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Posterior urethral valves: Metabolic consequences in a cohort of patients

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Summary

Background
Despite the improvements in diagnosis and management of posterior urethral valves (PUVs), about one third of patients develop chronic kidney disease (CKD). Children with PUVs might have abnormal calcium, phosphorus, vitamin D and parathyroid hormone levels, which could affect their bone growth and overall health.

Objective
The aim was to determine the relationship between kidney function, vitamin D deficiency and secondary hyperparathyroidism in children with PUVs.

Patients and methods
Sixty-four children with PUVs were followed for a period of 3.64 ± 2.50 years after their initial presentation and management. Their laboratory parameters were compared with 20 age-, gender- and race-matched children in a control group, including: serum calcium, phosphorus, intact parathyroid hormone (iPTH), 25-hydroxyvitamin D levels, and kidney function.

Results
Children with PUVs had significantly lower estimated kidney function ($P = 0.006$) and vitamin D levels ($P < 0.001$) and higher iPTH levels ($P = 0.042$). There were no significant between-group differences in serum calcium, phosphorus, alkaline phosphatase, sodium, potassium, and bicarbonate levels. There was a strong correlation between the degree of vitamin D deficiency and hyperparathyroidism and the degree of kidney dysfunction ($r = 0.52$ and -0.52, respectively) in the PUV group. On a multivariate analysis, the kidney dysfunction was the only independent predictor of vitamin D deficiency ($\rho = 0.271$, $P < 0.001$), while kidney dysfunction, serum calcium and alkaline phosphatase were independent predictors for hyperparathyroidism ($\rho = 0.925$, $P < 0.001$, $\rho = 0.933$, $P < 0.001$ and $\rho = 0.913$, $P < 0.001$, respectively).

Discussion
The prevalence of CKD in children with PUVs ranges from 30 to 60%. Patients with CKD are more likely to have vitamin D deficiency and display more-prominent hyperparathyroidism. Compared with a control group with normal kidney function, the present cohort had lower 25-hydroxyvitamin D and higher iPTH serum levels. Abnormal kidney function was a major predictor for both serum levels.

In this cohort, there were no significant differences in serum calcium and phosphorus between children with PUVs and the control group, and also between those with and without CKD. On the contrary, vitamin D level decreased early in the disease and progressively declined thereafter, while iPTH was the opposite. These findings were comparable to previous studies.

This study had some limitations because it was a single center cross-sectional non-randomized study. However, the findings in this study can be extrapolated to children with PUVs and CKD from other origins because the unit is considered as a referral center in the Middle East region.

Conclusion
Abnormal kidney function, vitamin D deficiency, and secondary hyperparathyroidism are prevalent in children with PUVs. Kidney function is the main determinant of vitamin D and parathyroid hormone levels. Efforts should be directed toward managing CKD, and controlling vitamin D deficiency and hyperparathyroidism in children after ablation of PUV.

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Introduction

PUVs are the most common cause of congenital urethral obstruction and they affect male children with a broad spectrum of clinical severity and sequelae [1,2]. The main treatment goal for children with PUVs is to preserve renal and bladder functions. In recent decades, primary valve ablation has become the mainstay management of such cases [3–5]. Despite the improvement in diagnosis and management of PUV, 25–40% of children progress to renal failure [6,7]. The kidneys play a pivotal role in the complex regulation of mineral metabolism, so it is not surprising that children with chronic kidney disease (CKD) have bone disorders. Children with long-standing CKD display clinical symptoms of bone disease, including bony deformities and fractures, which contribute to long-standing disability [8,9].

The presence of vitamin D deficiency, both in the general population and in children with CKD, is based mainly on the effects of vitamin D on calcium homeostasis and bone health. Serum levels of 25-hydroxyvitamin D are inversely associated with serum PTH level both in patients with CKD [10] and in those without this disease [11]. Serum 25-hydroxyvitamin D is also an inverse predictor of disease progression and death in people with CKD [12,13].

Currently, there is clinical evidence supporting a strong link between vitamin D insufficiency or deficiency and the risk of CKD [8–11]. Previous reports have come from small clinic-based samples and may not represent the true association between vitamin D status and kidney function in the CKD population [12,13]. Moreover, no clinical studies in children with PUVs and CKD population have been performed to support this assertion. Therefore, the present study aimed to determine the relationship between kidney function and vitamin D deficiency, and secondary hyperparathyroidism in children with PUVs.

Patients and methods

Out of the 89 children treated for PUVs at the present outpatient clinic, a cross-sectional study was carried out on 64 boys and a control group of 20 boys (age-, gender- and race-matched) between January 1st and December 31st 2013. Control cases were consecutively recruited from boys with normal kidney function who were scheduled for distal hypospadias repair and orchidopexies at the same hospital during the same period of the study. All of them had a complete renal panel, along with serum 25-hydroxyvitamin D and intact parathyroid hormone (iPTH) levels checked. All of the children's medical records were reviewed to collect a detailed medical history. This study was approved by the hospital Human Research Ethics Committee and consent was obtained from the participants' parents prior to their inclusion in the study.

Inclusion criteria were: children with history of PUV, who were managed at the present hospital, who were willing and had the mental competence to participate in the study. Exclusion criteria were: renal transplantation; history of parathyroidectomy; use of calcimimetics and medications known to affect bone metabolism such as glucocorticoids; and life-threatening comorbid conditions such as HIV, malignancy, active infection, and hepatic disease. For the purposes of the present study, participants were excluded if they were missing serum creatinine, calcium, phosphorus, alkaline phosphatase, 25-hydroxyvitamin D and iPTH information.

Serum creatinine was analyzed using the enzymatic method, calibrated to be traceable to isotope dilution mass spectrometry. An estimate of the glomerular filtration rate (eGFR) was obtained by the Schwartz formula [14]. The stage of CKD was determined according to recommendations from the National Kidney Foundation [15].

Serum calcium and phosphorus were measured by automated techniques. Intact parathyroid hormone (iPTH) was measured by a radioimmunometric assay (RIA) (Scantibodies, Santee, CA) – the normal range is 14–66 pg/ml; intra-assay and inter-assay coefficients of variation were <5 and $<7\%$, respectively. Serum 25-hydroxyvitamin D concentrations, as a reliable measure of overall vitamin D status, was measured by electrochemiluminescence immunoassay (ECLIA) on a Roche Elecsys 10100/201 system (Roche Diagnosis Elecsys, Mannheim, Germany); intra-assay and inter-assay coefficients of variation were below 5% and 9%, respectively. A 25-hydroxyvitamin D deficiency was defined as having levels <20 ng/ml (<50 nmol/l).

Statistical analysis

Descriptive data were examined for all variables. For continuous variables, results were presented as mean $\pm$ SD. Statistical differences in variables were compared using one-way analysis of variance (ANOVA) and unpaired Student's *t*-test for normally distributed variables and Kruskal–Wallis test for abnormally distributed variables. Categorical variables were recorded as frequency counts, and intergroup comparisons were analyzed by Chi-squared test. Associations between vitamin D, iPTH status, and kidney function were analyzed by multivariate logistic regression analysis [OR with 95% CI after including significant variables in the univariate study]. Statistical significance was accepted if $P < 0.05$. Data analysis was performed using SPSS for Windows, version 17.0 (SPSS, Chicago, IL, USA).

Results

Sixty-four children with a history of PUV, and 20 children in an age-, gender- and race-matched control group were included in the study. The mean age of the study group was 3.8 years versus 4.5 years for the control group. The median age at valve ablation was 6 months (five were born prematurely) with a mean follow-up period of 3.64 $\pm$ 2.50 years. The baseline age and biochemical values in both groups are displayed in Table 1. All children in the control group had normal kidney function, while 23 (35.9%) in PUV group had CKD Stage 2–5 (12 with CKD Stage 2, five with Stage 3, four with Stage 4 and two with Stage 5 not on dialysis).

Corrected serum calcium levels were in the reference interval in both groups. Serum phosphorus levels were within the reference interval in all children except three with CKD in the PUV group who had hyperphosphatemia (one with Stage 3, one with Stage 2, and one with Stage 5