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Serum 25-Hydroxyvitamin D Level and Acute-Phase Reaction Following Initial Intravenous Bisphosphonate

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To the Editor:

Children often will complain of severe musculoskeletal pain and will develop fever with a first course of intravenous bisphosphonates. Acute-phase reaction (APR) can be severe enough for the child to refuse further therapy.[1,2] The mechanism underlying the APR from intravenous bisphosphonates is not known.[3,4] However in a double-blind, randomized, crossover, placebo-controlled study in 12 children, treatment with Atorvastatin did not alleviate the APR.[1] Recently, Bertoldo and colleagues[5] reported an association between serum 25-hydroxyvitamin D [25(OH)D] level and APR after bisphosphonate infusion. In essence, lower levels of vitamin D were associated more frequently with APR, and vice versa.[5] We report the results of reanalysis of our data in order to evaluate a possible association between serum 25(OH)D level and APR following initial intravenous bisphosphonate treatment in children.

In our bone and mineral disorder clinic, intravenous infusion of bisphosphonates is given on two consecutive days, referred to as a *cycle*. In our published study, children received two cycles given 3 to 4 months apart.[1] Children completed the visual analogue pain scale (0 to 100 mm) at baseline before the infusion (pain scale 1). Pain scale 2 was completed on day 1 late in the evening, pain scale 3 on day 2 in the morning prior to the second infusion, pain scale 4 was completed on day 2 late in the evening after the infusion, and pain scale 5 in the morning of day 3. The children's families also recorded whether they needed medications to alleviate their pain or fever as either "Yes" or "No." For musculoskeletal pain, children were given oxycodone, considered not to interfere with the inflammatory markers that were being evaluated. For fever ($\geq$39°C), if tepid sponging did not bring the temperature down, patients were instructed to take acetaminophen. APR was categorized as presence of fever needing acetaminophen and/or musculoskeletal pain requiring oxycodone. Nonparametric Spearman correlation between serum 25(OH)D level and pain scales and multivariate regression modeling with backward elimination were performed using SPSS 18.0. A p value less than .05 was considered significant.

The mean age of 12 children (10 girls and 2 boys) was 12.1 $\pm$ 4.2 years. In the first cycle, 7 children (58.3%) developed APR. There was no significant correlation between serum 25(OH)D level (Mayo Medical Laboratories, Rochester, MN, USA) and pain scale prior to bisphosphonate infusion. In contrast, following bisphosphonate infusion, an inverse correlation was found between pain scale and serum 25(OH)D (Table 1 and Fig. 1). These findings remained true for the second cycle (2 children developed APR) and for the two cycles combined together (data not shown). The two cycles then were combined for multivariate analysis. The correlation between serum 25(OH)D level and sum of pain scales after infusion remained significant even after adjusting for confounding variables such as treatment arms (placebo versus Atorvastatin), body mass index (BMI), parathyr-

Table 1. The Statistical Correlation of 25-Hydroxyvitamin D and Visual Analogue Pain Scale Obtained at Different Time Points With the Initial Intravenous Bisphosphonate Therapy

	Correlation coefficient	p Value
Pain prior to bisphosphonate infusion (pain scale 1)	−0.323	0.306
Postinfusion pain (pain scale 2)	−0.752	0.005
Postinfusion pain (pain scale 3)	−0.545	0.067
Postinfusion pain (pain scale 4)	−0.555	0.061
Postinfusion pain (pain scale 5)	−0.591	0.043
Sum of postinfusion pain scales (pain scales 2 to 5)	−0.696	0.012

Note: There is a robust inverse correlation between 25-hydroxyvitamin D and pain following bisphosphonate infusion.

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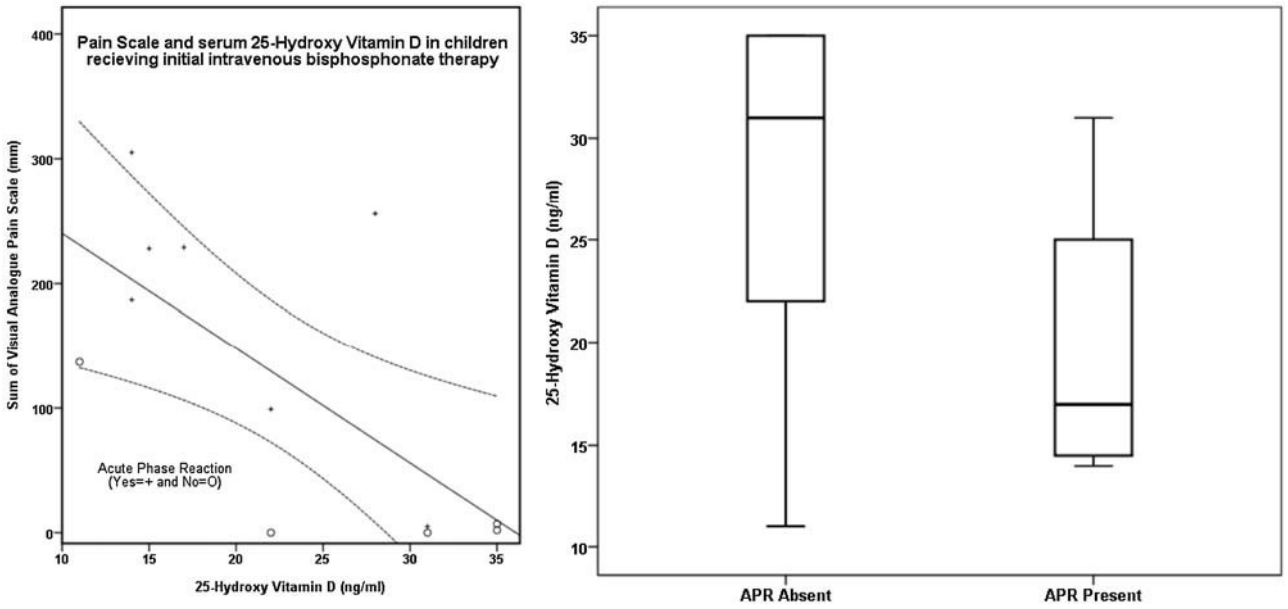

Fig. 1. (*Left*) The distribution of the sum of postinfusion pain scales across serum 25-hydroxyvitamin D levels. The lines represent the linear regression line with 95% confidence interval. (*Right*) The box-plot distribution of serum 25-hydroxyvitamin D level in children with and without acute-phase reaction (APR). The centerline in the box-plot is the median (50th percentile). The ends of the box are the 25th and 75th percentiles. The lower and upper whiskers stand for minimum and maximum.

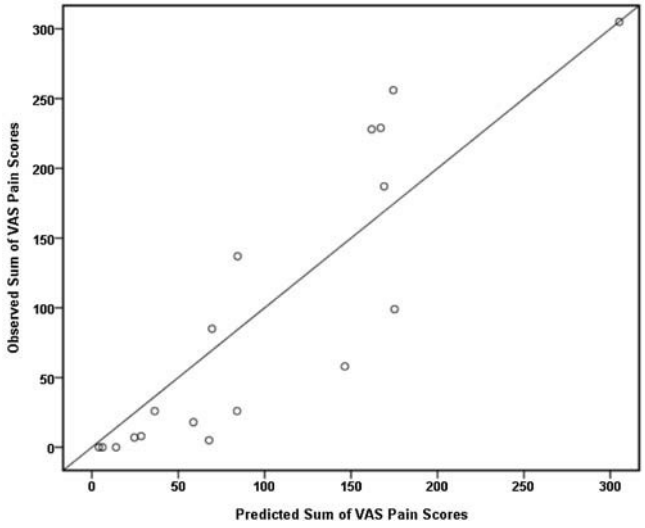

Fig. 2. The observed sum of postinfusion pain scales versus predicted sum of postinfusion pain scales adjusted for serum 25-hydroxyvitamin D levels.

oid hormone, osteocalcin, bone-specific alkaline phosphatase, and urinary *N*-telopeptides. Serum 25(OH)D was the only protective variable that reduced the postinfusion pain scale by 32.5 ± 13.5 mm (adjusted $p = .0315$) on the visual analogue scale (VAS) for every 10 ng/mL increment in serum 25(OH)D when all other variables were held constant (adjusted $R^2 = 0.74$; Fig. 2).

We thus believe that our data support the findings reported by Bertoldo and colleagues[5] and can be extrapolated to children as well. We believe that low serum vitamin D is a risk factor for APR and thus would recommend that children be replete with vitamin D prior to giving bisphosphonate therapy until we have a better understanding of the underlying mechanism of APR following intravenous bisphosphonate therapy.

Acknowledgments

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