Visceral adipose tissue loss and 24-hour urinary profile changes post-bariatric surgery

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Introduction: *The relationship between obesity and nephrolithiasis is a well-documented phenomenon. Visceral adipose tissue (VAT) has been proposed to be an accurate indicator of metabolic derangement. We present a study that investigates the relationship between computed tomography (CT) delineated VAT measurements and 24-hour urine (24 HU) profiles in the context of profound weight loss.*

Materials and methods: *A total of 86 patients with a history of nephrolithiasis who underwent bariatric surgery were reviewed. All patients had pre and postoperative 24 HU analysis and CT kidney and urinary bladder performed. CT-based fat delineation program, AnalyzePro, was used to measure VAT at levels L4-L5 (VAT 1) and L1-L2 (VAT2). Univariate and multivariate analysis was utilized to examine associations between VAT measurements and comorbidities, 24 HU values, and postoperative urinary changes.*

Results: *Preoperative VAT2 was correlated with preoperative serum creatinine and all 24 HU (R^2: 0.23-0.43, p = < 0.001-0.030). Only VAT1 and VAT2 had relationships with hypertension, dyslipidemia, and metabolic syndrome (R^2: 0.25-0.30, p = 0.004-0.015). The percent change in VAT1 and VAT2 was a significant predictor of change in 24 HU uric acid (respectively, R^2: 0.14, beta: -0.03, p = 0.002 and R2: 0.13, beta: -0.03, p = 0.003).*

Conclusions: *This study found VAT to have strong correlations with urinary outcomes in obese patients, especially in the excretion of uric acid. These findings support a potential use of CT delineated measurements of fat as a surrogate measure for urinary metabolites, and may be used as a marker for patient counseling in stone prevention.*

Key Words: visceral adipose tissue, 24-hour-urine, uric acid, nephrolithiasis, bariatric surgery

Introduction

Obesity is a rising epidemic that is linked to several comorbidities that negatively affect patient mortality and morbidity.[1] From a urological perspective, obesity and the resultant risk of nephrolithiasis is a well-documented phenomenon.[2,3] Traditionally, body mass index (BMI) (kg/m^2) is a commonly used obesometric parameter that determines total body adiposity and assists the clinician in decision making, treatment recommendations, and treatment response monitoring. However, BMI has also been shown to be a poor predictor of adipose tissue distribution and metabolic sequelae.[4,5] Subsequently, there have been propositions for the use of visceral adipose tissue (VAT) measurements as a more accurate indicator of metabolic derangement in the obese population, as VAT stronger correlates with obesity-linked disorders than when compared to BMI.[6,7]

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The relationship between VAT and nephrolithiasis has recently become an area of interest in urology,[8-11] though the effects of rapid changes in VAT and BMI in relationship to urinary metabolites is yet to be explored. We present a retrospective study that evaluates the relationship between computed tomography (CT) delineated VAT measurements and 24-hour urinary (24 HU) profiles in the context of bariatric surgery.

Materials and methods

Data retrieval

Retrospective data from patients who underwent either laparoscopic Roux-en-Y gastric bypass (RYGB) or laparoscopic sleeve gastrectomy (SG) at our academic tertiary medical center were accessed following approval from our institutional research ethics board. As part of our local bariatric institutional guidelines, all patients with a history of kidney stones undergo urological assessment. A history of nephrolithiasis was defined as spontaneous passage of a kidney stone, presence of kidney stones on imaging, and/or history of a stone procedure. These assessments included obesometric factors (BMI), 24 HU profile (volume, pH, uric acid, sodium, phosphate, citrate, oxalate, and calcium), blood serum levels (creatinine), and CT imaging of the kidneys, ureters, and bladder (CT KUB). These assessments were repeated 1 year post-bariatric surgery. 24 HU profiles and annual imaging were conducted in high risk stone formers at our center, and the authors utilized CT imaging for stone surveillance given limitations of ultrasound and plain film x-ray for the obese population.

CT-based visceral fat extraction

Pre and postoperative CT KUB scans were performed for each patient. VAT was extracted utilizing commercially available software AnalyzePro (Version 14. Overland Park, KS, USA) using previously reported methodology.[8,10,12,13] Adipose tissue was identified by isolating pixels between -190 to -30 Hounsfield units using a semi-automatic segmentation technique. Visceral fat was differentiated from superficial tissues by utilizing the inner boundaries of abdominal muscles, as well as the psoas, as the external boundary of VAT. These calculations were conducted at the level of the umbilicus, at levels L4 and L5 (VAT1), as well as L1-L2 (VAT2), Figure 1.

Total area (cm^2) of adipose tissue at VAT1 and VAT2 was calculated pre and postoperatively. Absolute changes in fat measurements (BMI loss, VAT1 loss, VAT2 loss), and percent changes in fat measurements (%BMI loss, %VAT1 loss, %VAT2 loss) were determined.

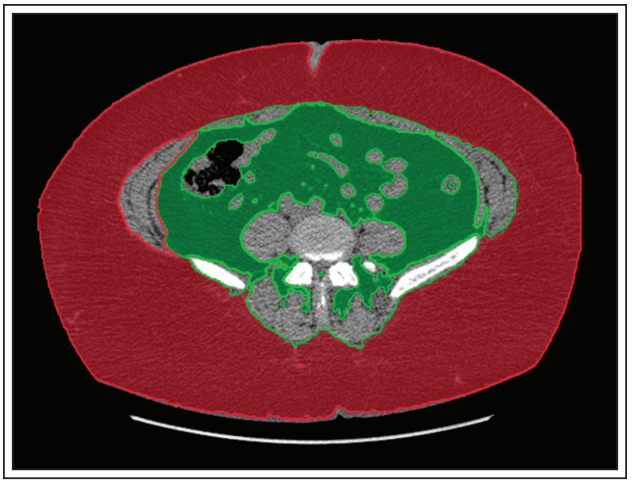

Figure 1. VAT 1 slice. Axial computed tomography slice at the level of VAT 1 (L4 and L5). Visceral adipose tissue is highlighted in green, and subcutaneous adipose tissue is highlighted in red.

Statistical analysis

Patient demographics are reported descriptively. Student's t-tests (2-tailed, paired) were used to compare means between pre and postoperative obesometric measurements, as well as weight loss based on type of surgery. Pearson correlations determined relationships between fat measurements and pre and postoperative 24 HU values, as well as preoperative comorbidities. Due to the mechanistic changes of oxalate absorption associated with RYGB,[14] we also performed a correlation analysis for obesometric factors with 24 HU oxalate based on type of surgery. Simple linear regression was used to explore the relationship between %VAT1 and %VAT2 loss and changes in 24 HU levels. The α-level was set at 0.05 for statistical significance for all tests. Statistical analysis was performed using commercially-available software (IBM SPSS Statistics version 26.0. Armonk, NY, USA).

Results

Patient demographics

A total of 86 cases were included in the study. All patients had a documented history of nephrolithiasis prior to surgery, and had completed pre and postoperative assessments between June 2013 and July 2019. Of the sample, 51 patients underwent RYGB and 35 underwent SG. The sample population had a mean age of 52.0 ± 9.2 years and was composed of 67.4% female patients. The average time from bariatric surgery to postoperative CT assessment was 12.1 ± 2.0 months.

TABLE 1. **Changes in obesometric measurements**

Obesometric measurement	Preoperative	Postoperative	p value
BMI (kg/m^2, mean ± SD)	48.7 (7.6)	33.1 (7.3)	0.000
VAT1 (cm^2, mean ± SD)	340.7 (121.9)	189.1 (108.3)	0.000
VAT2 (cm^2, mean ± SD)	360.1 (143)	205.6 (113.1)	0.000

Means compared via 2-Tailed T-Test for two independent samples, equal variances assumed.
BMI = body mass index; VAT = visceral adipose tissue

TABLE 2. **Fat loss by surgical group**

	RYGB	SG	p value
BMI loss (kg/m^2, mean ± SD)	16.7 (4.7)	14.0 (5.2)	0.015
VAT 1 loss (cm^2, mean ± SD)	174.3 (83.3)	118.4 (75.6)	0.002
VAT 2 loss (cm^2, mean ± SD)	176.9 (109.1)	121.8 (70.0)	0.010
% BMI loss (%, mean ± SD)	35.2 (9.1)	27.7 (8.4)	0.000
% VAT 1 loss (%, mean ± SD)	53.4 (18.1)	33.7 (17.9)	0.000
% VAT 2 loss (%, mean ± SD)	50.3 (21.1)	32.2 (14.4)	0.000

Means compared via 2-tailed t-test for two independent samples, equal variances assumed; proportions compared via chi-squared tests; RYGB = Roux-en-Y gastric bypass; SG = sleeve gastrectomy; BMI = body mass index; VAT = visceral adipose tissue

TABLE 3. **Significant correlations between fat measurements and 24 hour urine values**

	Urinary pH	Serum Cr	24 HU UA	24 HU Na	24 HU PO3	24 HU Ox	24 HU Citrate	24 HU CA
Preoperative								
BMI (kg/m^2)	-0.07 (0.532)	-0.09 (0.354)	0.40 (0.001)	0.27 (0.020)	0.40 (0.000)	0.23 (0.019)	-0.04 (0.692)	0.12 (0.224)
VAT1 (cm^2)	-0.08 (0.488)	0.22 (0.036)	0.21 (0.050)	0.37 (0.001)	0.19 (0.071)	0.45 (0.001)	0.24 (0.021)	0.14 (0.197)
VAT2 (cm^2)	-0.04 (0.734)	0.39 (0.001)	0.26 (0.013)	0.39 (0.001)	0.26 (0.013)	0.43 (0.001)	0.26 (0.012)	0.23 (0.030)
Postoperative								
BMI (kg/m^2)	-0.13 (0.381)	0.14 (0.210)	0.40 (0.001)	0.25 (0.028)	0.01 (0.962)	0.07 (0.564)	0.12 (0.321)	0.17 (0.142)
VAT1 (cm^2)	0.02 (0.907)	0.28 (0.010)	0.27 (0.019)	0.19 (0.105)	0.10 (0.395)	-0.07 (0.549)	0.11 (0.340)	0.21 (0.075)
VAT2 (cm^2)	0.01 (0.937)	0.41 (0.001)	0.27 (0.020)	0.17 (0.151)	0.04 (0.737)	-0.06 (0.619)	0.18 (0.136)	0.16 (0.178)

Relationships between obesometric measurements assessed via Pearson correlations where R^2 values are presented, with p values in brackets
Cr = creatinine; 24 HU = 24-hour urine; UA = uric acid; Na = sodium; PO3 = phosphate; Ox = oxalate; Ca = calcium; BMI = body mass index; VAT = visceral adipose tissue

TABLE 4. **Significant correlations between preoperative fat measurements and comorbidities**

	T2DM	HTN	DLPD	Metabolic syndrome
Preoperative BMI (kg/m^2)	-0.08 (0.425)	-0.06 (0.543)	-0.02 (0.838)	0.01 (0.717)
Preoperative VAT1 (cm^2)	0.14 (0.178)	0.29 (0.006)	0.25 (0.015)	0.30 (0.004)
Preoperative VAT2 (cm^2)	0.11 (0.311)	0.26 (0.012)	0.18 (0.095)	0.26 (0.014)

Relationships between comorbidities assessed via Pearson correlations where R^2 values are presented, with p values in brackets; T2DM = type 2 diabetes mellitus; HTN = hypertension; DLPD = dyslipidemia; BMI = body mass index; VAT = visceral adipose tissue

Changes in obesometric measurements

There were significant decreases in all fat measurements after surgery, irrespective of surgical group or obesometric measurement (Table 1, all p = 0.000). However, RYGB had higher rates of weight loss at 1 year post-bariatric surgery versus SG when measured via BMI loss, VAT1 loss, and VAT2 loss (p = 0.015, 0.002, and 0.010, respectively), Table 2. These differences were more pronounced when assessed by % loss of BMI, VAT1, and VAT2 (all p = 0.000).

Relationships of obesometric measurements with 24-hour urine and comorbidities

Preoperatively, VAT1 and VAT2 were more significantly related to preoperative 24 HU than when compared to preoperative BMI, Table 3. Specifically, preoperative VAT2 was correlated with preoperative serum creatinine and all 24 HU metabolites (R^2: 0.23 - 0.43, p = 0.001-0.030). Preoperative VAT1 had similar correlations (R^2: 0.21-0.45, p = 0.001-0.050), but was not significantly related to 24 HU phosphate and calcium (p = 0.071 and 0.197, respectively). Urinary pH was not related to any obesometric measurement. Subgroup analysis of 24HU oxalate based on type of bariatric surgery found correlations between preoperative VAT1 and VAT2 in the RYGB group only (R^2: 0.38, p = 0.008 and R^2: 0.35, p = 0.014, respectively). In regards to preoperative comorbidities, only VAT1 and VAT2 had relationships with hypertension, dyslipidemia, and metabolic syndrome (R^2: 0.25-0.30, p = 0.006-0.015), Table 4.

Postoperatively, there was less concordance of relationships between all fat measures and 24 HU, except for 24 HU uric acid which was consistent with all obesometric measures at both time points (R^2: 0.21-0.40, p = 0.001-0.050), Table 3. The percent change in VAT1 and VAT2 were significant predictors of change in 24 HU uric acid only (R^2: 0.14, beta: -0.03, p = 0.002 and R^2: 0.13, beta: -0.03, p = 0.003, respectively), Table 5 and Figure 2. This relationship was not present in

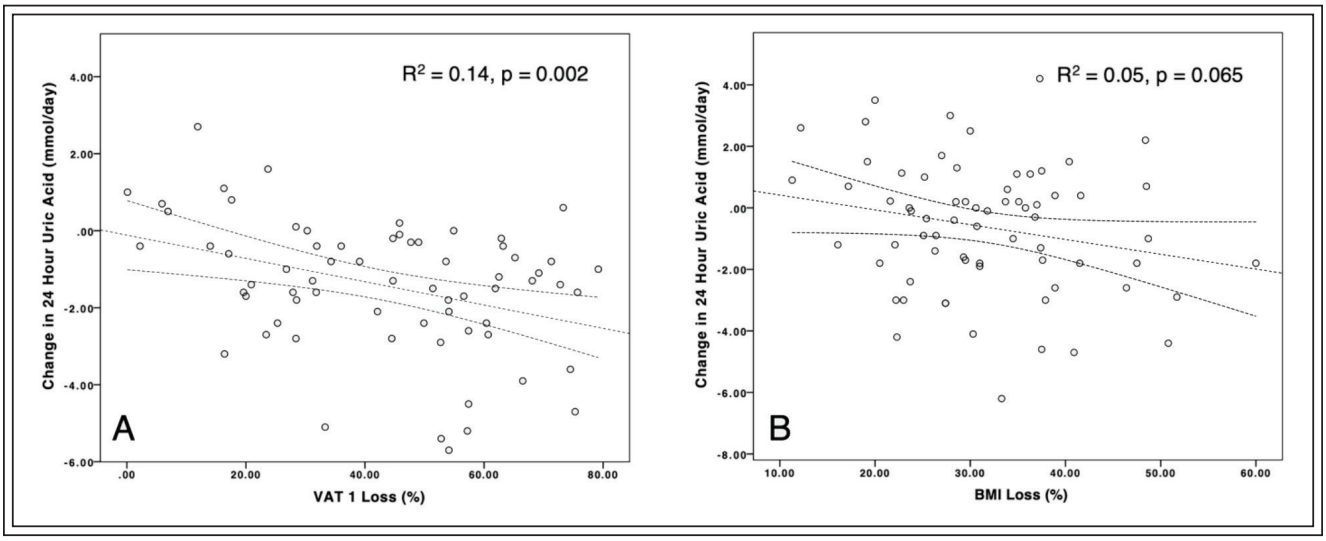

Figure 2. Linear regression between **(A)** VAT 1 loss (%) by change in 24-hour urine uric acid (mmol/day) **(B)** BMI loss (%) by change in 24-hour urine uric acid (mmol/day).

TABLE 5. **Significant relationships between % VAT loss and change in 24 HU**

	Δ24 HU Uric acid	**Δ24 HU Phosphate**	**Δ24 HU Sodium**	**Δ24 HU Oxalate**	**Δ24 HU Citrate**	**Δ24 HU Calcium**
% BMI loss	0.05, -0.23 (0.065)	0.03, -1.81 (0.143)	0.06, -0.26 (0.247)	-0.13, 0.03 (0.782)	0.36, -0.33 (0.075)	0.09, -0.32 (0.090)
%VAT1 loss	0.14, -0.03 (0.002)	0.01, -0.09 (0.320)	0.01, -0.14 (0.709)	0.015, 1.88 (0.311)	0.01, -0.01 (0.643)	0.03, -0.01 (0.170)
%VAT2 loss	0.13, -0.03 (0.003)	0.01, -0.04 (0.659)	0.02, -0.19 (0.771)	0.03, 0.78 (0.656)	0.01, -0.01 (0.366)	0.02, -0.01 (0.653)

Relationships assessed via simple linear regression assuming normality of both variables, where data is presented as R^2, beta value, p value in brackets; 24 HU = 24-hour urine

percent change in BMI versus any of the 24 HU values (p = 0.065-0.782), Table 5 and Figure 2.

Discussion

The association between VAT and urinary metabolites is a relatively new phenomenon being explored. Our study is hypothesis generating in that it investigates the changes in 24 HU profiles following drastic changes to visceral adiposity due to bariatric surgery. Our results showed that after 1 year post-bariatric surgery, patients who undergo either RYGB or SG have substantial changes in VAT as measured by CT-guided fat delineation. These VAT measurements were more closely related to 24 HU profiles and comorbidities than BMI in the preoperative setting. Furthermore, the change in percent VAT was able to significantly predict decreases in 24 HU uric acid, a known lithogenic urinary metabolite. These results suggest that VAT may be an independent factor in urinary metabolites and may be used as a surrogate marker for counseling in stone prevention, especially in obese patients with uric acid stones.

In our cohort, VAT had more significant preoperative associations with 24 HU profiles and metabolic comorbidities than when compared to BMI, especially VAT measures at the level of L1-L2 (VAT2), Table 3. Previous studies have suggested that the abdominal VAT compartment is a metabolically active entity that directly influences serum blood levels, insulin resistance, and even kidney function.[15] It is then no surprise that VAT levels also correlated well with urinary metabolites in our patient population. These findings are complementary to other studies around VAT. Akarken et al performed a retrospective study and matched 149 patients with stones with 139 healthy controls. These authors found that the patients with stones had higher VAT measurements (VAT > 180 cm^2, p = < 0.05). Multivariate regression from their population suggested that hyperlipidemia, hypertension, and VAT over 180 cm^2 were significant factors to stone formation.[11] Additionally, Bos et al found in their prospective study of 110 patients undergoing renal stone treatment that patients with higher VAT measurements had lower stone free rates over a 5-year period, when compared to lower VAT measurements (47.1% versus 72.2%, p = 0.004).[10] These studies highlight the metabolic activity of the VAT compartment, and support our findings of the relationship between VAT and urinary outcomes. Overall, it seems that VAT may be an independent factor for urinary metabolites, and may be better correlated to urolithic outcomes than compared to BMI.

The relationship between most obesometric factors decreased as our patients lost weight over the course of a year postoperatively, Table 3. As previously mentioned, studies found that higher levels of VAT lead to worse stone outcomes. Proposed pathophysiological mechanisms include VAT-related insulin resistance with the subsequent urinary acidification, as well as extrinsic compression by VAT on lymphatic pathways leading to increased interstitial pressure of kidney parenchyma.[9,16] We theorize that as VAT levels decrease and normalize, mechanisms that drive lithogenic urinary changes decrease or abate. This is supported by the results of Fram et al in their study of 382 patients with kidney stones, in which they found that VAT predicted increases in serum creatinine, 24 HU sodium and volume, but these findings were not consistent with urinary parameters in their non-obese sub-population.[9] In short, VAT relationships with urinary outcomes decrease at lower quartiles of VAT measurements, and this fat measurement parameter may be better suited for obese stone patients only.

Interestingly, the percent change in VAT1 and VAT2 was a significant predictor of change in 24 HU uric acid (R^2: 0.14, beta: -0.03, p = 0.002 and R^2: 0.13, beta: -0.03, p = 0.003, respectively), a known urinary stone metabolite. In other words, as %VAT decreased, there was a predictable decrease in 24 HU uric acid. This finding is supported by other authors' observations on the association between obesity and uric acid stones. Zhou et al studied 269 patients, who underwent percutaneous nephrolithotomy, and found that high VAT was an independent risk factor for uric acid stone composition (OR 3.64, 95% CI 1.22-10.85, p = 0.020).[13] Kim et al performed a retrospective study of 203 patients with kidney stones and found that VAT measurements were associated with uric acid stones.[15] Patel et al also postulates that VAT leads to lower pH, thus precipitating uric acid stones.[17] Overall, these authors propose that higher VAT levels and associated insulin resistance lead to defective ammonium production and lower urinary pH, leading to the formation of uric acid stones.[12] However, urinary pH was not related to VAT levels in our cohort. Alternatively, based on our data, we hypothesize that visceral adiposity rather affects the rate of urinary uric acid excretion, Figure 2. This has only been previously elucidated in mice models, and is explained by adipose tissue induced hypoxia leading to low grade inflammation and subsequent upregulation of xanthine oxidoreductase – the enzyme responsible for the catabolism of uric acid.[18] With this unique relationship, clinicians may utilize VAT measurements as a surrogate marker for stone prevention in counseling obese patients with uric acid stones, especially since the majority of patients already receive CT imaging.

The application of CT delineation software is relatively simple and integrates with most hospital picture archiving and communication system (PACS) software. The authors of this study utilized AnalyzePro (Version 14. Overland Park, KS, USA), though there are several applications with similar functionality. Understanding the basics of voxel and pixel identification will allow clinicians to easily capture VAT measures on axial CT scans. The learning curve is anecdotally low, and capture of these fat measures can be compared to the ease of today's urologists identifying Hounsfield units for nephrolithiasis density on patient imaging.

Though our study is unique and hypothesis generating, there are some limitations. These include the retrospective nature of the data collection and the potential group of patients who did not undergo their postoperative work up, such as patients who were not motivated to continue with their urological follow up due to a lack of symptoms. Secondly, stone analysis data were not available, as the majority of patients did not undergo an operative procedure that allowed for laboratory analysis. Finally, our cohort consisted of patients with a history of kidney stones, and these findings may not be generalizable to the kidney stone naïve population.

Conclusions

In conclusion, this study found visceral adipose tissue to have strong correlations with urinary outcomes in obese patients, especially in the excretion of uric acid. These findings support the potential use of CT delineated measurements of fat as a surrogate measure for urinary metabolites and may be used as a marker for patient counseling in stone prevention, particularly in the obese population with uric acid stones. Further investigation is necessary to examine these relationships in kidney stone naïve patients. □

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