies, linear regression, correlations coefficients with corresponding 95% confidence intervals (CI), Chi-squared test with Yates´ continuity correction and chi–squared for linear association were used. Differences among groups were evaluated using One-way Analysis of Variance (ANOVA) followed by Tukey-Kramer Multiple Comparisons Test (Statistical Package GraphPad 3.0, San Diego, CA, USA). Mean ± standard deviation were calculated and a probability value of <0.05 was considered to be statistically significant.

The protocol was approved by the Bioethics Committee of Faculty of Medical Sciences-National University Cuyo (CUDAP-EXP-FCM: 8995/2010) in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants.

RESULTS

A metabolic evaluation has been carried out on a total of 421 patients, 57 % women and 43 % men, with suspicion to be formers of renal stones. The mean age of the women was 44.73±13.73 years and the men 43.76±13.99 years, with a range of 20 to 75 years in both sexes. The frequency distribution of age in adult women and men are represented by histogram (Figure1A, B). The mean women weight was 64.63±13.15 kg and 85.83±14.69 kg in men. The frequency distribution of body weight is also represented by histogram in both sexes (Figure 1 C, D). Total BMI in women and men were 24.9 kg/m^2 and 28.2 kg/m^2 respectively. Overall, 58.0% of female and 25.9% of male stone formers were normal body weight, 31.6% of female and 41.6% of male stone formers were overweight, and 25% and 9.6% were obese, respectively.

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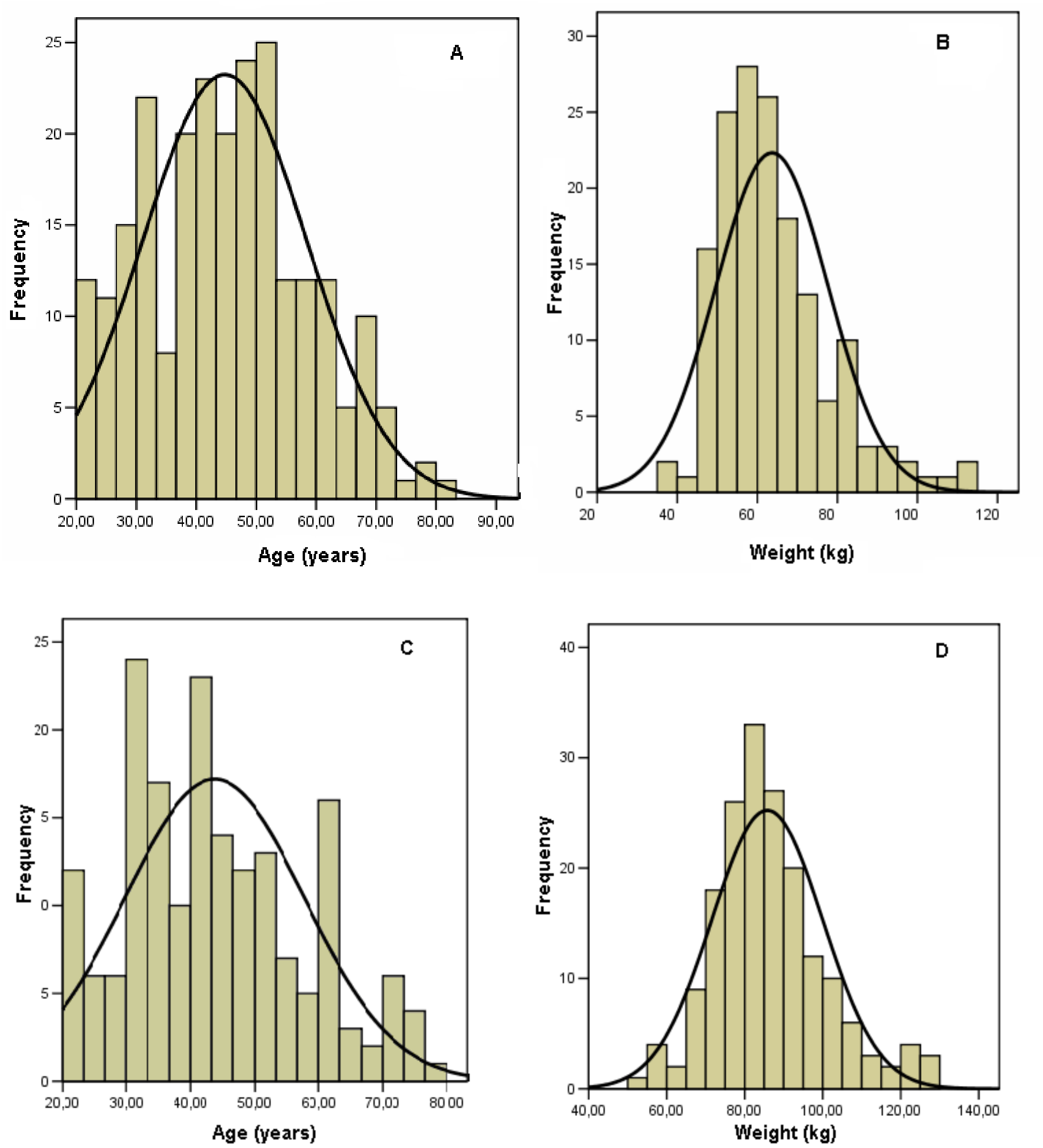

Figure 1. Representative frequency distribution age and weight in adult women and men studied population. A) Women age, B) Women weight, C) Men age, D) Men weight.

Screening evaluation consisting of serum chemistries are shown in Table 1. The subjects were classified as normal (N), overweight (OV) or obese (OB). The median serum uric acid concentration in the OB women patients was increasing significantly than N body weight ($p<0.001$), no statistically significant differences between N and OB men subgroups were found. Significant differences in serum uric acid concentration in N, OV and OB women patients respect to N, OV and OB men subgroups were found, respectively ($p<0.001$). Serum creatinine in OB men was significantly differences than N body weight ($p<0.05$) with no significant differences between women subgroups. Statistically significant differences in serum creatinine between N, OV, OB men and N, OV, OB women, respectively were registered ($p < 0.001$). No statistically significant differences between these subgroups in both sexes were found for serum chemistries of calcium, ionized calcium, phosphorus, urea,

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sodium, potassium and magnesium. Significant differences in urea between OB women and OB men was determined ($p<0.05$). Serum PTH levels have been shown increased from N to OB women patients ($p<0.01$), no statistically significant differences in men subgroups were registered.

TABLE 1. Mean serum chemistries stratified by body mass index groups in adult women and men.

	Women				Men			
	Normal	**Overweight**	**Obese**	**p Value**	**Normal**	**Overweight**	**Obese**	**p Value**
Calcium (mg/dl)	9.14±0.37	9.21±0.46	9.18±0.45	ns	9.09±0.86	9.20±0.44	9.21±0.41	ns
Calcium ionized (mg/dl)	4.93±0.15	4.93±0.17	4.95±0.14	ns	4.94±0.14	4.93±0.14	4.96±0.12	ns
Phosphorus (mg/dl)	3.43±0.60	3.33±0.65	3.34±0.70	ns	3.47±1.11	3.38±0.71	3.33±0.75	ns
Uric acid (mg/dl)	3.95±0.99	4.42±1.44	5.87±1.38	<0.001	5.73±1.49	6.04±1.42	6.70±1.78	ns
Urea (mg/dl)	28.14±9.88	30.35±16.53	29.42±14.65	ns	33.60±12.06	34.46±10.76	37.92±17.45	ns
Sodium (mmol/l)	137.89±3.01	138.82±3.39	138.14±2.42	ns	138.48±2.12	138.64±3.06	139.23±3.39	ns
Potassium (mmol/l)	3.84±0.29	3.92±0.31	3.91±0.28	ns	3.89±0.30	3.95±0.29	3.96±0.37	ns
Magnesium (mg/dl)	2.02±0.28	2.02±0.21	2.02±0.24	ns	2.02±0.22	2.00±0.40	1.89±0.47	ns
Creatinine (mg/dl)	0.83±0.21	0.86±0.22	0.87±0.25	ns	1.03±0.19	1.08±0.23	1.20±0.42	<0.05
PTH (ng/l)	37.98±25.72	47.96±29.49	63.04±42.20	<0.01	30.88±11.72	38.66±17.25	45.53±25.64	ns

Uric acid: N, OV, OB women vs N, OV, OB men, $p<0.001$ respectively
Creatinine: N, OV, OB women vs N, OV, OB men, $p<0.001$ respectively
Urea: OB women vs OB men , $p<0.05$
PTH= parathyroid hormone, OB women vs OB men, $p<0.01$

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TABLE 2. Mean 24-hour urine parameters by body mass index in adult women and men

	Women				Men			
	Normal	**Overweight**	**Obese**	**p Value**	**Normal**	**Overweight**	**Obese**	**p Value**
Calcium (mg)	193.8±94.8	213.0±96.6	216.5±126.6	ns	197.1±91.4	220.3±98.1	236.2±121.3	ns
Phophorus (mg)	428.0±229.2	625.1±269.1	599.6±243.7	<0.05	620.7±299.8	760.0±387.7	740.9±303.5	ns
Magnesium (mg)	89.3±64.6	84.0±40.3	83.6±33.9	ns	86.8±32.2	93.8±36.1	99.5±43.2	ns
Uric acid (mg)	413.0±146.1	486.9±209.0	548.9±193.2	<0.01	606.2±241.7	664.2±186.8	700.4±258.7	ns
Creatinine (mg)	1000.9±238.8	1048.9±234.4	1182.6±244.5	<0.05	1487.5±371.7	1686.8±330.7	1868.9±359.2	<0.01
Sodium (mEq)	107.7±60.1	143.8±74.9	148.8±83.6	<0.05	133.2±84.8	149.8±72.3	186.2±86.4	<0.05
Citrate (mg)	508.7±248.1	520.6±232.5	525.5±263.1	ns	460.6±225.2	490.7±254.9	457.6±289.7	ns
Oxalate (mg)	26.5±11.0	30.9±10.1	28.4±10.4	ns	27.0±9.1	29.1±10.3	29.7±10.3	ns
CrCl (ml/min)	85.77±21.60	89.31±23.87	98.62±27.02	<0.05	102.19±27.19	111.50±26.86	118.88±30.72	<0.05

Calcium: N, OV, OB women vs N, OV, OB men, p<0.001 respectively
Phosphorus: N women vs N men p<0.01; OV women vs OV men p<0.001
Uric acid: N, OV, OB women vs N, OV,OB men p<0.001
Creatinine: N, OV, OB women vs N, OV, OB men p<0.001
Creatinine Clearance (CrCl): N women vs N men p<0.01; OV, OB women vs OV, OB men p<0.001

Screening urine chemistries showed increases in the urinary excretion of solutes in obese patients (Table 2). Obese women patients had increased significantly urinary excretion of phosphorus (p<0.05), uric acid (p<0.01), creatinine (p<0.05) and sodium (p<0.05). Obese men had increased concentration of urinary sodium (p<0.01) and creatinine (p<0.05). Mean calcium, citrate and oxalate excretion was higher in obese women patients than normal body weight, no significant differences were found. Calcium, phosphate, magnesium, uric acid and oxalate increased no significantly in obese men. Magnesium in obese women and citrate in obese men decreased no significantly. In the 24-hour urine sample, mean creatinine clearance was higher significantly in patients obese than normal weight in both sexes (p<0.05). OB, OV and N women patients had increased significantly of creatinine clearance compared with the OB, OV and N men patients, respectively (p<0.001).

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The correlation analyses of BMI with clinical parameters revealed that the BMI was positively correlated with serum uric acid (women: $r = 0.33$, $p < 0.0001$; men: $r= 0.32$, $p<0.0001$), sodium (women: $r= 0.15$, $p<0.01$; men: $r= 0.17$, $p<0.01$) and potassium (women: $r= 0.15$, $p<0.01$; men: $r= 0.15$, $p<0.02$). The degree of obesity showed a positive correlation with serum PTH in both sexes (women: $r= 0.29$, $p<0.0002$; men: $r= 0.30$, $p<0.0008$), data shown in Figure 2.

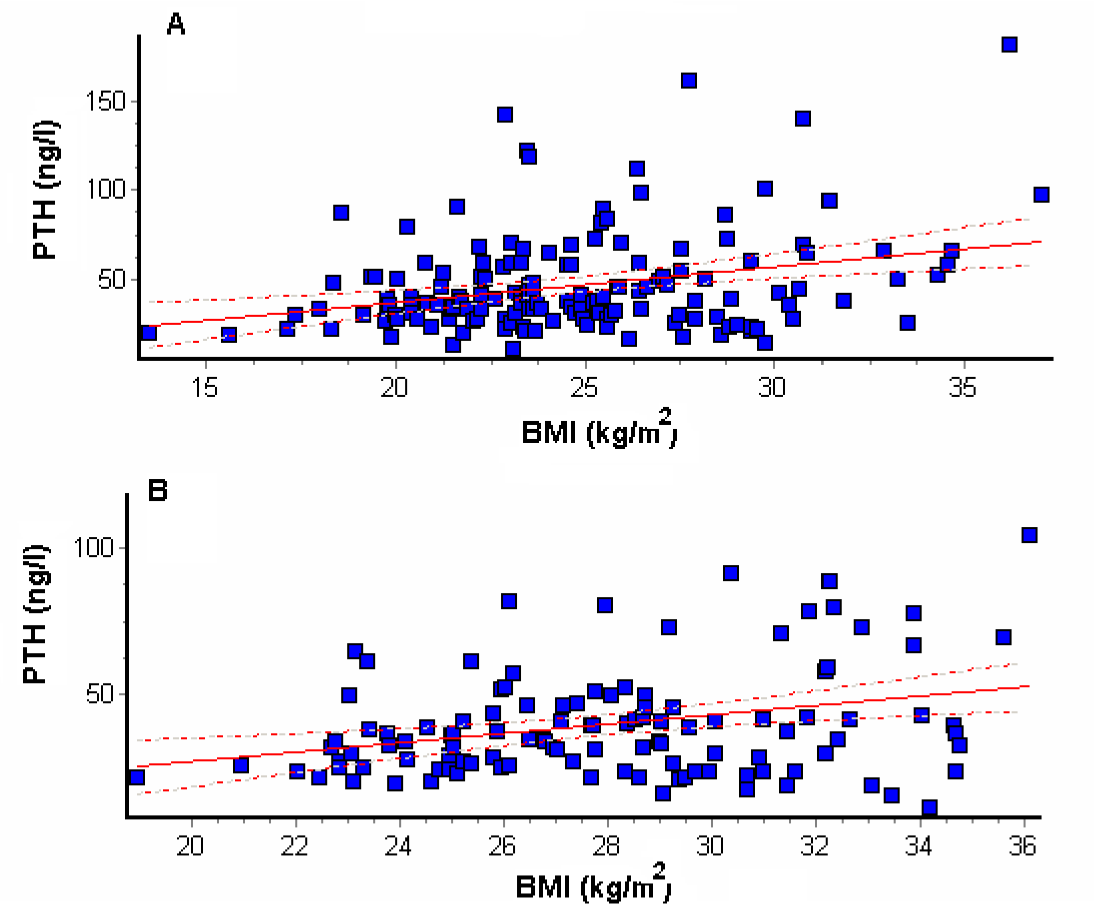

Figure 2. Relationship between BMI and PTH in both sexes. The degree of obesity showed a positive correlation with serum PTH. A) Women: *r= 0.29, p<0.0002*; B) Men: *r= 0.30, p<0.0008*.

We investigated associations of BMI with urinary excretion of solutes in women and men subjects. There was a significant positive association between BMI and uric acid (women: $r= 0.40$, $p<0.0001$; men: $r= 0.64$, $p<0.0001$), calcium (women: $r= 0.19$; $p<0.002$; men: $r=0.16$, $p<0.02$), sodium (women: $r= 0.28$, $p<0.0001$; men: $r= 0.27$, $p<0.0004$). Significant positive association phosphate in women ($r= 0.17$, $p<0.009$) was found. Body weight was positively correlated with oxalic acid (women: $r= 0.19$, $p<0.003$, men: $r=0.14$, $p<0.05$). However, we found that urinary pH was inversely related to BMI, more obese people have lower urinary pH values in women and men.

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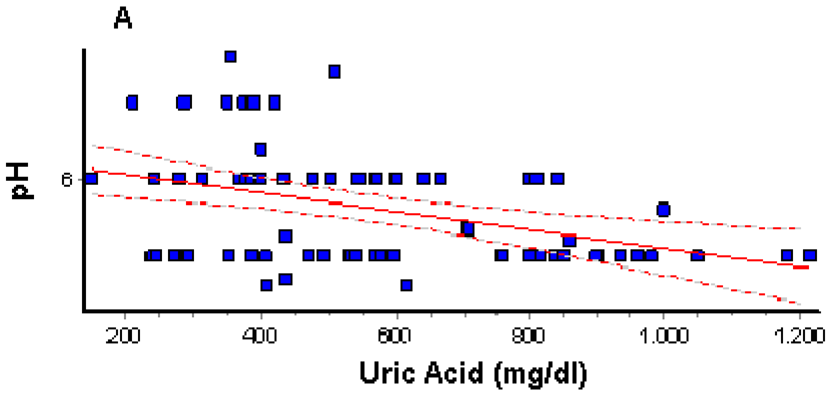

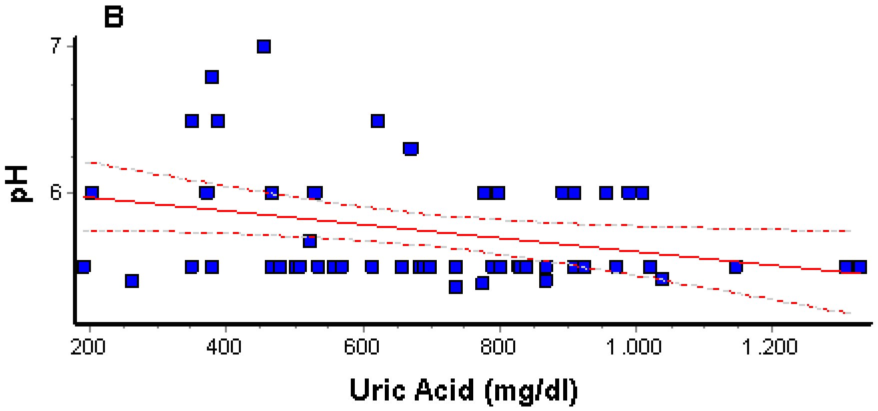

Figure 3. Relationship between uric acid and pH in obese patients. Inverse correlation between uric acid and pH urinary in obese women and men. A) OB women: *r=-0.32, p<0.01*, B) OB men: *r=-0.30, p<0.02.*

Progressive decreased in pH while serum uric acid levels were increasing in OV (*r=-0.24, p<0.05) and* OB (*r=-0.32, p<0.01)* women were found, and also in OB men (*r= -0.30, p<0.02*) (Figure 3). The association of glomerular filtration rate (GFR) in both sexes with BMI were studied, there was an inverse association (women: *r*=-0.45, *p*<0.0001, men: *r= -0.20, p<0.006*). We also analyzed the relationship between BMI and urinary volume, we found significantly positive correlations in both sexes (women: *r=0.13, p<0.03*; men: *r= 0.14*

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p<*0.04*). Therefore, we also found that the BMI was negatively correlated with urine specific gravity in women ($r=-0.24$, $p<0.0002$) and men ($r=-0.15$, $p<0.04$). The urine specific gravity results above 1.010 could be indicating mild dehydration. More obese people have lower urinary density values.

There were no significant correlations between the BMI and others metabolites urinary lithogenic risk profile. No relevant changes in others serum and urinary chemistries parameters were found.

Uric acid is much more commonly encountered as a stone constituent among our patients. There is a clinical predominance of uric acid stone forming in obese women (86.36%) and overweight men (86.66%).The composition of stone-patients forming shown a higher percentage of calcium oxalate stones, we could be explain that increasing uric acid crystallization possibly leading to increased risk to promote heterogeneous nucleation of calcium oxalate in body weight gain individuals.

DISCUSSION

As most patients with stone disease have identifiable risk factors, it is worthwhile to evaluate for underlying causes of stone formation. One of the major problems with kidney stones is the high rate of recurrence after an initial stone. In the present study a comparison has been made of the metabolic profiles in men and women in order to identify possibly significant differences as well as the identification of specific metabolic derangements that may be contributing to risk. Little information is available on the metabolic changes found in relation to gender in patients with nephrolithiasis. The metabolic evaluation, led us to investigate of metabolites in serum and urine with renal stone-forming; it requires a several number of biochemical analyses in blood and urine. The obese individuals have a tendency to form urinary stones because of metabolic factors have been modifying according to body weight increased. The present study suggests that the weight gain affects 51.8% the adult population with prevalent percentage of adult men. Proportionally higher percentage of overweight and obese men was found respect to the women population. Obese men were on average 10 years younger stone forming respect to the women. Women are also impacted by weight gain. Obese women did show a slightly increased incidence of parameters studied of renal stone forming. This incidence may be due to the increased mean age, more frequency distribution at postmenopausal period and parallel increased the body weight. Hormonal changes and postmenopausal status, differences in sex-specific life expectancy could be contributed to this phenomenon, and the women were more inclined to agree to a metabolic evaluation.

The serum and urinary electrolytes in obese stone formers differ from their nonobese.

Evaluation of serum chemistries showed that obese women stone-forming patients had significantly higher uric acid and PTH when compared to normal body weight. The PTH have tendency to increase in obese women and there are significant differences between sexes. Serum PTH levels have been shown to be elevated in morbidly obese patients (Hjelmesaeth et al., 2009). Epidemiological study demonstrate that a significant positive relation between serum PTH and BMI (Kamycheva et al. 2004, Snijder et al. 2005, Moreiro et al., 2007).This finding would support the theory that the elevated PTH in obese women

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patients could be related with renal health problem. Information concerning their hormonal levels and menopausal status are unknown, and definitive conclusions cannot be made.

Significant differences we observed in obese men in serum creatinine, but not significant differences in women. The calcium, urea, sodium and potassium increased not significantly in obese women and men, the serum magnesium were within the range of the normal values in women and decreased not significantly in men. These data are different in both sexes; it could be the first changes in serum chemistries to propensity to kidney stone forming.

Evaluation of 24-hour urine collections showed significantly higher levels for obese patients in several metabolites, although the urinary volume was also greater in obese patients. The urine in obese patients was more concentrated as evidenced by an increased density.

The concentration of each urinary metabolite in women revealed that the primary contributing factors to the increased density were sodium, phosphorus, creatinine and uric acid, small differences approached statistical significance. In men increase significantly sodium and creatinine. The clearance creatinine parameters were significantly different between sexes. There are a positive correlation in serum potassium and sodium with gain weight; the association was more significantly in urinary metabolites calcium, sodium, phosphate and uric acid when the body weight was increasing. It is well documented by regression analysis that uric acid was significant determinant factors of changes in body mass index. These results demonstrated that serum uric acid could be predicting subsequent weight gain (Masuo et al., 2003); the serum uric acid level is determined by the balance between its production and urinary excretion. Previous reports have found significant increases in serum uric acid in obese subjects; it is suggested to be due to overproduction of uric acid (Matsuura et al., 1998, Ter Maaten et al., 1997). It has been reported that hyperuricemia in obese subjects is mainly attributable to impaired renal clearance of uric acid owing to the influence of hyperinsulinemia secondary to insulin resistance (Cappuccio et al., 1993, Quinones Galvan et al., 1995). Our data on the relationship between hyperuricemia and incidence kidney stone disease in obese patients, indicating that hyperuricemia seems to be a possibly risk factor for the development of renal stone forming.

Urinary density measurement is useful to assess the disorders of water balance. Fluid management is an important topic of intensive care medicine. Moreover, the usefulness of specific gravity measurement of urine could help interpreting our findings. The urine metabolites in obese patients were more concentrated as evidenced by a significant increased urinary density in both sexes. The higher concentration of urinary metabolites indicated that those could be contributing factors to the increased renal stone forming in our studied population.

On the other hand, decreased urinary acidity excretion was found. The decreased urinary acidity led to less dissociation of uric acid, we concluded that increased the risk for uric acid stone formation. The concentration of serum and urinary uric were significantly elevated in obese women and men. However, the data showed that urinary pH was inversely related to BMI, more obese people have lower urinary pH values. Previous report suggest that obesity may sometimes cause uric acid nephrolithiasis, a possible explanation for the progressive decline in urinary pH with increasing body weight is possibly insulin resistance, which decreases renal ammonia excretion and impairs hydrogen ion buffering. In addition, the mechanism that urinary pH decrease could be explains for defective ammonium excretion with kidney aging (Maalouf et al., 2004).

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The variations in the parameters seen such as urate, phosphate, sodium, potassium and calcium metabolism in the obese patients, led us to suggest that obesity appear to confer an increased risk factors to development urinary stones.

These data showed the existence of different lithogenic metabolic profiles in men and in women that could explain the different clinical analysis. We have demonstrated that differences are seen in the serum and urinary chemistries between obese and nonobese stone-forming patients and it is compatible with the report that uric acid is much more commonly encountered as a stone constituent among patients studied. There is a clinical predominance of uric acid nephrolithiasis in obese women and overweight men. This finding led us to speculate whether obesity has a role in the development of uric acid stone. The acidic urinary environment influence the formation of uric acid stones by direct precipitation or commonly in most of our patients have a tendency to develop calcium oxalate stones by heterogeneous nucleation of calcium oxalate by uric acid. The major risk factors in the development of uric acid stones are low urine volume, hyperuricosuria, and abnormally acidic urine pH. The direct relationship between urinary uric acid to BMI was found, similar to data publishing by Taylor et al.(2005).

In general, higher body weight, especially obesity, could be associated with an increased risk of renal stone. Our analyses suggest some gender differences in the relationship between obesity and the risk of kidney stone forming.

We estimated that higher percentage of our renal stones cases among men and women could be related to overweight and obesity. Obesity increases the risk for nephrolitiasis in the general population, and the association appears to be stronger in women than in men.

In conclusion, obesity is very common among patients with urinary stones. In this paper, we described the pattern of biochemical investigations routinely used for the clinical management of stone-forming outpatients. We have demonstrated the differences in the serum and urinary chemistries between obese and nonobese stone-forming patients. Obesity could be one of the factors that could increase the risk of urinary stone disease in these patients. Obese women did show a slight increase in the uric acid stone formers, and higher percentage of overweight men was found. The exact cause for this increase is unknown. Further studies in patients with respect to metabolism parameters and stone composition, and hormonal status could be necessary to elucidate this finding.

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