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Conventional Therapy in Adults With X-Linked Hypophosphatemia: Effects on Enthesopathy and Dental Disease

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Abstract

X-linked hypophosphatemia (XLH), the most common form of heritable rickets, is a dominant disorder of phosphate homeostasis whose prevalence is estimated at 1 in 20 000 (1). The pathophysiology of this disease is related to loss of function mutations in the phosphate-regulating endopeptidase gene (PHEX) (2). PHEX is normally expressed in bone and teeth and its disruption results in increased circulating levels of fibroblast growth factor 23

(FGF23) (3). FGF23 acts in an endocrine manner at the kidney to both decrease renal tubular reabsorption of phosphate and renal 1α-hydroxylase activity, resulting in the combined findings of hypophosphatemia and inadequate levels of circulating 1,25 dihydroxyvitamin D observed in XLH (2).

Hypophosphatemia, low 1,25 dihydroxyvitamin D, and, perhaps independently, elevated FGF23 and disruption of PHEX contribute to the broad range of severity in skeletal and dental morbidities in XLH (1). Common skeletal abnormalities observed in XLH include bowing of the legs, anteromedial rotation and torsion of the tibiae, and poor bone mineralization (osteomalacia) with resultant growth retardation and rachitic bone disease (4). However, later in life, patients often experience mineralization of tendons and ligaments (enthesopathy) (1). Dental morbidities include delayed dentition and dental abscesses with the latter continuing throughout adult life (1).

The current standard of therapy for XLH is a regimen of active vitamin D metabolites, usually calcitriol, and phosphate beginning at time of diagnosis and continuing to growth completion (1). The administration of these therapies intermittently increases serum phosphate, providing necessary mineral to the growing skeleton and thereby partially correcting leg deformities (5). After growth completion, the rationale for therapy is directed toward symptomatic osteomalacia and prevention or correction of fractures and insufficiency fractures (1). It remains to be

established whether therapy affects the other major adult sequelae of XLH, particularly enthesopathy and dental disease.

Continuing conventional treatment into adulthood has been controversial both because its efficacy is not well studied and because it is burdensome and potentially toxic (4). Long-term therapy with calcitriol and phosphate may result in hyperparathyroidism, hypercalcemia, hypercalciura, nephrocalcinosis, and in extreme cases, chronic kidney disease (4). However, if monitored for safety, treatment has been shown to improve certain features of the disease, including pain and osteomalacia (6). Therefore, it is of great clinical importance to establish the effect of therapy on enthesopathy and dental disease during adult life. Using data from a relatively large cohort of XLH patients, this study examined the association between conventional XLH therapy and two significant morbidities experienced in the adult phase of the disease: enthesopathy and dental abscess formation.

Materials and Methods

Subjects and design

The study sample included 52 XLH patients aged 18 years or older. Patients were offered participation during clinical visits to the Yale Bone Center or upon referral from other physicians. The study population consisted of 18 males and 34 females. Exclusion criteria included presence of other diseases likely to impact bone and mineral metabolism (eg,

renal, hepatic, gastrointestinal disorders, and malignancy), treatment with estrogen or bisphosphonates, and pregnancy. The study was approved by the Human Investigation Committee at the Yale University School of Medicine (number 0607001636). Informed consent was obtained from all patients.

Data collection

Biochemical measures reflecting pathophysiology or therapeutic toxicity were obtained for each study participant. Participant characteristics, including age at onset of treatment, years with treatment, frequency of pain medication use, previous osteotomies, and number of dental abscesses were obtained from both medical records and extensive questioning of history. Research nursing staff measured participant height using a stadiometer and weight using a calibrated scale. These measurements were used to calculate both height z-scores and body mass index (BMI) with the latter calculated as kilogram body weight per height in meters squared. Body fat percentage was determined by dual-energy x-ray absorptiometry (Hologic Discovery). Participants were genotyped by Sanger sequencing to determine the nature of their PHEX mutations. We categorized frame-shift and splice-site mutations as severe and missense and point mutations as nonsevere. Sites of enthesopathy were determined via skeletal survey examined by a radiologist. The specific anatomic sites surveyed included shoulders, elbows, hands, wrists, pelvis, knees, ankle, and thoracic-lumbar spine. Serum PTH was measured

as area under the curve (PTHauc) from samples obtained at eight consecutive intervals over 26 hours using a midregion assay (7). FGF23 was measured as a single value from a fasting morning sample using the Kainos intact ELISA kit (kindly provided by Kyowa Hakko Kirin Pharma, Inc).

Exposures of interest

The primary exposure of interest in this study was treatment with calcitriol (or high dose vitamin D) and phosphate. Because of the importance of age in the natural history of this disease, treatment exposure was assessed as a proportion of both total years of life and total years of adult life. All years of life for age 18 years and older were counted toward adult life. Proportion of adult life with treatment was calculated by dividing total years of treatment in adult life by total years of adult life. This exposure variable was categorized into three levels based on the distribution of the sample: 0.0 of adult life with treatment, greater than 0.0 but less than 1.0 of adult life with treatment, and 1.0 of adult life with treatment. Proportion of total life with treatment was calculated by dividing total years of treatment throughout life by total years of life. This exposure variable was categorized into four levels based on the quartile distribution of the sample: 0–0.435, 0.436–0.587, 0.588–0.880, and 0.881–1.0.

Outcomes of interest

There were two primary outcomes of interest in this study: number of sites of enthesopathy identified on an a priori-designed skeletal survey, and number of dental abscesses

experienced per participant. Because the number of enthesopathy sites was distributed normally, it was assessed as a continuous variable. In contrast, the number of dental abscesses followed a highly skewed distribution and was therefore assessed as a dichotomous variable: a history of more than five dental abscesses (severe dental disease) vs a history of five or fewer dental abscesses (nonsevere dental disease), in keeping with a clinical impression of the disease severity.

Statistical analysis

The association between each of our two primary exposure variables, proportion of adult life and proportion of total life with treatment, and number of sites of enthesopathy was assessed using multiple linear regression. The association between each of our two primary exposure variables and dental disease severity was assessed using multiple logistic regression, modeling the odds of having severe vs nonsevere dental disease. In a similar manner, we also assessed bivariate associations of age, sex, BMI, mutation severity, PTHauc, FGF23, and proportion of treatment in childhood with enthesopathy and dental disease severity, respectively. Because of the importance of age in the natural history of XLH, all further models included age as a covariate. Age-adjusted models included only the primary exposure variable of interest and age. In addition, the following variables were assessed as potential confounders of the relationship between the respective exposure variables and enthesopathy: sex, BMI, mutation severity, PTHauc, and FGF23. Covariates

were retained in the model if their addition resulted in a 10% or greater change in the parameter estimate for the primary exposure variable. Both fully adjusted models for enthesopathy included age, sex, BMI, mutation severity, and PTHauc. Both fully adjusted models for dental disease included age, sex, and mutation severity. For all models assessing proportion of life with treatment as the primary predictor, proportion of childhood with treatment was also included as a covariate. Proportion of childhood with treatment was assessed as a dichotomous variable: less than 0.80 of childhood vs 0.80 or greater of childhood. *P* values for trend and global *P* values were obtained for the primary predictor variables. All analyses were performed using the statistical software package SAS version 9.3.

Results

Descriptive statistics

Table 1 presents selected participant characteristics across three groups defined by proportion of adult life with treatment. The mean age of the study sample was 39 years. The total years of childhood treatment (before age 18 y) were relatively similar across all groups, with an overall sample average of 13.9 years. For the entire sample (as well as for each treatment category), there were approximately 35% males and 65% females, consistent with the X-linked dominant mode of inheritance. Most participants had severe vs not severe mutations (65% vs 25%). On average, 1.8 sites of enthesopathy were identified per patient. Average number

of sites of enthesopathy across the three proportional treatment categories did not differ notably. A majority of our sample had severe dental disease vs nonsevere dental disease (61.5% vs 38.5%). There were notable differences in dental disease severity across the adult life treatment categories: 75% of those participants with no treatment (0%) during adult life had severe dental disease, whereas only 47% of those treated throughout all (100%) of adult life had severe dental disease. Table 2 presents bivariate regression models of the relationships between potential predictors and each outcome of interest. Age, BMI, PTHauc, and proportion of treatment in childhood were significantly associated with number of sites of enthesopathy. Approximately 38% of the variability in number of sites of enthesopathy was explained by age. Being in the first quartile of total life treatment, age, BMI, and proportion of treatment in childhood were significantly associated with dental disease severity.

Enthesopathy

Table 3 presents both age-adjusted and multivariate-adjusted multiple linear regression models of the relationship between proportion of adult life with treatment, as well as other predictors, and number of sites of enthesopathy. We found that after adjusting for age, proportion of adult life with treatment was not a significant predictor of number of sites of enthesopathy (age-adjusted global $P = 0.96$), and this finding remained after adjusting for confounders (multivariate-adjusted global $P = 0.90$). We did, however, find that age, BMI, and sex were important predictors of the

number of sites of enthesopathy. Age and BMI were positively associated with the number of sites of enthesopathy ($P < .0010$ for each covariate). Female sex was negatively associated with the number of sites of enthesopathy ($P = .0080$). We found that females on average had 0.42 fewer sites of enthesopathy compared with males. We found a borderline significant positive association between PTHauc and number of sites of enthesopathy. In contrast, mutation severity and proportion of treatment in childhood did not predict extent of enthesopathy ($P = .42$ and $P = .10$, respectively). Table 4presents age-adjusted and multivariate-adjusted multiple linear regression models of the relationship between proportion of total life, as well as other predictors, and number of sites of enthesopathy for the purposes of comparison. Proportion of total life with treatment was also not a significant predictor of this outcome (age adjusted global $P = .18$; multivariate-adjusted global $P = .90$). Results for other covariates were similar to those seen in the model for proportion of adult life with treatment: age, BMI, and PTHauc were positively associated with number of sites of enthesopathy, whereas female sex was negatively associated with this outcome. However, the PTHauc association did not achieve borderline significance in this model ($P = .10$).

Dental disease

Table 5 presents age-adjusted and multivariate-adjusted multiple logistic regression models of the relationship between the proportion of adult life with treatment, as well as

other predictors, and severity of dental disease. In both the age-adjusted and multivariate-adjusted analyses, the proportion of adult life with treatment was negatively associated with the odds of having severe dental disease (global $P = .038$ and $P = .0080$, respectively). After adjustment for confounders, we found a borderline significant trend between the increasing proportion of adult life with treatment and the decreasing odds of having severe dental disease (P for trend = .066). Those who were not treated at all during adult life were more likely to experience severe dental disease than those who were treated for 100% of adulthood (adjusted odds ratio [OR] 25 [95% confidence interval [CI] 1.2–520]). We found that age was a significant predictor of dental disease severity: for a 1-year increase in age, the odds of having severe dental disease increased by 10% (OR 1.1 [95% CI 1.0–1.2]). Furthermore, we found that sex was a borderline significant predictor of dental disease severity ($P = .061$). Females had lower odds of experiencing severe dental disease compared with males (OR 0.15 [95% CI 0.020–1.1]). Those treated for less than 80% of childhood had higher odds of experiencing severe dental disease compared with those treated for 80% or greater of childhood (OR 7.2 [95% CI 0.71–73]). Mutation severity was positively associated with severity of dental disease: those with severe mutations had higher odds of experiencing severe dental disease compared with those who did not have severe mutations (OR 3.9 [95% CI 0.63–25]). These relationships did not, however, achieve statistical significance.

Table 6 presents age-adjusted and multivariate-adjusted multiple linear regression models of the relationship between proportion of total life, as well as other predictors, and severity of dental disease. Proportion of total life with treatment was negatively associated with severity of dental disease (age-adjusted global $P = .012$; multivariate-adjusted global $P = .0010$). As proportion of total life with treatment increased, the odds of having severe dental disease decreased (age-adjusted P for trend = .046; multivariate-adjusted P for trend = .015). Results for other covariates were similar to those seen in the model for proportion of adult life with treatment: age and mutation severity were positively associated with dental disease severity while female sex was negatively associated with this outcome.

Discussion

The results of this study suggest that the extension of treatment for XLH with calcitriol and phosphate into adulthood neither prevents nor promotes enthesopathy but may prove beneficial for the prevention of dental abscesses. Most previous work on the efficacy of this therapeutic regimen has focused on the pediatric XLH population, and as a result there is currently not an established consensus regarding treatment of the adult patient. Moreover, the limited studies in the adult XLH population have not assessed the effect of therapy on the specific outcomes that were the focus of our study. Sullivan et al (8) conducted a prospective study of the relationship between phosphate and calcitriol treatment and biochemical, clinical, and

histological responses in 16 adult XLH patients. They found that 87% of participants reported significant improvement in musculoskeletal symptoms and osteoid thickness was significantly reduced as well (8). Costa et al (9) assessed five adult patients (defined as > 15 y of age) and six children with XLH and found that skeletal improvements were most pronounced in, but not limited to, the prepubescent patients. Although these studies examined certain skeletal outcomes, neither assessed enthesopathy as an outcome, and the sample sizes were too small to assess possible associations with treatment duration and skeletal outcomes.

Enthesopathy is well described in XLH patients. Hardy et al (10) performed a radiographic survey of 38 untreated adult patients and found that 68% of them had sites of enthesopathy and that all subjects older than 30 years had enthesopathy. This group also found that men had more than twice the number of affected sites than women. Our findings are consistent with this survey because we found that age and male sex were positive predictors of number of sites of enthesopathy. Our study is novel in that it assesses sites of enthesopathy radiographically in treated adult patients. Although we did not find proportion of adult life or proportion of total life with treatment to be important predictors of enthesopathy, the finding that BMI was positively associated with number of sites of enthesopathy may be of clinical importance in that the increased load to insertion sites evident with increasing BMI, may accelerate the disease process (11). Thus, the greater BMI, and resultant increased load on the insertion sites may be an important

factor in accelerating the development of this complication. Pharmacological therapy may not be effective for preventing enthesopathy however; weight-loss interventions may be helpful in the long term.

More numerous reports of dental complications exist, and a benefit to standard therapy in childhood years has been reported (12, 13). A beneficial effect of medical therapy on dental outcomes in adulthood, however, has yet to be established. Furthermore, the management of dental abscesses via pulpectomy and root canal often fails (14). Moreover, one dental abscess tends to predict the occurrence of future abscesses (9). In light of this information, the results of this study suggest that conventional therapy extended into adulthood may be beneficial for XLH patients who present with particularly burdensome dental disease. Our finding of higher odds of severe dental disease in males vs females is consistent with clinical observation: male patients have been shown to have more extensive dental disease than females (15). It is believed that the more severe dental phenotype in males can be at least partially explained by the hemizygous nature of the disease allele in males and that a more striking gene dose effect is evidence for the teeth than the skeleton (15). Such an effect may be mediated by lyonization (random X-chromosome inactivation), with resultant expression of the mutant X-chromosome in half of the cell population in females, whereas all male cells would express the mutant X in affected individuals (16).

In summary, we have assessed clinically significant outcomes of adult XLH that have not previously been explored. The identification and use of a database for cumulative treatment history in adult patients with XLH is unique and informative; however, the cross-sectional nature of the design limits interpretation. We have also considered that the multivariate-adjusted models may be overfitted due to the relatively small ratio of sample size to number of parameters. Nevertheless, similar findings were observed using age-adjusted models with fewer parameters, allaying these concerns. A randomized control trial directed toward adult morbidities in XLH patients would be important to confirm the safety and efficacy of continued treatment through adult years; however, such a study is likely to require a lengthy follow-up period to capture sufficient data for these age-dependent outcomes to develop.

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Abbreviations:

BMI
: body mass index

CI
: confidence interval

FGF23
: fibroblast growth factor 23

OR
: odds ratio

PHEX
: phosphate-regulating endopeptidase gene

PTHauc
: PTH measured as area under the curve

XLH
: X-linked hypophosphatemia.

References

1. Carpenter TO, Imel E, Holm I, Jan de Beur S, Insogna KL. A clinician's guide to X-linked hypophosphatemia. J Bone Miner Res. 2011;26:1381–1388. [PMCID: PMC3157040] [PubMed: 21538511]

2. Quarles LD, Drezner MK. Pathophysiology of X-linked hypophosphatemia, tumor-induced osteomalacia, and autosomal dominant hypophosphatemia: a perPHEXing

problem. J Clin Endocrinol Metab. 2013;86:494–496. [PubMed: 11157997]
3. Francis F, Henning S, Korn B, et al. A gene (PEX) with homologies to endopeptidases is mutated in patients with X-linked hypophosphatemic rickets. Nat Genet. 1995;11:130–136. [PubMed: 7550339]
4. Carpenter TO. New perspectives on the biology and treatment of X-linked hypophosphatemic rickets. Pediatr Clin North Am. 1995;44:443–461. [PubMed: 9130929]
5. Glorieux FH, Marie PJ, Pettifor JM, Delvin EE. Bone response to phosphate salts, ergocalciferol, and calcitrol in hypophosphatemic vitamin D-resistant rickets. N Engl J Med. 1980;303:1023–1031. [PubMed: 6252463]
6. Rasmussen H, Pechet M, Anast C, Mazur A, Gertner J, Broadus AE. 1981 Long-term treatment of familial hypophosphatemic rickets with oral phosphate and 1α-hydroxyvitamin D. J Pediatr. 1981;99:16–25. [PubMed: 6265614]
7. Carpenter TO, Mitnick MA, Smith C, Ellison A, Isogna KL. Noctural hyperparathyroidism: a frequent feature of X-linked hypophosphatemia. J Clin Endocrinol Metab. 1994;78:1378–1383. [PubMed: 8200940]
8. Sullivan W, Carpenter TO, Glorieux F, Travers R, Insogna KL. A prospective trial of phosphate and 1,25 dihydroxyvitamin D3 therapy in symptomatic adults with X-linked hypophosphatemic rickets. J Clin Endocrinol Metab. 1992;75:879–885. [PubMed: 1517380]
9. Costa T, Marie PJ, Scriver CR, et al. X-linked hypophosphatemia: effect of calcitriol on renal handling of

phosphate, serum phosphate, and bone mineralization. J Clin Endocrinol Metab. 1981;52:463–471. [PubMed: 6893992]
10. Hardy D, Murphy W, Siegel B, Reid I, Whyte M. X-linked hypophosphatemia in adults: prevalence of skeletal radiographic and scintigraphic features. Radiology. 1989;171(2):409–414.
11. Liang G, Katz L, Insogna K, Carpenter T, Macica C. Survey of enthesopathy of X-linked hypophosphatemia and its characterization in hyp mice. Calcif Tissue Int. 2009;85:235–246. [PMCID: PMC2988401] [PubMed: 19609735]
12. Baroncelli GI, Angiolini M, Ninni E, Galli V, Saggese R, Giuca MR. Prevalence and pathogenesis of dental and periodontal lesions in children with X-linked hypophosphatemic rickets. Eur J Paediatr Dent. 2006;7:61–66. [PubMed: 16842025]
13. Chaussain-Miller C, Sinding C, Septier D, Wolikow M, Goldberg M, Garabedian M. Dentin structure in familial hypophosphatemic rickets: benefits of vitamin D and phosphate treatment. Oral Dis. 2007;13:482–489. [PubMed: 17714351]
14. Seow WK. The effect of medical therapy on dentin formation in vitamin-D resistant rickets. Pediatr Dent. 1992;13:97–102. [PubMed: 1652747]
15. Rakocz M, Keating J, Johnson R. Management of the primary dentition in vitamin D-resistant rickets. Oral Surg Oral Med Oral Pathol. 1982;54:166–171.[PubMed: 6289221]

16. Lyon MF. Gene action in the X-chromosome of the mouse (*Mus musculus* L.). Nature. 1961;190:372–373. [PubMed: 13764598]

Figures and Tables

Table 1.

Selected Participant Characteristics by Proportion of Adult Life With Treatment[a]

Characteristic	0% of Adult Life With Treatment[b] (n = 8)	0% < x < 100% of Adult Life With Treatment[b] (n = 27)	100% of Adult Life With Treatment[b] (n = 17)	Full Sample[b] (n = 52)
Age, y	31.8 (11.3)	40.7 (11.9)	39.9 (18.4)	39.0 (14.4)
Age at onset of treatment, y	4.7 (8.3)	6.6 (11.5)	4.0 (6.9)	5.4 (9.7)
Yrs of treatment as adult (≥ 18 y)	1.6 (4.3)	6.4 (6.7)	20.9 (17.8)	10.5 (13.5)
Yrs of treatment as child (< 18 yrs)	14.0 (6.3)	13.5 (6.1)	14.5 (4.6)	13.9 (5.6)
Sex				

Characteristic	0% of Adult Life With Treatment[b] (n = 8)	0% < x < 100% of Adult Life With Treatment[b] (n = 27)	100% of Adult Life With Treatment[b] (n = 17)	Full Sample[b] (n = 52)
Male	3 (37.5)	9 (33.3)	6 (35.3)	18 (34.6)
Female	5 (62.5)	18 (66.7)	11 (64.7)	34 (65.4)
BMI, kg/m^2	34.1 (11.2)	34.2 (10.4)	31.4 (5.9)	33.3 (9.2)
Body fat, %	36.9 (11.1)	34.3 (11.7)	35.4 (12.4)	35.1 (11.5)
Height Z-score				
≥−1.0	0 (0.0)	4 (14.8)	0 (0.0)	4 (7.7)
−1.1 to −1.5	1 (12.5)	2 (7.4)	3 (17.7)	6 (11.5)
−1.6 to −2.0	2 (25.0)	2 (7.4)	2 (11.8)	6 (11.5)

Characteristic	0% of Adult Life With Treatment[b] (n = 8)	0% < x < 100% of Adult Life With Treatment[b] (n = 27)	100% of Adult Life With Treatment[b] (n = 17)	Full Sample[b] (n = 52)
< −2.1	5 (62.5)	19 (70.4)	12 (70.6)	36 (69.2)
Use of pain medications				
Never	1 (12.5)	7 (25.9)	5 (31.3)	13 (25.5)
Less frequently	2 (25.0)	4 (14.8)	5 (31.3)	11 (21.6)
Weekly	3 (37.5)	5 (18.5)	2 (12.5)	10 (19.6)
Daily	1 (12.5)	7 (25.9)	4 (25.0)	12 (23.5)
More than once per day	1 (12.5)	4 (14.8)	0 (0.0)	5 (9.8)
Previous osteotomies, n				

Characteristic		0% of Adult Life With Treatment[b] (n = 8)	0% < x < 100% of Adult Life With Treatment[b] (n = 27)	100% of Adult Life With Treatment[b] (n = 17)	Full Sample[b] (n = 52)
	None	4 (50.0)	11 (40.7)	3 (17.7)	18 (34.6)
	One	0 (0.0)	0 (0.0)	2 (11.8)	2 (3.9)
	Two	2 (25.0)	7 (25.9)	3 (17.7)	12 (23.1)
	More than two	2 (25.0)	9 (33.3)	9 (52.9)	20 (38.5)
Mutation status[c]					
	Not severe	1 (12.5)	9 (33.3)	3 (17.7)	13 (25.0)
	Severe	6 (75.0)	17 (63.0)	11 (64.7)	34 (65.4)
Sites of enthesopathy, n		1.63 (0.74)	1.85 (0.86)	1.82 (0.64)	1.81 (0.77)

Characteristic	0% of Adult Life With Treatment[b] (n = 8)	0% < x < 100% of Adult Life With Treatment[b] (n = 27)	100% of Adult Life With Treatment[b] (n = 17)	Full Sample[b] (n = 52)
Dental abscesses, n				
Five or fewer	2 (25.00)	9 (33.3)	9 (52.9)	20 (38.5)
More than five	6 (75.00)	18 (66.7)	8 (47.1)	32 (61.5)
PTHauc[d]	1068.5 (889.9)	985.6 (392.4)	1260.7 (751.8)	1088.3 (616.5)
FGF23, pg/mL	1976.5 (972.4)	6156.9 (140 508.8)	4604.2 (7260.8)	5006.2 (11 233.0)

[a]Table values are mean ± SD for continuous variables and n (column %) for categorical variables.
[b]Numbers may not sum to total due to missing data, and percentages may not sum to 100% due to rounding.
[c]Mutation analyses from five subjects were either not performed or not definitive and were included in a "missing" category.
[d]PTHauc samples taken every 4 hours over a 26-hour period.

Table 2.

Bivariate Regression Models of the Relationship Between Potential Predictors and Number of Sites of Enthesopathy (Linear Regression) and Severity of Dental Disease (Logistic Regression), Respectively

Characteristic	**Enthesopathy**			**Dental Disease**		
	β (SE)	***P* Value**	**R^2**	**OR (95% CI)**	***P* Value**	**R^2**
Proportion of adult life with treatment			0.011			0.045
0	−0.20 (0.33)	.56		3.4 (0.52–22)	.20	
0 < x < 1	0.028 (0.24)	.91		2.3 (0.65–7.8)	.20	
1	Reference			1.00		
Proportion of total life with treatment			0.090			0.16
0–0.435	0.16 (0.30)	.61		8.8 (1.3–57)	.023	

Characteristic		Enthesopathy			Dental Disease		
		β (SE)	*P* Value	R^2	OR (95% CI)	*P* Value	R^2
	0.436–0.587	0.31 (0.30)	.30		5.3 (0.97–29)	.055	
	0.588–0.880	−0.31 (0.30)	.30		1.4 (0.29–6.5)	.69	
	0.881–1.0	Reference			1.0		
Age, y		0.033 (0.0060)	<.00010	0.38	1.1 (1.0–1.1)	.0040	0.18
Sex				0.040			0.026
	Male	Reference			1.0		
	Female	−0.29 (0.22)	.19		0.49 (0.14–1.7)	.25	

Characteristic	Enthesopathy			Dental Disease		
	β (SE)	*P* Value	R^2	OR (95% CI)	*P* Value	R^2
BMI, kg/m^2	0.035 (0.011)	.0019	0.17	1.2 (1.0–1.3)	.010	0.19
Mutation severity[a]						0.11
Not severe	Reference			1.0		
Severe	0.21 (0.25)	.41	0.042	1.9 (0.52–6.9)	.34	
PTHauc[b]	0.00 034 (0.00 017)	.049	0.075	1.0 (0.99–1.0)	.40	0.015
FGF23, pg/mL	0.000 015 (0.0 000 094)	.11	0.049	1.0 (1.0–1.0)	.33	0.040
Proportion of treatment in childhood			0.15			0.23

Characteristic	Enthesopathy			Dental Disease		
	β (SE)	*P* Value	R^2	OR (95% CI)	*P* Value	R^2
<0.80	0.64 (0.21)	.0041		19.0 (2.3–160)	.0067	
≥0.80	Reference			1.00		

[a]Mutation analyses from five subjects were either not performed or not definitive and were included in a "missing category."
[b]PTHauc samples taken every 4 hours over a 26-hour period.

Table 3.

Age-Adjusted and Multivariate-Adjusted Multiple Linear Regression Models of the Relationship Between Proportion of Adult Life With Treatment, Other Predictors, and Number of Sites of Enthesopathy

Characteristic	Age-Adjusted R^2 = 0.38		Multivariate-Adjusted R^2 = 0.63	
	β (SE)	*P* Value	β (SE)	*P* Value
Proportion of adult life with treatment				
0	0.071 (0.27)	.80	−0.092 (0.23)	.69
0 < x < 1	0.0040 (0.19)	.99	−0.0 000 015 (0.17)	1.0
1	Reference		Reference	
Global *P* value		.96		.90
P value for trend		.68		.50
Age, y	0.033 (0.010)	<.0010	0.023 (0.006)	<.0010
Sex				

Characteristic	Age-Adjusted R^2 = 0.38		Multivariate-Adjusted R^2 = 0.63	
	β (SE)	*P* Value	β (SE)	*P* Value
Male			Reference	
Female			−0.42 (0.16)	.0080
BMI, kg/m^2			0.034 (0.0090)	<.0010
Mutation severity[a]				
Not severe			Reference	
Severe			0.14 (0.18)	.42
PTHauc[b]			0.00 028 (0.00 014)	.051
Proportion of treatment in childhood				

Characteristic	Age-Adjusted R^2 = 0.38		Multivariate-Adjusted R^2 = 0.63	
	β (SE)	*P* Value	β (SE)	*P* Value
<0.80			0.30 (0.18)	.10
≥0.80			Reference	

[a]Mutation analyses from five subjects were either not performed or not definitive and were included in a "missing category."
[b]PTHauc samples taken every 4 hours over a 26-hour period.

Table 4.

Age-Adjusted and Multivariate-Adjusted Multiple Linear Regression Models of the Relationship Between Proportion of Total Life With Treatment, Other Predictors, and Number of Sites of Enthesopathy

Characteristic	Age-Adjusted R^2 = 0.41		Multivariate-Adjusted R^2 = 0.61	
	β (SE)	*P* Value	β (SE)	*P* Value
Proportion of total life with treatment				
0–0.435	0.012 (0.24)	.96	0.094 (0.21)	.66
0.436–0.587	0.19 (0.24)	.43	0.027 (0.23)	.91
0.588–0.880	−0.20 (0.24)	.41	−0.050 (0.21)	.81
0.881–1.0	Reference		Reference	
Global *P* value		.18		.90
P value for trend		.72		.54
Age, y	0.031 (0.0060)	<.0010	0.0270 (0.0060)	<.0010

Characteristic	Age-Adjusted R^2 = 0.41		Multivariate-Adjusted R^2 = 0.61	
	β (SE)	*P* Value	β (SE)	*P* Value
Sex				
Male			Reference	
Female			−0.42 (0.60)	.012
BMI, kg/m^2			0.030 (0.010)	.0020
Mutation severity[a]				
Not Severe			Reference	
Severe			0.17 (0.18)	.34
PTHauc[b]			0.00 025 (0.00 015)	.10

[a]Mutation analyses from five subjects were either not performed or not definitive and were included in a "missing category."
[b]PTHauc samples taken every 4 hours over a 26-hour period.

Table 5.

Age-Adjusted and Multivariate-Adjusted Multiple Logistic Regression Models of the Relationship Between Proportion of Adult Life With Treatment, Other Predictors, and Severity of Dental Disease

Characteristic	**Age-Adjusted R^2 = 0.25**		**Multivariate-Adjusted R^2 = 0.44**	
	OR (95% CI)	***P* Value**	**OR (95% CI)**	***P* Value**
Proportion of adult life with treatment				
0	7.8 (0.85–71)	.069	25 (1.2–520)	.038
0 < x < 1	2.3 (0.51–11)	.27	7.1 (0.88–58)	.067
1	1.0		1.0	
Global *P* value		.038		.0080

Characteristic	Age-Adjusted R^2 = 0.25		Multivariate-Adjusted R^2 = 0.44	
	OR (95% CI)	***P* Value**	**OR (95% CI)**	***P* Value**
P value for trend		.20		.066
Age, y	1.1 (1.0–1.2)	.0030	1.1 (1.0–1.2)	.019
Sex				
Male			1.0	
Female			0.15 (0.020–1.1)	.061
Mutation severity[a]				
Not severe			1.0	
Severe			3.9 (0.63–25)	.14

Characteristic	Age-Adjusted R^2 = 0.25		Multivariate-Adjusted R^2 = 0.44	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Proportion of treatment in childhood				
<0.80			7.2 (0.71–73)	.10
≥0.80			1.0	

[a]Mutation analyses from five subjects were either not performed or not definitive and were included in a "missing category."

Table 6.

Age-Adjusted and Multivariate-Adjusted Multiple Linear Regression Models of the Relationship Between Proportion of Total Life With Treatment, Other Predictors, and Severity of Dental Disease

Characteristic	Age-Adjusted R^2 = 0.28		Multivariate-Adjusted R^2 = 0.44	
	OR (95% CI)	***P* Value**	**OR (95% CI)**	***P* Value**
Proportion of total life with treatment				
0–0.435	8.8 (1.1–70)	.040	31 (2.2–450)	.012
0.436–0.587	5.6 (0.84–38)	.075	25 (1.8–340)	.017
0.588–0.880	2.0 (0.33–12)	.45	4.8 (0.49–51)	.20
0.881–1.0	1.0		1.0	
Global *P* value		.012		.0010
P value for trend		.046		.015
Age, y	1.1 (1.0–1.1)	<.0010	1.1 (1.0–1.2)	.010

Characteristic	Age-Adjusted R^2 = 0.28		Multivariate-Adjusted R^2 = 0.44	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Sex				
Male			1.0	
Female			0.080 (0.0090–0.71)	.023
Mutation severity[a]				
Not severe			1.0	
Severe			5.2 (0.82–33)	.080

[a]Mutation analyses from five subjects were either not performed or not definitive and were included in a "missing category."