Journal of Oral Rehabilitation

Journal of Oral Rehabilitation 2012 **39**; 144–150

Periapical and endodontic status of permanent teeth in patients with hypophosphatemic rickets

M. G. ANDERSEN*, S. S. BECK-NIELSEN†‡, D. HAUBEK*, H. HINTZE§, H. GJØRUP*¶ & S. POULSEN* **Department of Pediatric Dentistry, School of Dentistry, Aarhus University, Aarhus, †Department of Pediatrics, H.C. Andersen Children's Hospital, Odense University Hospital, Odense, ‡Institute of Clinical Research, University of Southern Denmark, Odense, §Department of Oral Radiology, School of Dentistry, Aarhus University, Aarhus and ¶Center for Oral Health in Rare Conditions, Aarhus University Hospital, Aarhus, Denmark*

SUMMARY Hypophosphatemic rickets (HR) is a rare hereditary disease in which dental problems in terms of spontaneous periapical infections are frequently reported. Most previous reports have been based on a small number of HR patients and have been published before the disease could be confirmed genetically. The aim of the present study was to describe the periapical and endodontic status of permanent teeth in patients with genetically and/or biochemically confirmed HR. The patients were recruited from a medical study on HR patients. The patients underwent a dental examination including a digital panoramic radiograph, which was scored for endodontically affected teeth (i.e. teeth with periapical radiolucencies and/or endodontically treated teeth). A total of 52 patients (age range: 5·7–74·5 years; 17 males and 35 females) were included. HR patients were characterised by a high number of endodontically affected teeth (mean: 4·2; s.d.: 5·0). The number of affected teeth rose significantly with age ($P < 0{\cdot}01$), and no statistically significant gender difference was found. The relative distribution of endodontically affected teeth in the three tooth groups (incisors and canines, premolars, and molars) varied according to age. In the youngest age group, only incisors and canines were affected, while the relative proportion of affected premolars and molars increased with age. Endodontically affected teeth are common in HR patients, and the number of affected teeth increased significantly with age. Hence, the need for endodontic treatment among HR patients is comprehensive.

KEYWORDS: hypophosphatemic rickets, endodontics, genetics, adults, radiography

Accepted for publication 26 July 2011

Introduction

Rickets is primarily known as a disease caused by nutritional deficiencies of vitamin D or calcium, but rarely the disease is hereditary caused by inborn genetic disorders. Hypophosphatemic rickets (HR) is the most common type of hereditary rickets with a prevalence of 4·8 per 100 000 (1) in Denmark. The most predominant type is inherited in an X-linked fashion and caused by mutation in the gene encoding for the phosphate-regulating endopeptidase homolog, X-linked (*PHEX*), identified in 1995 (2).

The literature on dental manifestations in HR patients consists of more than 60 case reports or case series with small numbers of cases of which, however, only a few have been published in 2000 or later (3–16). Thus, many studies were performed before the genetic analysis was available. The genetic analysis unravels the underlying disease mechanism and confirms the diagnosis of HR. The HR diagnosis may be distinguished from other hereditary and acquired forms of hypophosphatemia by reassuring a history of rickets in addition to clinical and biochemical diagnostic criteria. In many papers, the diagnosis of HR

doi: 10.1111/j.1365-2842.2011.02250.x

was based on the following two criteria, only: (i) a history of rickets, (ii) persistence of reduced levels of PO_4 and TPO_4/GFR; or clinical symptoms and radiological signs of rickets. Resort to these criteria makes it likely that rickets of other types than HR may have been included (16–22). In only one paper was the diagnosis genetically confirmed by identification of a mutation in *PHEX* in 11 of the 48 patients studied (11). In addition, several papers state their study population to be X-linked hypophosphatemic rickets patients without any genetic analysis being performed.

Periapical problems are a commonly reported finding in patients with rickets, and presents special challenges to the general dental practitioner both in terms of diagnosis and treatment due to spontaneous periapical infections and mineralisation abnormalities of the dentine, which may compromise the prognosis of endodontic treatment.

The purpose of the present report was to describe the periapical and endodontic status of permanent teeth in patients with genetically and/or biochemically confirmed HR.

Materials and methods

Study population

The patients described in this report were recruited from a medical cross-sectional study on hereditary rickets in Denmark (23). As the study has been described in detail elsewhere, only a brief account of the method of patient inclusion is given in this paper. Originally, the patients were identified in the Danish National Patient Registry by a search based on the diagnosis codes of vitamin D-resistant rickets. The inclusion area was Jutland and Funen, covering approximately 3·0 million inhabitants and thereby 55% of the total Danish population. The diagnosis was confirmed by review of the patients' medical files. By contacting the treating doctors, we identified patients with HR who did not appear in the register. Finally, family screening added additional cases. The diagnostic criteria of HR were genetically verified HR and/or biochemically verified HR. Biochemical criteria of HR were at least one of the following parameters: serum phosphate below normal range, low renal threshold value for reabsorption of phosphate in the urine, or elevated fibroblast growth factor 23. In addition, a history of childhood rickets or spontaneous dental abscesses was required. Only patients with verified HR were included. Patients with secondary rickets due to malabsorption or tumour-induced osteomalacia, or patients with hereditary vitamin D-dependent rickets type 1 were excluded. Figure 1 shows a flowchart describing the recruitment of patients.

Radiographic examination

All patients were given a clinical and a radiographic dental examination at the School of Dentistry, Aarhus University. Only the findings from the radiographic examination are reported here.

The radiographic examination included a digital panoramic radiograph taken in a ProMax unit*. Exposure parameters were adjusted to the individual patient. If the image of the permanent teeth was blurred, supplementary digital intraoral radiographs were taken of these teeth using a GX 1000 dental X-ray unit[†] with rectangular collimation. We used a sensor (Sidexis[‡]) for anterior teeth and a photostimulable phosphor plate (Digora, FMX scanner[§]) for posterior teeth. Receptor holders were used for all intraoral radiographs. The radiographs were viewed on a 19″ monitor placed in a dark room. The panoramic images were assessed in the Dimaxis Pro software (version 4·2·0), whereas the intraoral radiographs were assessed using a general software with facilities to adjust brightness, contrast, gamma curve, and magnification. All image enhancement facilities could be used as wanted.

The radiographs were examined for endodontically treated permanent teeth and periapical radiolucencies (apical periodontitis). All teeth were viewed individually. The criteria for assessment of endodontic treatment were the presence of radiopaque root filling material in the root channel and/or radiopaque retrograde root filling material at the apex of the tooth. A diagnosis of apical periodontitis was based on a clear, radiolucent lesion surrounding the apex of the tooth. This will roughly correspond to a

*Planmeca, Helsinki, Finland.
[†]Gendex, Des Plaines, IL, USA.
[‡]Sirona, Bensheim, Germany.
[§]Soredex, Helsinki, Finland.

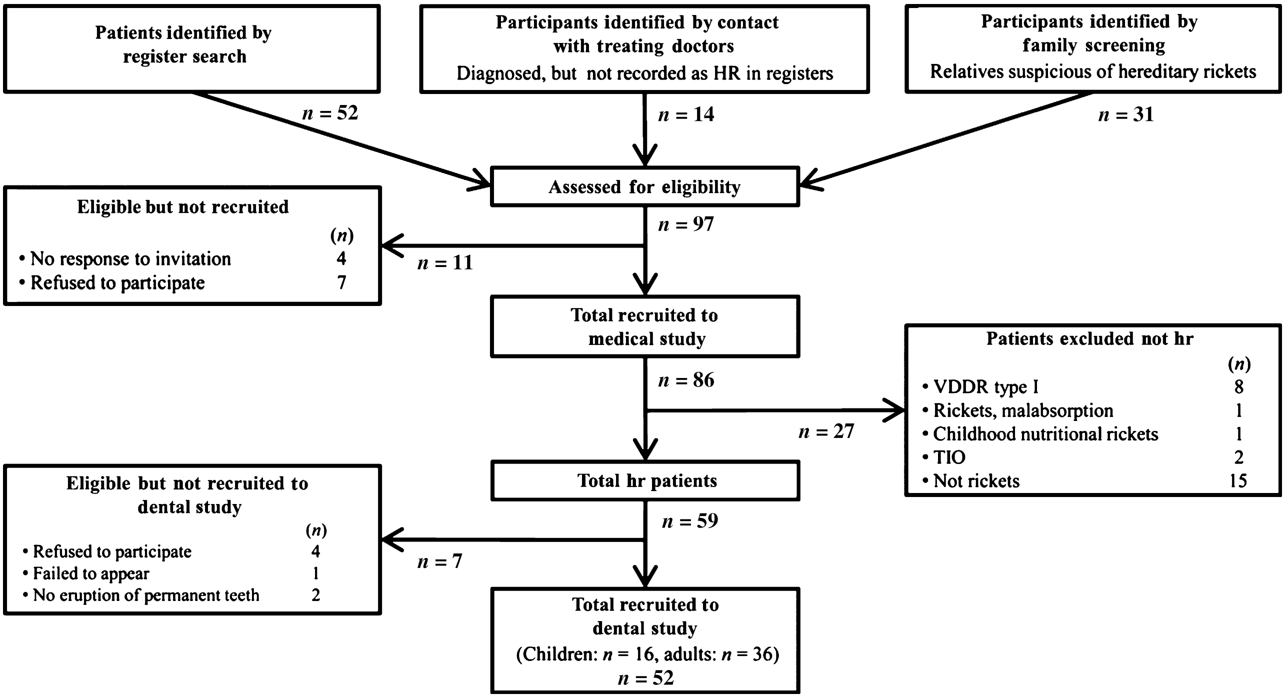

Fig. 1. Flow diagram showing patient inclusion (VDDR, vitamin D-dependent rickets type 1; TIO, tumour induced osteomalacia).

periapical index (PAI) score of 3, 4, or 5 (24). The radiographic assessments were performed by one examiner (MGA) after three rehearsal sessions, together with an experienced dento-maxillofacial radiologist (HH).

Only findings relating to permanent teeth are presented as the number of children with only deciduous teeth was very low (n = 2).

Statistical analysis

The following variables were calculated:

Variable 1: endodontically treated teeth without periapical radiolucency.

Variable 2: Endodontically treated teeth with periapical radiolucency.

Variable 3: Teeth with periapical radiolucency, but without endodontic treatment.

Variable 4: Endodontically affected teeth as the sum of the variables 1–3.

The data were summarised using mean, standard deviation (s.d.), median, and first and third quartile.

Differences between genders were tested using Mann–Whitney U-test and differences between age groups were tested using Kruskal–Wallis test. The level of significance (α) was set at 0·05.

Ethical approval

The study was approved by the Ethics Committee of Southern Denmark (record #M-2678-05) and by the Danish Data Protection Agency (record #2008-41-2187). Written informed consent was obtained from all patients and/or their parents.

Results

The medical cross-sectional study included 21 children (<18 years) and 38 adults with HR (Fig. 1). The present study excluded seven of these patients: five patients declined participation or did not appear at the dental examination and two children had no permanent teeth erupted. Thus, a total of 52 HR patients (age range: 5·7–74·5 years) underwent dental examination. Among these patients, a disease-causing mutation in *PHEX* was identified in 37 (71%). In one family, which accounted for 12 (23%) of the patients, the mode of heritage was X-linked dominant and a genome-wide linkage scan revealed strong evidence of linkage to locus, *PHEX* (23). In three patients (6%), no gene mutations were identified. Table 1 depicts the patient distribution according to age and gender and number of permanent teeth present.

Table 1. Distribution of 52 patients with HR according to age and gender, and descriptive statistics of number of permanent teeth present

	<18 years	18–39 years	40 + years	All
Gender				
Females	11	11	13	35
Males	5	5	7	17
Both	16	16	20	52
Number of permanent teeth present				
Mean (s.d.)	15·8 (10·4)	25·7 (5·5)	21·4 (7·2)	21·0 (8·7)
Median (first and third quartile)	14·0 (4·5; 27·0)	28·0 (26·0; 28·0)	24·0 (19·3; 26·8)	25·0 (15·3; 28·0)

Table 2. Descriptive statistics of number of endodontically treated permanent teeth with and without periapical radiolucency, number of permanent teeth with periapical radiolucencies, but without endodontic treatment, and number of endodontically affected teeth in 52 patients with HR rickets

Age	Variable 1: endodontically treated teeth without periapical radiolucencies	Variable 2: endodontically treated teeth with periapical radiolucencies	Variable 3: teeth with periapical radiolucencies, but without endodontic treatment	Variable 4: endodontically affected teeth
<18 years				
Mean (s.d.)	0·3 (0·7)	0 (0·0)	0·1 (0·3)	0·3 (0·9)
Median (first and third quartile)	0·0 (0·0; 0·0)	0·0 (0·0; 0·0)	0·0 (0·0; 0·0)	0·0 (0·0; 0·0)
18–39 years				
Mean (s.d.)	2·4 (3·4)	0·9 (1·4)	0·3 (0·8)	3·6 (3·9)
Median (first and third quartile)	1·0 (0·0; 3·8)	0·0 (0·0; 1·0)	0·0 (0·0; 0·0)	3·0 (0·0; 6·5)
40 + years				
Mean (s.d.)	5·7 (4·4)	1·0 (1·5)	1·2 (3·1)	7·8 (5·3)
Median (first and third quartile)	4·5 (2·3; 9·5)	0·0 (0·0; 1·8)	0·0 (0·0; 0·8)	7·0 (3·0; 12·8)
All				
Mean (s.d.)	3·0 (4·0)	0·6 (1·3)	0·6 (2·0)	4·2 (5·0)
Median (first and third quartile)	1·0 (0·0; 4·8)	0·0 (0·0; 1·0)	0·0 (0·0; 0·0)	20·5 (0·0; 7·0)

The number of endodontically affected teeth was strikingly high (Table 2). No statistically significant difference in affected teeth was found between males and females ($P = 0{\cdot}09$). The number of affected teeth rose significantly with age ($P < 0{\cdot}01$) with a median number of affected teeth varying from 0 for patients aged less than 18 years to 7·0 for patients aged 40 + years. In addition, the inter-individual variation in the number of endodontically affected teeth was large with interquartile ranges of 6·5 and 9·8 in the two oldest age groups (18–39 and 40 + years).

Figure 2 describes the variation according to age in the relative distribution of endodontically affected teeth in the three tooth groups (a: incisors and canines; b: premolars; c: molars). In the youngest age group (<18 years), only incisors and canines were affected,

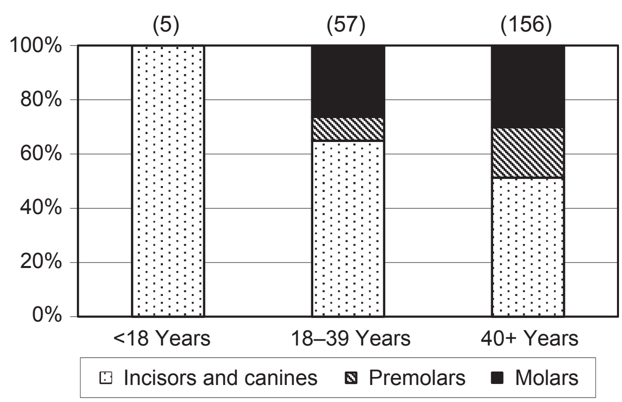

Fig. 2. Relative distribution of 218 endodontically affected teeth on three tooth groups (a: incisors and canines; b: premolars; c: molars) according to age in 52 patients with HR. The total number of endodontically affected teeth in each age group is given in parenthesis above each column.

Fig. 3. Panoramic radiograph of a 22-year-old male with HR showing a dentition with nine teeth with endodontic treatment (16, 11, 21, 22, 27, 43, 42, 41, 31), four of which has periapical radiolucencies (21, 22, 42, 31). One premolar had been extracted due to complication during endodontic treatment.

while the relative proportion of affected premolars and molars rose with age. Figure 3 illustrates the typical distribution of the endodontically affected teeth in a 22-year-old male.

In the youngest age-group (<18 years) a total of five endodontically affected teeth were found. One of these was a lower lateral incisor with a periapical radiolucency, but no endodontic treatment, and four were endodontically treated teeth without periapical radiolucencies. The proportion of endodontically affected teeth with periapical radiolucencies [(variable 2 + variable 3)/variable 4] was 33% for 18–39 year olds and 28% for patients 40 + years of age. The proportion of endodontically treated teeth with periapical radiolucencies [variable 2/(variable 1 + variable 2)] was 27% and 14% for patients aged 18–39 and 40 + years, respectively.

Discussion

The main finding of this paper is that it documents previous claims of a high number of endodontically affected teeth in HR patients. Only incisors and canines were endodontically affected in the younger patients, while number of affected posterior teeth rose with age.

Comparison of the data from the present study with data from a recent radiographic study of the periapical and endodontic status of a representative sample of healthy Danish adults (25) is complicated by the fact that our data were based on panoramic radiography, while data in the study by Kirkevang *et al.* were based on a 14-film periapical radiographic status. We used a diagnostic threshold presumed to be equivalent to a PAI score of 3 or higher, which is equivalent to the diagnostic threshold used by Kirkevang *et al.* (25). However, the difference in radiographic methodology may still bias our results towards an underestimation of periapical radiolucencies. Furthermore, the study by Kirkevang *et al.* (25) did not include individuals below the age of 20 years. As our study included one 18-year-old, we recalculated our data after exclusion of this patient in order to allow comparison with the reference material.

The mean number of endodontically treated teeth (with or without periapical radiolucencies) in the 15 HR patients aged 20–39 years was 3·2; a number that was considerably higher than in the reference material (mean: 0·6) (25). Considerable differences between the present study and the reference material were also found for the oldest age groups (40 + years) (6·7 versus 1·8). Thus, endodontic treatment is comprehensive in HR patients compared with the background population, and the need for treatment rises with age.

In teeth without endodontic treatment, which is probably the category with the highest risk of being underestimated in the present study, the occurrence of periapical radiolucency in the 20–39-year olds (0·3 versus 0·4) and in the group of 40 + -year olds (1·2 versus 1·3) in the present study was almost similar to the occurrence reported in the reference material.

To our knowledge, this is the first study describing the intraoral distribution of endodontically affected permanent teeth according to age in HR patients. The higher number of endodontically affected teeth in the older age groups could be due to the long pulp chambers and extended pulp horns reported in HR patients (26) combined with attrition of the enamel which, in turn, exposes the defective dentine (4, 6, 27) and allows bacterial entrance into the dentinal tubules with subsequent pulpal involvement and necrosis. This process is initiated immediately after eruption and will thus involve incisors earlier than premolars and molars.

It might be speculated that the poor mineralisation of the dentine in HR patients could also entail a higher risk of periapical complications to endodontic treatment. However, our data do not support this because we found lower rates of periapical complications in HR patients than found by Kirkevang *et al.* in their study (52%) (25).

Further understanding of the pathogenesis of pulpal involvement and endodontic problems in HR patients will require more detailed insight into the histology and the formation of the dentine in these patients. Longitudinal studies are therefore needed to determine the influence of attrition and the presence of infractions on the development of pulpal complications and to determine the prognosis of endodontic treatment in HR patients.

Finally, it should be noted that these patients have received a considerable amount of dental care. For children up to the age of 18 years, dental care is provided free of cost in the Municipal Dental Service in Denmark. For adults, only limited economic support is presently available. The high level of dental care received by these patients reflects the maintenance of a high number of teeth, but it also represents a considerable economic burden carried by the patients themselves. As this study shows an increasing frequency of endodontic complications in the permanent teeth in HR patients from early adulthood, alternative ways of supporting dental care for these patients should be considered.

Our study had some limitations: The cross-sectional design of this study limits evaluation of the possible effects of medical treatment on the severity of dental disease. The design used does not take differences in disease severity at time of treatment start into account, whereby those treated might be those more severely diseased. Thus, differences in severity of skeletal or dental disease upon treatment might primarily reflect differences in disease severity.

In conclusion, endodontically affected teeth are common in HR patients and the number of affected teeth increase significantly with increasing age. In the younger patients, the proportion of affected incisors and canines is high. Hence, the need for endodontic treatment among HR-patients is comprehensive.

Acknowledgments

The study received financial support from The Danish Dental Association and The Aarhus University Research Foundation (E-2006-SUN-1-137).

We wish to thank Chair side Dental Assistant Inge Møller for her invaluable help in organising the practical arrangements necessary for the study.

References

1. Beck-Nielsen SS, Brock-Jacobsen B, Gram J, Brixen K, Jensen TK. Incidence and prevalence of nutritional and hereditary rickets in southern Denmark. Eur J Endocrinol. 2009; 160:491–497.
2. The HYP Consortium. A gene (PEX) with homologies to endopeptidases is mutated in patients with X-linked hypophosphatemic rickets. The HYP Consortium. Nat Genet. 1995;11:130–136.
3. Seow WK. Diagnosis and management of unusual dental abscesses in children. Austr Dent J. 2003;48:156–168.
4. Batra P, Tejani Z, Mars M. X-linked hypophosphatemia: dental and histologic findings. J Canad Dent Assoc. 2006;72:69–72.
5. Zambrano M, Nikitakis NG, Sanchez-Quevedo MC, Sauk JJ, Sedano H, Rivera H. Oral and dental manifestations of vitamin D-dependent rickets type I: report of a pediatric case. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2003;95:705–709.
6. Murayama T, Iwatsubo R, Akiyana S, Amano A, Morisaki I. Familial hypophosphatemic vitamin D-resistant rickets: Dental findings and histologic study of teeth. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000;90:310–316.
7. 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.
8. Su JM, Li Y, Ye XW, Wu ZF. Oral findings of hypophosphatemic vitamin D-resistant rickets: report of two cases. Chin Med J (Engl). 2007;120:1468–1470.
9. Alexander S, Moloney L, Kilpatrick N. Endodontic management of a patient with X-linked hypophosphataemic rickets. Austr Endod J. 2001;27:57–61.

10. Boukpessi T, Septier D, Bagga S, Garabedian M, Goldberg M, Chaussain-Miller C. Dentin alteration of deciduous teeth in human hypophosphatemic rickets. Calcif Tissue Int. 2006; 79:294–300.
11. Chaussain-Miller C, Sinding C, Wolikow M, Lasfargues JJ, Godeau G, Garabedian M. Dental abnormalities in patients with familial hypophosphatemic vitamin D-resistant rickets: prevention by early treatment with 1-hydroxyvitamin D. J Pediatr. 2003;142:324–331.
12. 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.
13. Douyere D, Joseph C, Gaucher C, Chaussain C, Courson F. Familial hypophosphatemic vitamin D-resistant rickets-prevention of spontaneous dental abscesses on primary teeth: a case report. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009;107:525–530.
14. Gaucher C, Boukpessi T, Septier D, Jehan F, Rowe PS, Garabedian M *et al.* Dentin noncollagenous matrix proteins in familial hypophosphatemic rickets. Cells Tissues Organs. 2009;189:219–223.
15. Page LA. Vitamin-D-resistant rickets: report of a case. N Z Dent J. 2008;104:111–114.
16. Pereira CM, de Andrade CR, Vargas PA, Coletta RD, de Almeida OP, Lopes MA. Dental alterations associated with X-linked hypophosphatemic rickets. J Endod. 2004;30:241–245.
17. Gardner DE, Davis WB, Prescott GH. Hereditary hypophosphatemia. ASDC J Dent Child. 1969;36:199.
18. Harrell RM. The importance of the dental exam. N C Med J. 1983;44:505–506.
19. Harris R, Sullivan R. Dental sequelae in deciduous dentition in vitamin D resistant rickets. Aust Dent J. 1960;5:200–203.
20. Herbert FL. Hereditary hypophosphatemia rickets: an important awareness for dentists. ASDC J Dent Child. 1986;53:223–226.
21. Larmas M, Hietala EL, Simila S, Pajari U. Oral manifestations of familial hypophosphatemic rickets after phosphate supplement therapy: a review of the literature and report of case. ASDC J Dent Child. 1991;58:328–334.
22. Wihr NL. Abnormal dentition in vitamin D resistant rickets. A case report. ASDC J Dent Child. 1970;37:222–224.
23. Beck-Nielsen SS, Brusgaard K, Rasmussen LM, Brixen K, Brock-Jacobsen B, Poulsen MB *et al.* Phenotype Presentation of Hypophosphatemic Rickets in Adults. Calcif Tissue Int. 2010;87:108–119.
24. Ørstavik D, Kerekes K, Eriksen HM. The periapical index: a scoring system for radiographic assessment of apical periodontitis. Endod Dent Traumatol. 1986;2:20–34.
25. Kirkevang L-L, Hörsted-Bindslev P, Ørstavik D, Wenzel A. Frequency and distribution of endodontically treated teeth and apical periodontitis in an adult Danish population. Int Endod J. 2001;34:198–205.
26. 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.
27. Abe K, Ooshima T, Sobue S, Moriwaki Y. The crystallinity of human deciduous teeth in hypophosphataemic vitamin D-resistant rickets. Arch Oral Biol. 1989;34:365–372.

Correspondence: Sven Poulsen, Department of Pediatric Dentistry, School of Dentistry, Aarhus University, Vennelyst Boulevard 9, DK-8000 Aarhus C, Denmark. E-mail: sven.poulsen@odontologi.au.dk