Obesometric factors associated with increased skin-to-stone distances in renal stone patients

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Introduction: *Obese patients are at increased risk for renal stones as well as treatment failures due to increased skin-to-stone distances (SSD) and harder stone compositions. We investigated the relationships between obesometric parameters (body mass index [BMI], body fat distribution and obesity-related hormone levels) with SSD and stone hardness.*

Materials and methods: *We prospectively enrolled patients undergoing stone interventions at our institution. Computed tomography (CT) scans were analyzed; adipose tissue was identified according to Hounsfield units (HU) and separated into subcutaneous (SAT) and visceral (VAT) components. The pixels were averaged at three levels to calculate fat distribution: %VAT = (VAT)/(VAT + SAT). SSD was measured and HU were used as a surrogate for stone hardness. Obesity-related hormones leptin and adiponectin were measured by ELISA.*

Results: *Seventy-nine patients were prospectively enrolled. Mean BMI and %VAT were 30.02 kg/m2 and 40.13 kg/m2. Mean leptin and adiponectin levels were 17.5 ng/mL and 7.67 mcg/mL indicating high risk for metabolic consequences of obesity. Females had greater proportions of subcutaneous fat than males (%VAT 28.4 versus 46.94, $p < 0.001$) and greater SSD (11.26 cm versus 9.86 cm, $p = 0.025$). Among obese patients, subcutaneous fat correlated with SSD independently of BMI ($r = 0.454$, $p = 0.008$). Obese patients with %VAT > 40 versus < 40 had SSD of 11.35 cm versus 13.7 cm ($p = 0.005$). Diabetics had harder stone compositions as measured by HU than non-diabetics (982.86 versus 648.86, $p = 0.001$).*

Conclusion: *Obesometric parameters such as BMI, body fat distribution, and the presence of diabetes mellitus are important considerations in the management of renal stone disease. A large proportion of subcutaneous fat, which can be estimated by physical examination, predicts SSD among obese patients and may aid treatment decisions in patients, particularly those without pre-treatment CT scans. Further studies are needed to refine the role of obesometrics in personalizing treatment decisions.*

Key Words: obesometric, renal stone

Introduction

Obesity is a major risk factor for renal stone disease, and the rising incidence of renal stones in North America is likely related to the obesity epidemic.[1] Body mass index (BMI) is typically used to define obesity, but is limited in its ability to discriminate body fat from lean body mass.[2] A more precise definition of obesity should be used to define relationships between obesity and its associated morbidity, including urolithiasis. The proportion of visceral adipose tissue (%VAT) better predicts metabolic and cardiovascular outcomes than BMI.[3-5] Likewise, serum levels of the hormones leptin and adiponectin predict metabolic consequences of obesity; elevated leptin and reduced adiponectin are independent predictors of the metabolic syndrome and cardiovascular disease.[6-9]

The metabolic syndrome affects stone composition as well as the skin-to-stone distance (SSD), each of which are predictive of shockwave lithotripsy (SWL)

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failures.[10-16] The relationships between fat distribution and circulating hormone levels with stone formation and treatment outcomes have not been described thus far.

The objectives of this study were to 1) characterize the prevalence and severity of obesity in a contemporary cohort of renal stone patients using BMI and the more informative obesometric parameters: body fat distribution (% visceral adipose tissue - VAT) and serum adiponectin and leptin levels; 2) investigate the relationships between obesometric parameters (BMI, %VAT and serum obesity-related hormones) with SSD and stone hardness.

Materials and methods

This was a prospective cohort study. After informed-consent and institutional review board approval, all patients undergoing any treatment (SWL, percutaneous nephrolithotomy, or uretereoscopy) for renal stone disease at St. Joseph's Healthcare - a McMaster University-affiliated hospital in Hamilton, Ontario, Canada - were prospectively offered participation from November 2009 through June 2010. Patients underwent pre-treatment computed tomography (CT) scans (manufacturer General Electric; CT kidney-ureters-bladder collimation settings: 40 mm detector coverage, 1.25 mm helical thickness; 120kV, 200mA, pitch 1.375:1). Patients were excluded if pre-treatment CT scans were not performed as part of their standard of care. Height and weight were measured at the time of enrollment to determine BMI (weight/height^2). The incidence of diabetes mellitus was determined by history. Serum levels of leptin and adiponectin were drawn after an overnight fast and measured in triplicates using dedicated ELISA kits (B-Bridge International, Inc.).

Fat distribution was measured on pre-treatment CT scans using commercially available software (Photoshop and Clear Image Demo); tissue of fat density (defined as Hounsfield units (HU) -250 to -50) was isolated and pixels summed and averaged across three fixed axial slices (the L2 vertebral body, the umbilicus, and the anterior superior iliac spine),[17] Figure 1. The %VAT was defined as the number of pixels comprising visceral adipose tissue divided by the number of pixels comprising total adipose tissue, where total adipose tissue equals visceral plus subcutaneous.[2,18]

Since increased stone HU are associated with SWL failures,[14,19] the HU of stones were measured as a surrogate for stone hardness. As described by Pareek et al,[20] SSD was measured as the mean of distances at 0, 45, and 90 degrees from the skin edge. To eliminate variability owing to stone position within the kidney or ureter, measurements were standardized from the skin to the most lateral midpole calyx.

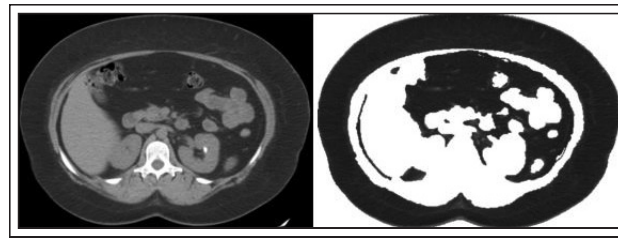

Figure 1. Demonstration of %VAT calculation in a patient with a left renal stone. Axial slices (left image) at three fixed levels are analyzed separately and averaged. Tissue of fat density (right image- black coloured) is isolated and pixels comprising subcutaneous and visceral fat are separately summed. %VAT = number of pixels of visceral fat/total number of fat pixels. This patient had a BMI of 38.7 kg/m^2, %VAT of 29.3, and a SSD of 13.9 cm.

Descriptive statistics were performed. Categorical variables are reported as counts and percentages, and continuous variables as means with standard deviations. To compare continuous outcome measures between groups, t-test for independent samples was used if it was normally distributed and Mann-Whitney U test was used if it was not normally distributed. Pearson correlation coefficient or Spearman's rho analysis was used to examine the linear association between two continuous outcome measures. Scatter plot and graphs of mean with 95% confidence intervals (CI) were used to visually demonstrate the relationship between variables. Linear regression analysis was used to examine the predictors of SSD (cm) increase. R^2 was reported to indicate the proportion of variability in a dataset that is accounted for in the model and coefficients with 95% CI are reported for the predictors. Statistical analyses were performed with SPSS software and consisted of two-tailed tests, with p values < 0.05 taken as statistically significant.

Results

One hundred thirteen patients were offered participation of whom 110 enrolled. A final cohort of 79 patients remained after excluding 31 without pre-treatment CT scans; 51 (64.6%) were male. The mean age was 54 years (range: 19-89). Sixty-nine patients underwent serum hormone testing; 10 patients were excluded from serum hormone testing for having failed to fast prior to this office visit

TABLE 1. **Baseline patients' characteristics**

Total number of patients	79
Number of males (%)	51 (64.6)
Mean age (St Dev)	54.45 (14.04)
Type of procedure no. (%)	
URS + laser lithotripsy	50 (63.3)
ESWL	21 (26.6)
PCNL	8 (10.1)
Mean height (St Dev) (cm)	171.53 (10.47)
Mean weight (St Dev) (kg)	87.17 (21.42)
Mean BMI (St Dev) (cm/m^2)	30.02 (7.63)
Number of diabetics (%)	17 (21.5)
Mean SSD (St Dev) (cm)	10.34 (2.7)
Mean HU (St Dev)	910.51 (378.55)
Mean %VAT (St Dev)	40.13 (12.96)
Mean Adiponectin (St Dev) (mcg/mL)	7.67 (6.85)
Mean Leptin (St Dev) (ng/mL)	17.5 (23.65)

URS = ureteroscopy; ESWL = extraocorporeal shockwave lithotripsy; PCNL = percutaneous nephrolithotomy; St Dev = standard deviation; HU = Hounsfield units; VAT = visceral adipose tissue; SSD = skinto-stone distance; BMI = body mass index

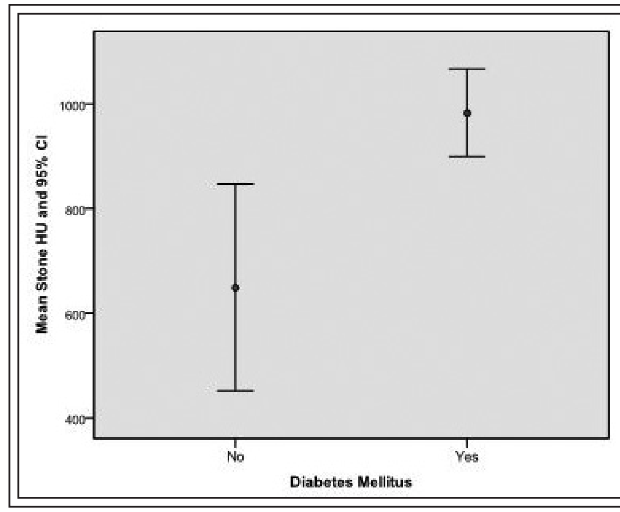

Figure 2. Mean stone Hounsfield units in diabetics and non-diabetics (p = 0.001).

Table 1 shows baseline patient characteristics. Seventeen (21.5%) patients were diabetic. The mean BMI was 30.02 (7.63) kg/m^2 and the mean %VAT was 40.13 (12.96). Only 23% of patients had BMI within the normal range (20 kg/m^2-24.9 kg/m^2) while 37% were overweight (25 < BMI < 29.9 kg/m^2), and 40% obese (BMI > 30kg/m^2). BMI did not correlate with %VAT (p = 0.363). The mean serum leptin and adiponectin levels were 17.50 ng/mL and 7.67 ug/mL respectively (normal values 10 ng/mL and 10 ug/mL respectively).

The gender differences in obesity-related measures are demonstrated in Table 2. The mean SSD was 11.26 (3.3) cm in females and 9.86 (2.1) cm in males (p = 0.025). Males and females had %VAT of 46.9 and 28.4 respectively (p < 0.001), indicating significantly greater proportions of visceral fat in males and subcutaneous fat in females, Table 2. Leptin levels were higher in females (30.35 versus 7.60, p < 0.001), as were adinoponectin levels (10.91 versus 5.55, p = 0061). There were no significant gender differences in mean stone HU.

Association of obesometric factors with stone HU

The mean stone HU was 910.51 (378.5). Diabetics had significantly higher HU than non-diabetics (982.86 (50.8) versus 648.86 (356.7), p = 0.001), Figure 2. Serum leptin level was negatively associated with HU (r = -0.273, p = 0.35). Gender, BMI, and %VAT were not associated with stone HU.

TABLE 2. **Gender differences in obesometric parameters and pre-treatment stone imaging characteristics**

	Males	**Females**	**p value**
Mean BMI (kg/m^2) (St Dev)	28.7 (6.0)	32.4 (9.5)	0.044
Mean %VAT (St Dev)	46.94 (9.6)	28.4 (9.0)	< 0.001
Mean leptin (ng/mL) (St Dev)	7.6 (9.0)	32.0 (30.3)	< 0.001
Mean adiponectin (mcg/mL) (St Dev)	5.55 (3.8)	10.91 (8.9)	0.006
Mean HU (St Dev)	921.26 (369.0)	919.36 (389.3)	0.982
Mean SSD (cm) (St Dev)	9.86 (2.1)	11.26 (3.3)	0.025

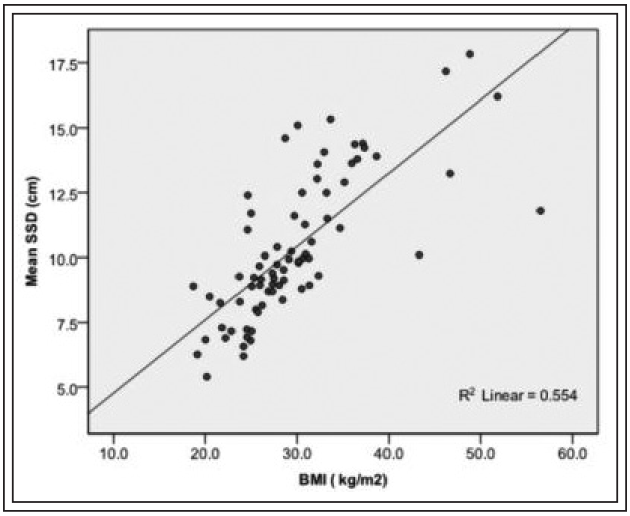

Figure 3. Mean skin-to-stone distance versus body mass index (p < 0.001).

Association of obesometric factors with skin-to-stone distance

The mean SSD was 10.34 (2.7) cm. Females had greater SSD than males (11.26 (3.3) cm versus 9.86 (2.1) cm, $p = 0.025$). SSD correlated with BMI ($r = 0.744$, $p < 0.001$), Figure 3. Obese patients (BMI > 30) and non-obese patients had mean SSD of 12.53 (2.4) cm and 8.79 (2.8) cm respectively ($p < 0.001$), Figure 4. Serum leptin level also correlated with SSD ($r = 0.600$, $p < 0.001$). In a linear multivariable regression including all patients, elevated BMI (0.17 (95%CI:0.7, 0.27), $p = 0.001$) and increased leptin (0.04 (95%CI: 0.01, 0.06), $p = 0.008$) were predictive of SSD ($r = 0.731$); age, gender, adiponectin and %VAT were not significant.

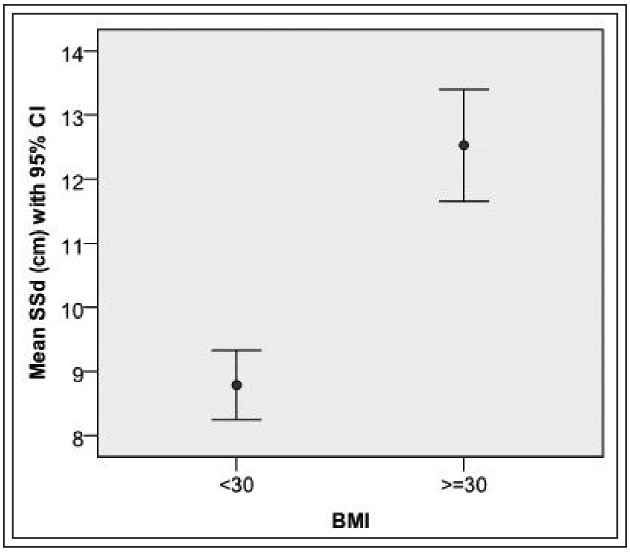

Figure 4. Mean skin-to-stone distance in obese versus non-obese patients (p < 0.001).

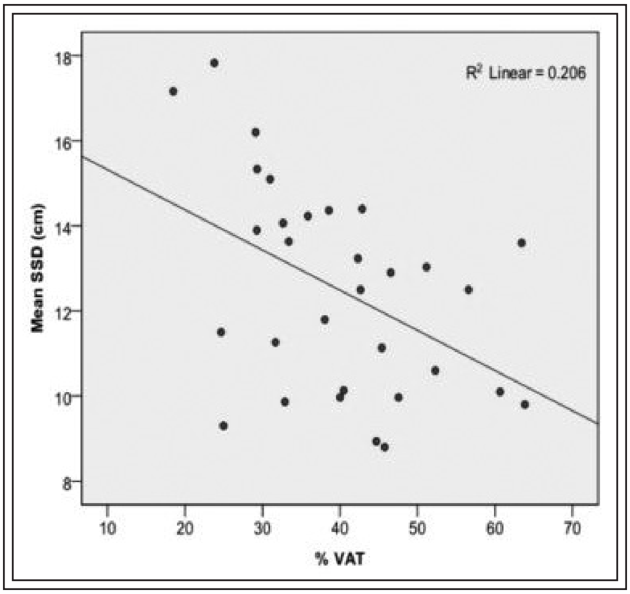

Figure 5. Mean skin-to-stone distance versus percentage of visceral adipose tissue among obese patients (p = 0.008).

In the subset of obese renal stone patients (BMI > 30kg/m²) SSD correlated negatively with %VAT ($r = -0.454$, $p = 0.008$), Figure 5. Among obese patients with a %VAT > 40 compared with < 40, the mean SSD were 11.35 (1.8) cm and 13.7 (2.5) cm respectively ($p = 0.005$), Figure 6. These findings suggest that while obesity correlates with SSD, subcutaneous fat has a greater impact on SSD than visceral fat (peri-nephric and intra-abdominal fat) in obese patients.

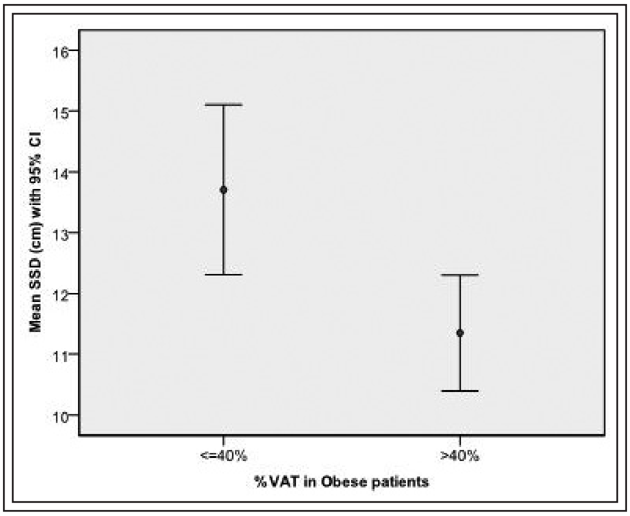

Figure 6. Mean skin-to-stone distance in obese patients with %VAT< 40 versus > 40 (p = 0.005).

Discussion

The obesity epidemic is estimated to affect more than 300 million people worldwide.[21] It is increasingly evident that renal stone disease is one of the many metabolic consequences of obesity.[22,23] Unfortunately, in addition to increasing the risk of stone disease, obesity may also increase perioperative morbidity.[22]

In this cohort of Canadian renal stone patients, only 23% had normal BMI while 40% were obese. These figures are in keeping with those of other studies which reported on BMI in renal stone patients.[12,24] Twenty-one percent of patients were diabetic; this contrasts with the estimated prevalence of 9% in the province of Ontario.[25] Mean levels of leptin and adiponectin were elevated and reduced respectively suggesting that this cohort is at risk for metabolic complications from obesity.[6-9]

The findings of this study suggest that obesometric parameters may be important predictors of treatment success in a subset of stone patients, namely obese women or those with significant proportions of subcutaneous adipose tissue. Previous studies have demonstrated that stones with HU > 900 are prone to SWL failures.[14,19] In this cohort, diabetics had stones with mean HU of 982.86 compared to 648.86 in non-diabetics ($p = 0.001$), suggesting that diabetes may be a risk factor for SWL failure. However, given the small sample of 17 diabetics in this study and the known propensity of diabetics towards low HU uric acid stones,[26] this possibility requires further study.

A skin-to-stone distance > 10 cm is also associated with SWL failures.[14,20] The mean SSD in obese patients was 12.53 cm contrasted with 8.79 cm in non-obese patients ($p < 0.001$). Furthermore, obese patients with a greater proportion of subcutaneous fat (%VAT < 40) had an even higher mean SSD (13.7 cm) than obese patients with less subcutaneous fat (11.35 cm, $p = 0.005$). Since females tend to have a greater proportion of subcutaneous fat than males,[3, 17] the possibility that obese females are at the greatest risk for SWL failures should be examined in future studies.

SWL failure can be predicted by measuring the SSD and the stone HU on pre-treatment CT scan.[10-16] However, in order to minimize patients' exposure to ionizing radiation, in select patients other imaging modalities are often preferred, including ultrasound and x-ray.[27] In our initial cohort of 110 patients, 31 (28%) were treated without pre-treatment CT scans. Among such patients the SSD might be estimated by physical examination to determine BMI and estimated body fat distribution.[2] We believe a patient's proportion of subcutaneous fat is readily apparent on physical examination, but our ability to predict %VAT (and consequently, SSD) remains to be tested. Our findings suggest that a high proportion of subcutaneous fat should be an important consideration in the treatment of obese patients, and the impact of fat distribution on treatment success should be investigated in further studies.

This study has notable limitations. It describes a cohort of patients at a single institution and may not be representative of other populations. Nevertheless, obesity rates in Canada are not significantly different than those in North America and Western Europe.[28] Furthermore, due to the referral pattern of our service, patients were not followed after treatment, and associations between %VAT and serum hormone levels on stone-free rates remains unknown. We do not have sufficient data relating to stone composition, and thus our estimation of stone hardness is limited to its HU. Nevertheless, to our knowledge, this is the first report on the association between obesometric parameters (other than BMI) and pre-treatment stone characteristics. Further studies are needed to refine the role of obesometric factors in personalizing treatment decisions for obese patients.

Conclusion

The incidence of renal stone disease is increasing, likely resulting from the obesity epidemic in North America.[1] The average renal stone former in this cohort was obese and had circulating hormone levels predictive of metabolic complications of obesity. Obesity, and in particular subcutaneous fat, is associated with an increased skin-to-stone distance, while diabetes is associated with harder stone compositions. Obesometric parameters should be considered when choosing treatment modalities for renal stone formers. □

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