Response to Letter to the Editor: Nephrocalcinosis and Nephrolithiasis in X-Linked Hypophosphatemic Rickets: Diagnostic Imaging and Risk Factors

Guido de Paula Colares Neto,1,2 Fernando Ide Yamauchi,3 Ronaldo Hueb Baroni,3 Marco de Andrade Bianchi,4 Andrea Cavalanti Gomes,4 Maria Cristina Chammas,4 and Regina Matsunaga Martin1,2

1Osteometabolic Disorders Unit, Endocrinology Department, Division of Internal Medicine, Hospital das Clinicas da Universidade de São Paulo HCFMUSP; Av. Dr. Enéas de Carvalho Aguiar, 155 - PAMB, 8 andar, bloco 3, CEP: 05403-900, São Paulo, SP, Brazil

2Endocrinology Department, Hormone and Molecular Genetics Laboratory (LIM/42), Hospital das Clinicas da Universidade de São Paulo HCFMUSP; Av. Dr. Enéas de Carvalho Aguiar, 155 - PAMB, 2 andar, bloco 6, CEP: 05403-900, São Paulo, SP, Brazil

3Department of Radiology and Oncology, Division of Radiology, Computed Tomography Unit, Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo, CEP: 05403-001 São Paulo, SP, Brazil

4Department of Radiology and Oncology, Division of Radiology, Ultrasound Unit, Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo, CEP: 05403-001, São Paulo, SP, Brazil

Corresponding author

Regina Matsunaga Martin

Av. Dr. Enéas de Carvalho Aguiar, 155 - PAMB, 2 andar, Bloco 6, CEP: 05403-900, São Paulo, SP, Brazil

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We thank Dr. Vaisbich and colleagues for their comments on our recent paper describing diagnostic imaging and risk factors for nephrocalcinosis (NC) and nephrolithiasis in X-linked hypophosphatemic rickets (XLH) [1].

In response to their letter, we reassessed each patient’s data to determine the number of episodes of hypercalciuria (calciuria ≥ 4 mg/kg/day) among the total number of urinary samples obtained during the study (episodes/samples). To validate the use of each urinary sample, twenty-four-hour creatinuria was measured simultaneously and was evaluated according to reference values for sex and age for each patient during follow-up.

Among the children, only one child with NC and one without NC had at least one episode of hypercalciuria (3/8 and 1/13 episodes/samples, respectively). On the other hand, three adults with NC (4/10, 1/9, and 1/10 episodes/samples) and two without NC (1/7 and 2/11 episodes/samples) had episodes of hypercalciuria. There was no difference between the age groups in terms of the number of episodes of hypercalciuria (p= 0.91).

Although hypercalciuria is a risk factor for NC, its low prevalence in our XLH cohort may be explained by low dietary calcium intake, irregular use of calcium carbonate and calcitriol by patients, and constant monitoring with frequent measurements of serum calcium, serum parathyroid hormone, and urinary calcium with adjustments of the dose of calcitriol or calcium salts when necessary.

With regard to the assessment of phosphaturia, XLH patients have impaired tubular reabsorption of phosphate (TRP) and tubular maximum reabsorption of phosphate per unit of glomerular filtrate (TmP/GFR), which are the parameters used to support the XLH diagnosis. Different authors [2-5] have demonstrated the importance of phosphate in the genesis of NC using the TRP and/or TmP/GFR to characterize patients, as was done in our study, but they did not compare these parameters between groups with or without NC.
However, the amount of phosphate excreted in the urine can reflect phosphate intake, which varies daily according to phosphate dosages, in XLH patients. This association was demonstrated by the difference in phosphaturia between age groups in our study, since children receive higher doses of phosphate and hence have higher levels of phosphaturia than adults.

In our cohort, the children, who received greater doses of phosphate during treatment than did the adults, had a higher prevalence of NC. In agreement with these data, several reports have suggested positive associations between daily oral phosphate doses and the risk of developing NC [6, 7], whereas relationships with active vitamin D therapy and/or with the presence of hypercalciuria have been observed less frequently [6].

Furthermore, the four adult patients who did not receive phosphate during childhood and developed NC had not been treated with calcitriol in the past and started using it (3-4 ng/kg/day) during the study. Only one of these patients experienced an episode of hypercalciuria in the entire follow-up (1/9 episode/samples). In these patients, hyperphosphaturia was the main metabolic factor for NC identified throughout follow-up, which may corroborate the positive association of hyperphosphaturia with NC.
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