

Calcification of the Epididymis and the Tunica Albuginea of the Corpora Caverosa in Patients on Maintenance Hemodialysis

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ABSTRACT: The aims of this study were to determine the incidence rates of genital calcification in male hemodialysis patients based on ultrasonography findings and to identify risk factors for this condition. Twenty-three male end-stage renal disease (ESRD) patients (mean age, 51.4 ± 12.1 years) who were on maintenance hemodialysis underwent penile and scrotal ultrasonography. For each case, we recorded the underlying renal disease and measured serum levels of phosphorus, intact parathormone, and calcium \times phosphorus product. Patients were also questioned about erectile dysfunction. The control group consisted of 22 consecutive patients (mean age, 51 years) with type 2 diabetes mellitus with normal renal function who underwent penile and scrotal ultrasonography for various reasons. In the ESRD group, ultrasound revealed calcification of the tunica albuginea of the corpora cavernosa in 15 patients (65%) and calcification of the epididymis in 16 patients (70%; 14 bilateral and 2 unilateral cases). Twenty patients (87%) showed calcification of the epididymis and/or the tunica, and 10 (43%) showed

calcification of both these tissues. The rates of epididymal and penile calcification in the ESRD patients and the controls were significantly different ($P < .001$ for both). There were no significant differences between patients with and without penile and epididymal calcification with respect to age, hemodialysis duration, frequencies of elevated serum phosphorus, elevated serum intact parathormone, elevated calcium \times phosphorus product, and frequency of erectile dysfunction (ED) ($P > .05$ for all). Ultrasonography revealed high rates of penile (tunica albuginea of the corpora cavernosa) and epididymal calcification (65% and 70%, respectively) in the ESRD patients studied, but no association was found between risk factors such as age, underlying renal disease, hemodialysis duration, frequencies of elevated serum phosphorus, elevated serum intact parathormone, and elevated calcium \times phosphorus product.

Key words: Peyronie disease, chronic renal failure, hemodialysis, ultrasonography, epididymis, end-stage renal disease.

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Soft-tissue calcification is common in patients with chronic renal disease. In most instances, these lesions remain clinically silent; however, in some patients, they cause many complications and may even become life threatening. Hemodialysis patients may exhibit soft-tissue calcification in various organs and tissues, including the heart, lungs, vessels, and skin (Kim et al, 2001; Matsuo et al, 2001; Leskinen et al, 2002; Raggi et al, 2002; Ventura et al, 2002; Rubel and Milford, 2003). One group of authors reported a 79% incidence of soft-tissue calcification in the dialysis patients they studied (Kuzela et al, 1977). Calcification within the penis can occur in the soft tissue and/or in vessels and can lead to calciphylaxis or arterial insufficiency, respectively.

In one investigation, 19% of the male hemodialysis patients studied showed calcification of the penile artery on

plain x-rays (Dalal et al, 1992). However, the current literature contains no information on the incidence of calcification of penile tissues other than vascular structures in patients with end-stage renal disease (ESRD).

Our main aim in this study was to determine the incidence of calcification of the genitalia of male ESRD patients based on ultrasound findings. To identify risk factors, we also investigated for links between genital calcification and age, hemodialysis features, cause of renal disease, and serum parameters in patients with and without calcification. Any relationship between ED and tunical calcifications was investigated.

Material and Methods

The study involved 23 male ESRD patients (mean age, 51.4 ± 12.1 years; age range, 25–70 years) who were on 3-times-weekly maintenance hemodialysis (mean dialysis duration, 32.3 ± 32 months; range, 3–120 months). The hemodialysis sessions were performed with hollow-fiber hemophane dialyzers at a dialysate flow rate of 500 mL/min and a blood flow rate of 200 mL/min

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for 4 hours. A bicarbonate dialysate containing sodium (140 mEq/L), potassium (2 mEq/L), calcium (3.5 mEq/L), magnesium (2 mEq/L), bicarbonate (30 mEq/L), and acetate (8 mEq/L) was used. Penile and scrotal ultrasonography were performed in each case using a 7.5-MHz linear-array high-resolution transducer, and ultrasonography was performed by 2 radiologists who interpreted the patients together. For each patient, we also recorded the underlying renal disease and measured predialysis serum levels of phosphorus, intact parathormone, and calcium \times phosphorus product. These measurements were performed once a month, and the results of the last 3 months were averaged to obtain a mean value. The serum level of phosphorus higher than 5.5 mg/dL, calcium higher than 9.5 mg/dL, and intact parathormone higher than 3 times the upper normal limits were accepted as elevated according to the Kidney Disease Outcomes Quality Initiative Guidelines (Massey, 2003). Nine patients with elevated phosphate were regularly receiving calcium containing phosphate binders (mean daily dose 1–1.5 g). Eleven patients with elevated iPTH were using calcitriol (mean dose; IV 0.5–1 μ g/3 times per week in the hemodialysis session). Patients were also questioned using a 5-item version of the International Index of Erectile Function (Rosen et al, 1999). The control group consisted of 22 consecutive individuals (mean age, 51 years; age range, 33–60 years) with type II diabetes mellitus and normal renal function (normal serum creatinine and creatinine clearance and without microalbuminuria) who underwent penile and scrotal ultrasonography for various reasons. None of the control subjects used any medication that might have affected the calcium and phosphate metabolism. The same ultrasonography equipment was used in all control cases. Informed consent was obtained from all patients.

Frequencies of calcification at different sites were determined, and rates in patients and controls were compared. Also, patients with and without penile calcification and patients with and without epididymal calcification were compared with respect to age, dialysis duration, underlying renal disease, frequency of ED, and frequencies of elevated serum phosphorus, intact parathormone, and calcium \times phosphorus product. Data were statistically analyzed using the chi-square test corrected for continuity (according to Yates) and logistic regression analysis.

Results

Ultrasound revealed calcification of the tunica albuginea of the corpora cavernosa in 15 patients (65%) and calcification of the epididymis in 16 patients (70%; 14 bilateral and 2 unilateral cases). Twenty patients (87%) showed calcification of the epididymis and/or the tunica, and 10 (43%) showed calcification of both these tissues. One patient (4%) exhibited testicular microlithiasis, and 1 patient (4%) exhibited calcification of the testicular tissue. The calcifications of the tunica albuginea were in linear configuration and the calcifications of the epididymis were in punctuate configuration. The sizes of the calcifications in the ESRD group ranged from 0.2 to 0.5 cm, and they were mainly seen in the epididymis as multifocal lesions,

and in cases in which the tunica albuginea was affected, the number of lesions at this site ranged from 1 to 3 (Figures 1 and 2). Four of the 15 calcifications of tunica albuginea were dense with acoustic shadows. The number and localization of the calcifications observed in the study and the control groups are shown in Table 1.

Of the 22 control subjects, 1 (5%) showed penile plaque, 1 (5%) had testicular microlithiasis, and none showed epididymal calcification. The differences between the ESRD and control groups with respect to frequencies of penile and epididymal calcification were statistically significant ($P < .001$ for both).

The primary cause of ESRD was diabetes mellitus in 10 patients (43%), hypertensive nephrosclerosis in 3 patients (13%), obstructive uropathy in 3 patients (13%), glomerulonephritis in 2 patients (8%), amyloidosis in 1 patient (4%), polycystic kidney disease in 1 patient (4%), and was unknown in 3 patients (13%). Eleven patients (48%) had elevated parathormone levels, and 9 (39%) had high serum phosphorus levels. Calcium \times phosphorus product was >55 in 4 patients (17%). There were no significant differences between patients with and without penile calcification with respect to age, hemodialysis duration, or elevated levels of serum phosphorus, serum intact parathormone, and calcium \times phosphorus product ($P > .05$ for all). The same was true for comparisons of patients with and without epididymal calcification ($P > .05$ for all). Fifteen patients (65%) reported having experienced various levels of ED, but ED was not statistically correlated with tunical calcification ($P > .05$). Characteristics of the patients are shown in Table 2.

Calcium-based phosphorus binders were used in each patient, and the doses of calcium-based binders were not found to be significantly different between the patients with or without calcifications.

Discussion

Many patients with ESRD develop soft-tissue calcification, but the pathogenesis of this process is not clearly understood. Although the elevated serum phosphorus level, increased calcium \times phosphorus product, severe secondary hyperparathyroidism, older age, and prolonged time on hemodialysis are known factors that are associated with uremic calcification, our study revealed no associations between penile or epididymal calcification and any one of these parameters (Drueke, 1996). This raises the question of whether other factors are responsible for the pathogenesis. Recent evidence indicates that uremic calcification is a cell-mediated process, which means that elevated levels of transforming growth factor; vitamin K-dependent proteins, such as osteocalcin and atherocalcin; and deficiencies in calcium-regulatory proteins, such as

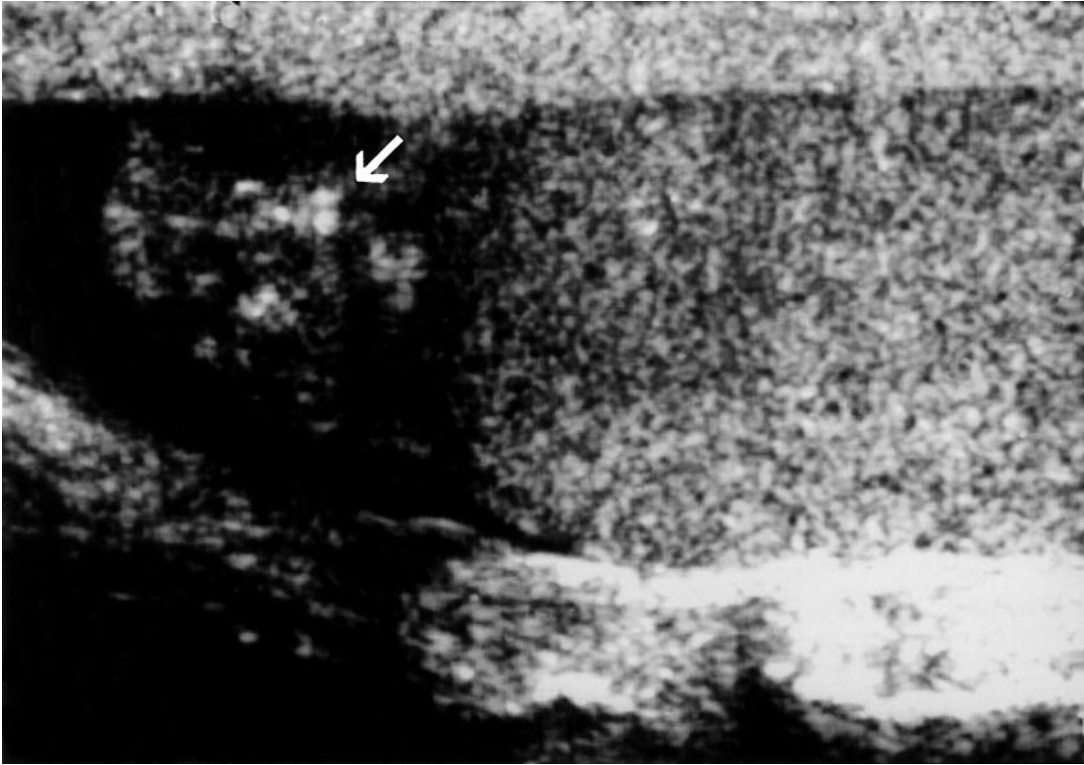


Figure 1. Longitudinal ultrasound examination shows multiple echogenic foci of the head of the epididymis.

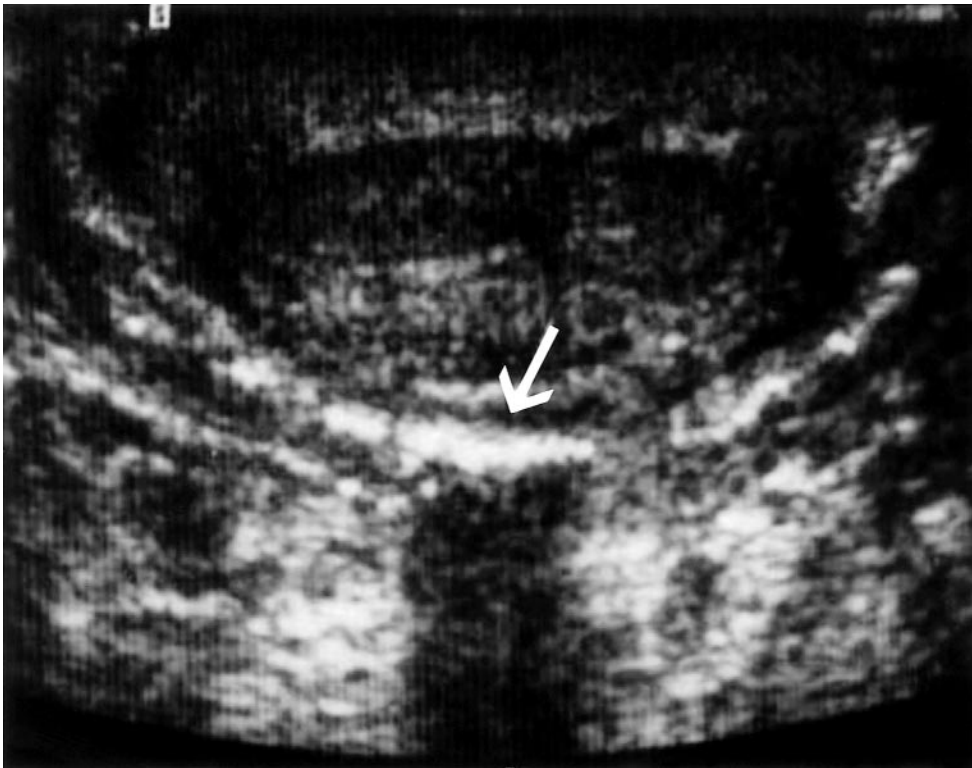


Figure 2. Axial image of the penis shows calcification with acoustic shadowing of the tunica albuginea.

Table 1. Characteristics of the study group

Number of patients	23
Age, y	51 (25–70)
Dialysis duration, mo	32.3 ± 32
Primary cause of ESRD (%)	
Diabetes mellitus	10 (43)
Hypertensive nephrosclerosis	3 (13)
Obstructive uropathy	3 (13)
Glomerulonephritis	2 (8)
Amyloidosis	1 (4)
Polycystic kidney disease	1 (4)
Unknown	3 (13)
Elevated CaXP product (>55) (%)	4 (17)
Elevated parathormone (%)	11 (48)
Elevated phosphorus (%)	9 (39)
Erectile dysfunction (%)	15 (65)

fetuin, may also be contributing factors (Jacoby and Semenkovich, 2001; Tintut and Demer, 2001; Ketteler et al, 2002; Jian et al, 2003).

The reported prevalence of ED in ESRD patients is approximately 80% (Rosas et al, 2001). ED in patients with chronic renal failure can be the result of many factors, including atherosclerosis, secondary hyperparathyroidism, diabetes mellitus, and side effects of medication. Vascular calcification may be one of the causes of ED in this patient group (Dalal et al, 1992). For the general population, the reported incidence rates of penile plaque range from 0.39%–3.2% (Gelbard et al, 1990; Schwarzer et al, 2001). In contrast, we observed a penile plaque frequency rate of 65% in the ESRD patients we studied. The tunica albuginea of the corpora cavernosa contributes to the elasticity, rigidity, and veno-occlusion of the penis, and thus plays an essential role in penile erection. Plaques may alter penile anatomy and negatively affect erectile function. Calcification of the tunica is one possible explanation for ED in ESRD patients, though our study did not demonstrate such a relationship.

Problems such as calciphylaxis and ischemic gangrene of the penis are well-known complications of ESRD; however, ours is the first study to have investigated the incidence of penile and epididymal calcification in this patient group (Guvel et al, 2004). Our ultrasound findings show that men with ESRD have very high rates of calcification of the tunica albuginea and epididymis (65% and 70%, respectively). However, we found no relationships between the prevalence of penile or epididymal calcification and age, dialysis duration, underlying renal disease, ED, or serum levels of phosphorus, intact parathormone and calcium × phosphorus product in the ESRD patients we investigated. Studies with long-term follow-up of ESRD patients with penile and epididymal calcification would provide valuable information about the pos-

Table 2. The findings of ultrasonography of the study and control groups

	n (%)	
	Study Group	Control Group
Calcification of the E*	16 (70)	0
Focal	0	
Multifocal	16	
Bilateral	14	
Unilateral	2	
Calcification of the TA	15 (65)	1 (4)
1	8	
2	5	1 (4)
3	2	
Proximal	12	
Distal	3	
Calcification of the E and/or TA	20 (87)	1 (4)
Calcification of the both E and TA	10 (43)	—
Testicular microlithiasis	1 (4)	1 (4)

* E indicates epididymis; TA, tunica albuginea.

sible occurrence of calciphylaxis, ischemic gangrene, and ED. In addition, in-depth study of the pathophysiology of uremic calcification in this patient group is needed.

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