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Does the Metabolic Syndrome or Its Components Affect the Outcome of Percutaneous Nephrolithotomy?

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ABSTRACT

***Purpose*: Metabolic syndrome is a cluster of cardiovascular disease risk factors. We assessed the impact of these medical disorders on the outcome of percutaneous nephrolithotomy (PCNL).**

***Patients and Methods*: Data from 430 consecutive PCNL procedures were retrospectively reviewed. The presence of serum lipid abnormalities (SLA), hypertension (HT), diabetes (DM), and obesity was investigated. Patients were determined to have the metabolic syndrome according to the definition of the International Diabetes Federation. Success rate, need for auxiliary procedures, and major complication rates of PCNL were analyzed separately for patients with or without DM, SLA, HT, obesity, and the metabolic syndrome, and were compared.**

***Results*: SLA, HT, and DM were observed in 123 (28.6%), 108 (25.1%), and 44 (10.2%) patients, respectively. Body mass index was >30 kg/m^2 in 74 (17.2%) patients. Metabolic syndrome was diagnosed in 41 (9.5%) patients. An overall success rate of 96.3% for PCNL was achieved. Success rates were not significantly ($P > 0.05$) influenced by the presence of SLA, HT, DM, obesity, or the metabolic syndrome. Major complications were encountered in 49 (11.4%) patients and were 2.5 to 2.7 times more common in patients with DM, HT, and the metabolic syndrome. In patients with DM, auxiliary treatment alternatives were necessary in 20.5%, while they were indicated in 10.9% of patients without DM ($P = 0.046$). Presence of the metabolic syndrome was also associated with an increased necessity for auxiliary treatments after PCNL ($P = 0.048$).**

***Conclusions*: Our results indicate that the metabolic syndrome and its components (DM and HT) significantly augment auxiliary treatment and complication rates after PCNL.**

INTRODUCTION

THE METABOLIC SYNDROME is a constellation of cardiovascular disease risk factors that includes dyslipidemia, hypertension (HT), central obesity, hyperglycemia (fasting plasma glucose >100 mg/dL), and diabetes mellitus (DM).[1] The age-adjusted prevalence of the metabolic syndrome was reported as 23.7% among 8814 U.S. adults.[2] It has been estimated that 190 million people worldwide have DM, a determinant component of the metabolic syndrome, and it is very likely that this will increase to 324 million by 2025.[3]

This epidemic, along with that of obesity, is taking place in both developed and developing nations. The combination of diabetes and obesity is now considered one of the major threats to human health in the 21st century.[1,4]

There is also strong evidence that obesity, weight gain, and DM are risk factors for the development of kidney stones as well as recurrence rates for stones.[5–7] Histopathologic studies have demonstrated lipid deposition in the medullary interstitium, which suggests the role of serum lipid and vascular pathologies in stone formation.[8]

Percutaneous nephrolithotomy (PCNL) has evolved into a highly effective minimally invasive technique, even in so-called high-risk patients.[9–11] However, there are studies that associate increased risk of surgical procedures and morbidity in patients with the components of the metabolic syndrome.[12,13] In recent

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studies, patients with endocrine comorbidities, including DM, were shown to be more likely to need longer hospitalization,[14] and that the presence of DM was associated with increased blood loss during PCNL.[15] There are also data concerning the outcome of PCNL in obese patients.[11]

It appears inevitable that we will see and treat an increasing number of patients with urinary stone disease coexisting with the metabolic syndrome in our routine practice. Therefore, we assessed the impact of these frequently encountered medical disorders and metabolic syndrome, described according to the recent consensus of the International Diabetes Federation (IDF),[1] on the success rates, need for auxiliary treatments, and major complications of PCNL.

PATIENTS AND METHODS

Between October 2002 and February 2005, 430 consecutive PCNL procedures in 418 patients (12 patients underwent bilateral PCNL in separate sessions) were performed at our institution. Patient data, which were entered and maintained prospectively in our PCNL registry, were retrospectively evaluated in this study.

Preoperative complete blood cell count, serum analysis including creatinine, fasting glucose, triglyceride, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol levels, platelet count, bleeding and coagulation profile, and urine culture were obtained from all patients. Preoperative radiologic evaluation included intravenous urography (IVU) and urinary tract ultrasonography, with the addition of noncontrast CT in selected patients. Stone burden was also determined.

Patients were determined to have the metabolic syndrome according to the latest definition of the IDF.[1] According to the IDF Metabolic Syndrome World-wide Definition, patients with central obesity (body mass index [BMI] >30 kg/m^2) were considered to have metabolic syndrome if at least two of the following coexisted: 1) Elevated serum triglyceride levels ($\geq$150 mg/dL), or specific treatment for this abnormality; 2) reduced HDL cholesterol ($<$40 mg/dL in men, $<$50 mg/dL in women), or specific treatment for this abnormality; 3) raised blood pressure (systolic $\geq$130 mm Hg, or diastolic $\geq$85 mm Hg), or treatment of previously diagnosed HT; 4) raised fasting plasma glucose ($\geq$100 mg/dL), or previously diagnosed type 2 DM.

Patients with metabolic syndrome were reviewed by one cardiologist (HK), and their treatment regimens were adjusted. BMI was calculated as weight in kilograms divided by square of height in meters. Patients did not undergo PCNL unless their serum glucose levels stabilized to normal ranges, and blood pressures were normalized with the adjustment of their therapy. Anticoagulant medications were terminated 1 week before surgery.

Each patient underwent PCNL beginning with cystoscopy and insertion of a ureteral catheter, as previously described.[16] Patients were then placed in the prone position, and percutaneous access was obtained by the urologist at a single setting using fluoroscopic guidance. After caliceal puncture, the tract was dilated with a high-pressure balloon dilator, and a 30F Amplatz sheath was placed.

Nephroscopy was performed with a rigid 26F nephroscope. Additional tracts were created when indicated in the same session. A 14F nephrostomy tube was placed into the renal pelvis or the involved calyx at the conclusion of the procedure in a majority of patients.

Antibiotic prophylaxis was maintained with quinolone. On postoperative day (POD) 1, the Foley and ureteral catheters were removed, if hematuria was not observed. A plain radiograph of the kidneys, ureters and the bladder was obtained. In patients rendered stone free or in those with no clinically significant residual fragments, the nephrostomy tube was removed on POD 2 after antegrade nephrostomography showing ureteral drainage down to the bladder. The nephrostomy tube was left in place if a second PNCL session because of residual stones was planned. Repeated PCNL (AQ1), ureteroscopy, and shockwave lithotripsy (SWL) were considered as accessory treatment alternatives when indicated.

All patients were seen 1 week after the procedure and a urine sample was cultured. Patients were evaluated with IVU 3 to 6 months postoperatively, and annually thereafter. Major complications, such as hemorrhage necessitating blood transfusion, adjacent organ injuries, and severe infections encountered during follow-up were documented.[17]

Results were classified as stone free, presence of clinically insignificant residual fragments (CIRF), and unsuccessful (presence of residual stones). CIRFs were considered as $\leq$4 mm, nonobstructing, noninfectious, and asymptomatic residual fragments. The PCNL procedure was considered successful if the patient was either free of stones or had any CIRF.[16]

The mean age, stone size, success rate, need for auxiliary procedures, and major complication rates were recorded separately for patients with or without DM, serum lipid abnormalities (SLA) (raised triglyceride and reduced HDL-cholesterol levels), HT, and metabolic syndrome, and were compared using the chi-square test. Comorbidities were analyzed as single variables, since their combinations were assessed as metabolic syndrome (Table 1).

Odd ratios for major complications in each medical disorder group were calculated. All statistical determinations were within 95% confidence interval (CI), and all *P* values were two-

Table 1. Cardiovascular Disease Risk Factors and Distribution of Diagnostic Criteria

Disease	*n (%)*
Serum lipid abnormalities (SLA)	123 (28.6)
Elevated triglyceride ($\geq$150 mg/dL)	71
Reduced HDL-cholesterol ($<$40–50 mg/dL)	67
Both	15
Hypertension (HT)	108 (25.1)
Diabetes mellitus (DM)	44 (10.2)
Type 1	6
Type 2	38
Central obesity (BMI >30 kg/m^2)	74 (17.2)
BMI 30.1–39.9 kg/m^2	66
BMI $\geq$40 kg/m^2	8
Metabolic syndrome	41 (9.5)
BMI >30 kg/m^2 + DM + SLA	19
BMI >30 kg/m^2 + DM + HT	10
BMI >30 kg/m^2 + SLA + HAT	7
BMI >30 kg/m^2 + DM + SLA + HT	5

tailed. P values < 0.05 were considered statistically significant. Data were expressed as mean ± standard deviation (SD).

RESULTS

There were 240 (55.8%) men and 190 (44.2%) women. SLA, HT, and DM were observed in 123 (28.6%), 108 (25.1%), and 44 (10.2%) patients, respectively. BMI was <25 kg/m^2 in 242 (56.2%) patients, and ranged between 25 and 30 kg/m^2 in 114 (26.5%). BMI was >30 kg/m^2 in 74 (17.2%) patients, who were considered to be obese. Morbid obesity (BMI >40 kg/m^2) was observed in eight (1.8%) patients. According to the IDF Metabolic Syndrome World-wide Definition, metabolic syndrome was the diagnosis in 41 (9.5%) patients (Table 1).[1]

The mean age and stone size of patients with and without these medical disorders were similar ($P > 0.05$; Table 2). Mean operative time, including cystoscopic ureteral catheter placement, was 88.4 ± 29.7 (range 45–225) minutes. The mean number of percutaneous access sites was 1.34 (range 1–5). A total of 323 (75.2%) patients had a single percutaneous access, while two accesses were indicated in 76 (17.6%) patients, 3 accesses in 24 (5.6%) patients, 4 accesses in four (0.9%) patients, and 5 accesses in three (0.7%) patients.

Major complications were encountered in 49 (11.4%) patients. Hemorrhage, necessitating blood transfusion, was observed in 42 (9.7%) patients. The operation had to be terminated in two of these patients, and they were stone free after a second PCNL session. Only one patient died 1 week after PCNL because of urosepsis, while another patient with complex stones that were managed with multiple accesses experienced perinephritic abscess formation that was drained with open surgery.

Hydrohemopneumothorax, observed in 2 (0.4%) patients, was managed with chest tube placement. Ureteral laceration, managed conservatively with prolonged Double J catheter placement, was encountered in two patients.

Mean hospital stay was 2.4 ± 0.6 (range 1–7) days. The nephrostomy tube was removed after a mean of 2.6 ± 0. 5 (range 1–14) days. Auxiliary treatment alternatives, including SWL in 26 (6.1%), repeated PCNL in 16 (3.7%), and ureteroscopy in nine (2%) patients, were performed in 51 (11.8%) patients. At follow-up at 3 months, an overall success rate of 96.3%, including CIRF observed in 21.8%, was achieved. Success rates were not influenced by the presence of SLA, HT, DM, central obesity, or metabolic syndrome (Table 2).

In patients with SLA, neither auxiliary treatment nor complication rates showed significant differences when compared with those of patients without SLA (Table 2). Auxiliary treat-

Table 2. Mean Age, Stone Size, Success, and Need for Auxiliary Treatment After PCNL and Occurrence in Patients With (+) or Without (−) Cardiovascular Disease Risk Factors

	n	*Mean age (years)*	*Mean stone size (cm^2)*	*Overall success*	*Auxiliary treatment*
Total	430	44.9 ± 13.3 (range 11–77)	7.5 ± 5.2 (range 1.5–2.8)	96.3% n: 414	11.8% n: 51
SLA					
(+)	123	39.3 ± 11.5	7.2 ± 4.7	95.9% n: 118	11.4% n: 14
(−)	307	44.1 ± 16.3	7.6 ± 5.7	96.4% n:296	12.1% n: 37
Hypertension					
(+)	108	46.7 ± 12.1	7.1 ± 2.1	95.3% n: 103	11.1% n: 12
(−)	322	41.4 ± 13.8	7.6 ± 5.3	96.6% n: 311	12.1% n: 39
DM					
(+)	44	48.2 ± 7.9	7.7 ± 4.8	90.4% n: 40	20.5%[a] n: 9
(−)	386	42.1 ± 17.9	7.5 ± 5.1	96.9% n: 374	10.9% n: 42
BMI <30 kg/m^2	74	46.2 ± 15.3	7.6 ± 4.9	93.2% n: 69	9.5% n: 7
BMI <30	356	41.9 ± 13.7	7.46 ± 5.1	96.9% n: 345	12.3% n: 44
Metabolic syndrome					
(+)	41	40.4 ± 13.9	7.9 ± 4.7	92.7% n: 38	17.1[b] n: 7
(−)	389	42.9 ± 16.3	7.4 ± 4.8	96.7% n: 376	11.3% n: 44

[a] $P = 0.046$.

[b] $P = 0.048$; χ^2 test.

PCNL = percutaneous nephrolithotomy; SLA = serum lipid abnormalities; DM = diabetes mellitus; BMI = body mass index.

ment and complication rates were also similar in patients with BMI <30 kg/m^2 and >30 kg/m^2.

However, in patients with DM, auxiliary treatment alternatives were necessary in 20.5%, while they were indicated in 10.9% of patients without DM ($P = 0.046$). Furthermore, 22.7% of patients with DM experienced major complications, while 10.1% of nondiabetic patients had such complications ($P = 0.02$). Similarly, the presence of the metabolic syndrome was also associated with an increased need for auxiliary treatment alternatives and augmented risk of major complications (Table 2).

HT was a significant predictor of major complications, because 19.4% of patients with HT but only 8.7% of normotensive patients experienced major complications ($P = 0.006$).

Patients with HT, DM, and metabolic syndrome were 2.5 times (95% CI 1.4–4.5), 2.7 times (95% CI 1.2–5.6), and 2.45 times (95% CI 1.1–5.4), respectively, more likely to experience major complications (Table 3).

DISCUSSION

PCNL has become the treatment modality of choice for large-volume, complex renal stones.[9] It has the advantages of higher rates of stone clearance, cost-effectiveness, and early convalescence compared with other modalities, such as SWL and open surgery.

However, major concerns about percutaneous renal surgery are serious complications, such as blood loss, adjacent organ injuries, and life threatening infections.[15–17] Stratifying complications of PCNL as major and minor ones, Lee and coworkers[17] reported major complications (i.e., death, bleeding necessitating intervention, significant infection, urinary tract injury, and injuries to adjacent organs) in 6% of patients, and minor complications (i.e., postoperative fever, bleeding necessitating transfusion, extravasation, tube dislodgment, pneumonia, prolonged urine drainage from the flank, etc.) in more than 50% of patients undergoing PCNL.[17] The relationship of hemorrhage during PCNL and patient and procedural factors has been extensively investigated in the literature.[15]

The association between vascular pathologies and stone formation has been underlined in a recent report.[8] Although urinary tract stone formation is considered a multifactorial process, the high content of cholesterol in stones as well as lipid droplets that were observed within the interstitial cells of the medulla support a new theory in stone formation.[8] Epidemiologic studies further underlined the association of stone formation and cardiovascular risk factors.[5,6] Taylor and colleagues[5,6] demonstrated that obesity, weight gain, and DM increased the risk of stone formation. They postulated that insulin resistance, which also plays a determinant role in the pathogenesis of metabolic syndrome, could be responsible for the increased risk.[6] Furthermore, Ekeruo and associates[7] underlined the observation that obesity had a significant role in recurrent stone formation. Dietary indiscretion and coexisting DM are regarded as responsible for the increased risk of stone recurrence in obese patients. Appropriate metabolic evaluation, institution of medical therapy, and strict dietary recommendations to decrease animal protein intake have been shown to diminish the risk of recurrent stone formation in these patients.[7]

In our study, SLA, HT, and DM, which are the predominant elements of the metabolic syndrome, were observed in 28.6%, 25.1%, and 10.2% of patients, respectively. Obesity, another important determinant of metabolic syndrome and defined as a BMI >30 kg/m^2, was encountered in 17.2% of patients. According to the IDF Metabolic Syndrome World-wide Definition, metabolic syndrome was the final diagnosis in 41 (9.5%) patients.[1] Further epidemiologic studies are needed to investigate the prevalence of cardiovascular risk factors and determinants of metabolic syndrome among stone formers.

Recent studies have demonstrated that patients with endocrine comorbidities, including DM, required longer hospitalization,[14] and that the presence of DM was associated with increased blood loss during PCNL.[15] Hemorrhage necessitating blood transfusion was the predominant major complication, observed in 9.7% of patients in the present series. Furthermore,

Table 3. Prevalence of Major Complications and Odd Ratios Within 95% Confidence Interval of Patients With and Without Cardiovascular Risk Factors

	n	*Major complications*	*P value (χ^2 test)*	*Odds ratio*	*95% CI*
Total	430	11.4%			
SLA					
(+)	123	11.3%	>0.05	0.99	0.5–1.93
(−)	307	11.4%			
Hypertension					
(+)	108	19.4%	0.006	2.5	1.4–4.5
(−)	322	8.7%			
DM					
(+)	44	22.7%	0.02	2.7	1.2–5.6
(−)	386	10.1%			
BMI >30 kg/m^2	74	13.5%	>0.05	1.27	0.6–2.6
BMI <30 kg/m^2	356	10.9%			
Metabolic syndrome					
(+)	41	21.9%	0.03	2.45	1.1–5.4
(−)	389	10.3%			

CI = confidence interval; SLA = serum lipid abnormalities; DM = diabetes mellitus; BMI = body mass index.

major complications were more commonly observed in patients with DM, HT, and metabolic syndrome. The risk for major complications was 2.5 times higher in patients with HT, 2.7 times higher in patients with DM, and 2.45 times higher in patients with metabolic syndrome.

Although there is a general tendency toward an increased risk of infections, especially in patients with DM, minor complications, such as elevated body temperature and urinary tract infections, were not assessed in the present series and need to be evaluated in further studies.

Elevated BMI (>30 kg/m^2) alone did not have a significant impact on the outcome of PCNL in the present study. Although the major complications rate was slightly higher in obese patients (Table 3), this difference was not statistically significant. Similar to our findings, other authors report that the success rates, need for auxiliary procedures, complication rates, and decrease in hemoglobin concentrations were comparable in obese and nonobese patients.[18–20] It has been further emphasized that the outcome of PCNL was independent of the patients' BMI.[19]

Multiple punctures, performed in 25% of patients in the present study, seem to be a significant risk factor for severe bleeding. Although all auxiliary treatment alternatives (SWL, rigid/flexible ureteroscopy, and flexible nephroscopy) are available at our institution, we insist on performing multiple punctures. As mentioned in a previous article from our institution,[16] almost half of the stones we encounter are complex and therefore frequently indicate multiple punctures. Furthermore, aggressive PCNL monotherapy using multiple tracts has been shown to be safe and effective by other investigators, who regard this option as the first choice for massive renal staghorn calculi.[21]

As determinant cardiovascular risk factors, DM, HT, and metabolic syndrome seem to have deleterious effects on systemic homeostasis mechanisms and healing processes. Chronic inflammation and thrombogenesis have been suggested as possible causes for vascular complications in patients with the metabolic syndrome.[22] In a recent study, total leukocytes, neutrophils, and lymphocytes were elevated in men with metabolic syndrome; these counts increased in accordance with the metabolic component counts.[22]

Adipose tissue, which is considered an endocrine organ, affects the function of other organs, including vascular walls throughout the body.[23] Dysregulation of the secretion of plasminogen activator inhibitor-1, tumor necrosis factor-α, and adiponectin from the adipose tissue has been shown to be an important molecular basis of the metabolic syndrome and needs to be investigated further in kidney stone formers.[23] Recent studies indicate that serum uric acid is significantly related to risk factors of the metabolic syndrome.[24]

The increased risk of hemorrhage necessitating blood transfusion in patients with DM, HT, and the metabolic syndrome observed in the present study as well as in other studies can be partly explained by the findings of a recent experimental study that showed an impaired hemorrhage tolerance in the rat model of metabolic syndrome.[25] In obese Zucker rats manifesting the metabolic syndrome, an earlier decompensation in arterial pressure in response to hemorrhage was observed.[25] With increasing hemorrhage, investigators were able to document an increased arteriolar tone in obese rats when compared with the controls, and this increase in active tone was caused by an elevated adrenergic contribution. Furthermore, norepinephrine-induced arteriolar constriction was greater, and arterioles demonstrated earlier closure in obese rats.[25] Therefore, a combination of elevated peripheral adrenergic activity and microvessel hyperreactivity as well as adipocyte dysfunction, resulting in systemic defects in vascular walls throughout the body, can be regarded as responsible for increased hemorrhage in addition to impaired tolerance to blood loss that necessitates more frequent blood transfusion.

There are also extensive data concerning the outcome of PCNL in obese patients.[11,18–20] Although it is generally difficult to position obese patients on the urologic table, and postoperative hospitalization is usually reported to be prolonged, the outcome, including success and complication rates, is not significantly influenced.[11] Similarly, in our study we did not observe any differences in the treatment of obese patients with PCNL, unless there was an association with the metabolic syndrome. The need for auxiliary treatments after PCNL was more common in patients with DM and the metabolic syndrome, but not in those with BMI >30kg/m^2 and SLA in the present study. However, studies with a larger series of patients with multivariate analysis have to be performed to reveal the exact impact of these disorders on the outcome of PCNL.

CONCLUSIONS

The metabolic syndrome and its determinants are frequent among urinary stone formers and affect the outcome of PCNL. Although success rates are not significantly influenced, the risk of major complications, especially hemorrhage, is significantly elevated in patients with DM, HT, and the metabolic syndrome. Furthermore, the need for auxiliary treatments after PCNL is more common in patients with DM and the metabolic syndrome. Obesity and SLA have no significant impact on the outcome of PCNL. Further experimental studies are needed to answer the hypothesis questioning systemic vascular and healing defects underlying our results.

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ABBREVIATIONS USED

CI = confidence interval; CIRF = clinically insignificant residual fragments; CT = computed tomography; DM = diabetes mellitus; HDL = high-density lipoprotein; HT = hypertension; IDF = International Diabetes Federation; IVU = intravenous urography; LDL = low-density lipoprotein; PCNL = percutaneous nephrolithotomy; POD = postoperative day; SD = standard deviation; SLA = serum lipid abnormalities; SWL = shockwave lithotripsy.