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The effect of medical therapy on dentin formation in vitamin D-resistant rickets

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Abstract

Vitamin D-resistant rickets (VDRR) is one of the most common forms of rickets in developed countries today. Widely practiced medical treatment regimens usually include replacing phosphorus and calcium lost through urination. In this study, 20 teeth from five patients with varying grades of dental manifestation of VDRR were examined to relate the institution of medical therapy with any observed improvement of dentin calcification. In all the teeth examined, there was no correlation between the time of appearance of dentin changes and the commencement of medical therapy. Furthermore, in several teeth from the patients with Grade III severity, there were no signs of improvement in dentin calcification even after prolonged medical therapy. This study suggests that current medical treatment of VDRR has no beneficial effect on the dental structures and dentists should not rely on medical treatment to correct dental calcification problems.

Introduction

Vitamin D-resistant rickets (VDRR), inherited in an X-linked dominant manner, is the most common form of rickets in developed countries today (Fraser and Scriver 1976). The pathogenesis of the disease is related to a selective abnormality in renal phosphate transport that results in hyperphosphaturia and hypophosphatemia (Harrison and Harrison 1964; Drezner 1987). Current medical treatment of VDRR includes replacement therapy with high doses of phosphate and calcitriol (Drezner 1987). Recently this regimen has been modified by the addition of thiazide diuretics to reduce urinary losses of phosphorus and calcium (Alon and Chan 1985).

The dental manifestations of VDRR have been well described (Harris and Sullivan 1960; Marks et al. 1965; Archard and Witkop 1966; Seow 1984; Seow and Latham 1986; Abe et al. 1988; Seow et al. 1989), and are characterized by "spontaneous" dental abscesses resulting from pulp infection through abnormally mineralized (interglobular) dentin.

Previous studies (Seow and Latham 1986; Seow et al. 1989; Seow and Seeto 1991) have shown that the dental manifestations of VDRR occur in a spectrum of severity ranging from mild (Grade I) to severe (Grade III) which may be correlated both clinically and histologically.

The reasons for the variability in appearance of dentin from different patients currently are unclear. Whether current medical therapy is effective in curing the dental abnormalities of VDRR is of clinical importance. Of particular relevance is a recent study by Stickler and Morgenstern (1989) which showed that there was no evidence that any form of treatment (i.e., vitamin D in high doses, vitamin D plus phosphate supplements, or calcitriol plus phosphate) had any effect on adult height, symptoms or alkaline phosphatase levels. Furthermore, significant side effects associated with medical treatment, such as hypercalcemia (Harrell et al. 1985), nephrocalcinosis (Goodyer et al. 1987), and renal failure (Stickler and Morgenstern 1989) may outweigh any possible benefits.

Thus, this study was conducted to determine the possible effects of medical therapy on the dental lesions of VDRR. To my knowledge, no such studies have been reported previously.

Patients and Methods

Patients

Five patients (two females and three males) with an established diagnosis of VDRR contributed a total of 18 primary and two permanent teeth. With the exception of five primary teeth which were exfoliated naturally, the teeth were extracted because of pulpal abscesses and orthodontic considerations. The ages of the patients at initial dental examination at the University Dental School ranged from 3 to 11 years.

Details of medical histories and treatment as obtained from hospital charts revealed that ages of diagnosis and

start of medical treatment ranged from 1.5 to 4.5 years. All the patients were placed on a standard regimen of phosphate replacement therapy, as well as calcitriol in doses sufficient to prevent hyperparathyroidism. They were closely supervised medically at either one of the two major Children's Hospitals in Brisbane, and the disease was reported to be well controlled in all the patients.

Histologic Sections

The teeth were embedded in plastic and sectioned in a true sagittal manner through the buccal and lingual cusps. The sections obtained using a Bovis Planometer® (Allied Hydraulics Pty Ltd, England) sectioning machine were approximately 100 µm; hand polishing further reduced the sections to 80 µm. The undecalcified sections were mounted on glass slides and examined under an inverted light microscope. Photographs were taken using an exposure control unit (Olympus Optical Co., Tokyo, Japan) coupled with a camera (Olympus Optical Co., Tokyo, Japan).

Assessment of dentin formation

To determine if medical therapy causes a change in the quality of dentin formation, it is pertinent to quantify the distribution of normal and abnormal (interglobular) dentin in each section. Using a micrometer grid mounted on a microscope eyepiece the thickness of interglobular dentin was measured from the dentinoenamel junction (DEJ) to the region where normal dentin started to appear (Fig 1). Three measurements were taken of each section, one directly below a cusp tip (or incisal edge) and two from the mid section of the cusp slopes on either side of the cusp tip. Means and standard deviations of the three measurements were obtained.

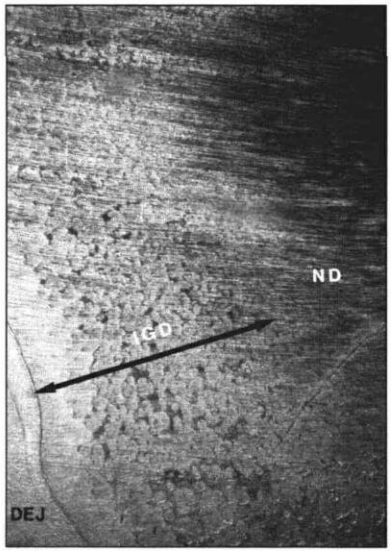

Fig 1. Appearance of dentin from tooth C from patient (1A) who has Grade I dental manifestations. Note the marked demarcation between interglobular and normal dentin. Line shows measurement of the thickness of interglobular dentin as used for analysis. Mag: original 40x.

Duration of interglobular dentin formation

The estimations of Schour and Poncher (1937), which were recently confirmed by Risnes (1986), were used to determine the duration of hard tissue formation in the sections. Thus primary dentin was estimated to form at the rate of 3.7 microns per day, compared with 2.7 microns in the permanent dentition. The duration of interglobular dentin (IG) formation was derived by dividing the thickness of interglobular dentin by the daily rate of dentin formation.

Ages at commencement of improved dentin

It is pertinent to determine the ages of the patients at the approximate time when improvement in the appearance of dentin formation commences to relate this to the time of institution of medical therapy. These ages were derived using the following formula for primary teeth that start calcification prenatally:

Age at commencement of normal dentin = (Duration of IG formation) minus (Age at start of tooth calcification)

For permanent teeth which commence calcification after birth, the following formula was employed :

Age at commencement of normal dentin = (Duration of IG formation) plus (Age of start of tooth calcification)

To determine if the commencement of better formed dentin formation may be correlated directly with the start of medical therapy, the differences between the ages at institution of medical treatment and ages of commencement of better formed dentin were noted.

Statistical analysis

The Student's *t*-test was used for statistical analysis of the data.

Results

The five patients studied in this investigation showed a spectrum of dental clinical and histological manifestations ranging from Grade I to Grade III (Seow and Latham 1986; Seow et al. 1989; Seeto and Seow 1991). Two patients, 1A and 1B, were classified as having Grade I dental manifestations. Another two, 3A and 3B had Grade III signs while the fifth patient, 2A, had Grade II dental manifestations.

Grade I patients

Table 1 (see next page) relates the appearance of better calcified dentin formation with commencement of medical therapy in the two patients with Grade I dental signs. To demonstrate the mathematical computations involved, the data from tooth C in patient 1A (Table 1) have been analyzed as follows:

Table 1. Relationship of improved dentin formation with commencement of medical therapy in two patients with Grade I dental signs

	Tooth	IG Thickness* (mean mm ± SD)	Duration of IG formation (mean yrs ± SD)	Age at start of tooth calcification§ (yrs)	Age at start of appearance of normal dentin‡ (yrs)	Difference between age at start of normal dentin and age at start of treatment* (yrs)
Patient 1A†						
	C	0.87 ± 0.21	0.64 ± 0.16	0.33 (iu)	0.31	−1.19
	D	0.93 0.11	0.69 0.08	0.29	0.49	−1.01
	D	0.93 0.12	0.69 0.09	0.29	0.49	−1.01
	E	0.93 0.17	0.69 0.13	0.35	0.34	−1.16
						Mean −1.09 ± 0.09
Patient 1B†						
	A	0.46 0.07	0.34 0.05	0.27	0.07	−1.43
	B	0.37 ± 1.20	0.33 ± 0.09	0.30 (iu)	0.03	−1.47
						Mean −1.45 ± 0.02

IG Interglobular dentin, iu = in utero

* Measured from the DEJ

† In both patients, medical therapy started at ages 1.5 years

‡ This age was derived by subtracting the age of start of tooth calcification from the duration of IG formation as all the primary teeth were calcified in utero.

§ Based on the estimations of Lunt and Law (1974).

Duration of IG formation (days)

$$= \frac{\text{Thickness of IG dentin (μm)}}{\text{Daily rate of dentin formation (μm)}} = \frac{870}{3.7} = 235$$

$$= \frac{235}{365} = 0.64 \text{ years}$$

Age of commencement of normal dentin

Duration of IG formation — Age of start of tooth calcification

= 0.64 − 0.33

= 0.31 years

Difference between age at commencement of normal dentin and age at start of treatment

= 0.31 − 1.5

= − 1.19 years

In patient 1A, in all the four primary teeth investigated, there was a mean of 1.09 ± 0.09 years difference in the time of institution of medical therapy and the appearance of better formed (normal-looking) dentin. Similarly, in patient 1B, there was a mean difference of 1.45 ± 2.02 years in time between the age of start of treatment and the age when dentin started to appear normal. In these patients with Grade I severity, the better formed dentin appeared normal with minimal globular dentin (Fig 1).

Grade II patients

In Table 2, the relationship of better formed dentin with commencement of medical therapy in a patient with Grade II dental manifestations is shown. In this patient, the time differences between the ages at start of treatment and ages at start of normal-appearing dentin ranged from 0.03 years for both Es to 1.57 for the first premolars. The overall mean time difference among the teeth was 0.76 ± 0.73 years. Fig 2 (see next page) shows evidence of a sharp improvement in dentin calcification after the formation of a band of interglobular dentin in a tooth from patient NS (Grade II).

Grade III patients

In sharp contrast to the above Grade I and II patients, the patients with Grade III dental manifestations had several teeth that showed no areas of apparent improvement in dentin calcification throughout its entire

Table 2. Relationship of improved dentin formation with commencement of medical therapy in a patient (2A) with Grade II dental signs

Tooth	*IG Thickness† (mean mm ± SD)*	*Duration of IG formation (mean yrs ± SD)*	*Age at start of tooth calcification§ (yrs)*	*Age at start of appearance of normal dentin‡ (yrs)*	*Difference between age at start of treatment* and age at start of treatment* (yrs)*
C	0.49 ± 0.06	0.36 ± 0.04	0.33 (iu)	–0.07	–0.68
E	1.53 0.24	1.13 0.18	0.35	0.78	–0.03
E	1.52 0.10	1.13 0.07	0.35	0.78	–0.03
4	1.06 0.05	1.07 0.05	2.00	3.07	+1.57
4	0.91 ± 0.03	0.92 ± 0.08	2.00 (iu)	2.92	+1.42
					Mean 0.76 ± 0.73

* In this patient, medical therapy started at 1.50 years of age.

IG Interglobular dentin, iu = in utero

† Measured from the DEJ

‡ This age was derived by subtracting the age of start of tooth calcification from the duration of IG formation in cases of teeth which start calcifying in utero. In the case of teeth which started calcifying after birth, this age was derived by adding the age at start of calcification to the duration of IG formation.

§ Based on the estimations of Lunt and Law (1974).

thickness (Table 3, see next page); this indicates that medical therapy possibly had no effect. In patient 3A, only one tooth showed evidence of improvement in dentin calcification. This occurred after 0.51 ± 0.08 mm of dentin has formed and corresponded to the patient's age of 0.5 years. As the patient commenced medical therapy at 2.5 years of age, it is evident that the change in dentin calcification occurred well before medical therapy was administered.

Similarly in the second Grade III patient 3B, only one out of four teeth examined showed evidence of improved dentin formation. In this tooth (C), better calcified dentin started to appear at age 0.78 years, although medical therapy commenced only at the age of 3.72 years.

Fig 3 (see next page) shows the typical appearance of a primary tooth from patient 1B. The tooth shpwed no improvement in dentin calcification throughout its thickness.

Comparison of all patients

The overall mean differences between the ages at start of treatment and ages at start of normal dentin among the five patients studied were statistically significant ($P < 0.01$). This indicates that even when there was evidence of better calcification in certain parts of dentin in certain patients, there was no consistent time difference between the ages at start of treatment and ages at start of appearance of better formed dentin among the five patients studied.

Discussion

The current therapeutic regimen for VDRR is replacement therapy with phosphate salts as well as calcitriol and thiazide diuretics to decrease losses of phosphorus and calcium in the urine (Gloreiux et al. 1972; Alon and Chan 1985; Tsuru et al. 1987).

Although the above regimen has been practiced widely, its therapeutic value has not been established clearly. A few short-term retrospective studies have indicated encouraging results based on analysis of growth velocity (Glorieux et al. 1972; Tsuru et al. 1987)

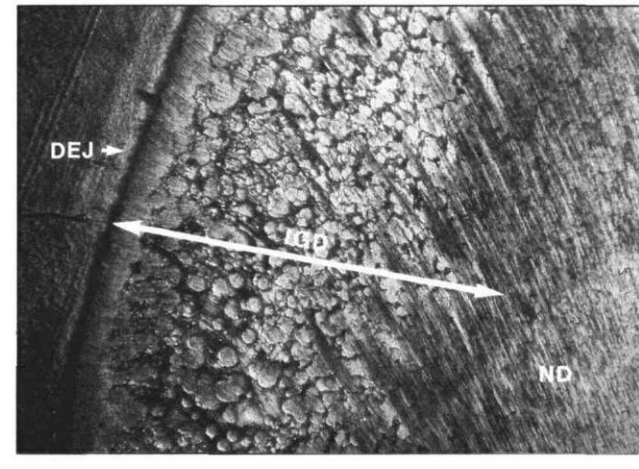

Fig 2. Dentin of tooth 4 from patient (2A) who has Grade II dental signs. Note the clear demarcation between interglobular and normal dentin. Mag: original 40x.

Table 3. Relationship of normal dentin formation with commencement of medical therapy in two patients with Grade III dental signs

	Tooth	*IG Thickness* (mean mm ± SD)*	*Duration of IG formation (mean yrs ± SD)*	*Age at start of tooth calcification# (yrs)*	*Age at start of appearance of normal dentin† (yrs)*	*Difference between age at start of treatment‡† and age at start of normal dentin* (yrs)*
Patient 3A‡						
	A	0.66 ± 0.08	0.66 ± 0.08	0.27 (iu)	NID	—
	C	1.09 0.12	0.81 0.09	0.33	NID	—
	C	1.65 0.20	1.22 0.15	0.33	NID	—
	D	1.17 0.20	0.86 0.15	0.29	NID	—
	1	0.51 0.08	0.51 0.06	0.00	0.51	–1.99
Patient 3B§						
	A	0.83 0.06	0.61 0.04	0.27	NID	—
	C	1.49 0.13	1.11 0.09	0.33	0.78	–0.72
	C	1.24 0.14	0.91 0.11	0.33	NID	—
	E	0.54 ± 0.05	0.40 ± 0.03	0.03 (iu)	NID	—

IG Interglobular dentin, iu = in utero, NID = no normal dentin detected

* Measured from the DEJ

† This age was derived by subtracting the age of start of tooth calcification from the duration of IG formation in cases of teeth which start calcifying in utero. In the case of teeth which started calcifying after birth, this age was derived by adding the age at start of calcification to the duration of IG formation.

‡ In this patient, medical treatment started at 2.5 years of age.

§ In this patient, medical treatment started at 4.5 years of age.

Based on the estimations of Lunt and Law (1974).

and standard deviation scores for height in treated patients (Chesney et al. 1983); other studies have not shown any positive effects of treatment. Early investigations by McNair and Stickler (1969) and Stickler et al. (1971) have shown no effect of vitamin D on growth or bone deformities, and a prospective study by Howard et al. (1979) indicated no evidence of catch-up growth in 16 VDRR patients treated with phosphate and vitamin D.

More recently, in the retrospective study of Stickler and Morgenstern (1989) of 52 adult patients with VDRR the clinical value of medical therapy was questioned seriously. In this study, there was no evidence that any form of treatment (i.e. vitamin D in high doses, vitamin D plus phosphate supplements, or calcitriol plus phosphate) had any effect on adult height. In addition, there was no difference in symptom scores between patients still on treatment and those not on treatment or never treated. Furthermore, some patients who underwent therapy experienced significant complications, such as renal failure, hypercalcemia and nephrocalcinosis.

The present study suggests that medical therapy also is not associated with improved calcification of the dental tissues. In all 20 teeth from five patients studied,

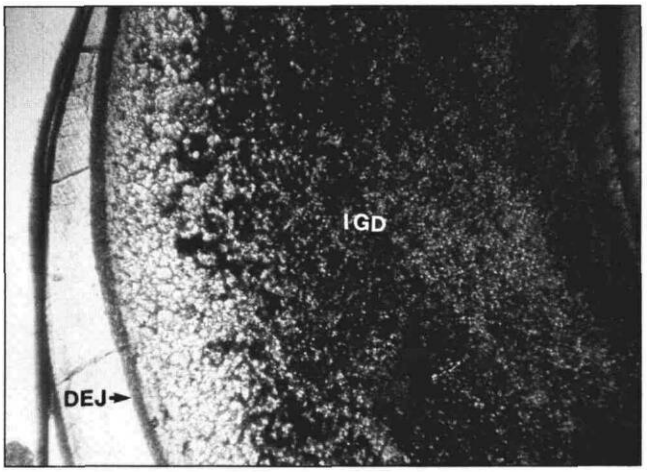

Fig 3. Typical appearance of dentin from a tooth of patient (3A) who has Grade III dental manifestations. Note that all dentin is interglobular in appearance. Mag: original 40x.

there was no direct correlation of the timing of changes in dentin to the start of medical therapy, indicating that it is unlikely that treatment with phosphate and calcitriol had caused any observed changes. It is possible that a delay in appearance of improved dentin may be caused by a delay in response of the dentin forming cells or by the time taken for homeostatic mechanisms to become fully operational. However, this theory is unlikely; Tables 1–3 show that in most of the teeth with improved dentin, the improved calcification had commenced before medical therapy was instituted.

The results of the present study are based on the assumption that the rates of dentin formation and dental development in VDRR are comparable to those of normal children. Although there have been no previous studies to prove the above directly, most clinical studies have reported normal dental eruption times (Harris and Sullivan 1960; Marks et al. 1965), suggesting normal rates of dental calcification and development. Furthermore, the calculations in this present paper were based on the dental developmental ages proposed by Lunt and Law (1974). Although this work has deficiencies, it is well accepted as the most valid and current reference for the chronology of dental development.

In VDRR, it is most likely that observed changes in dentin calcification are related to natural history of the disease in the dental structures, which may in turn be related to genetic factors. In the patients with Grades I and II dental manifestations, improvement in dentin calcification is observed consistently in all the teeth studied, in contrast to the patients with Grade III dental manifestations.

Conclusions

The present study has important clinical implications. It provides further evidence that current medical treatment regimens for VDRR may be of little clinical value, particularly when treatment is fraught with serious complications. Dental abscesses are an important clinical manifestation of VDRR and may be one of the reasons for instituting medical therapy. However, the present study suggests that treated patients are unlikely to benefit dentally from treatment. Therefore, dentists should not rely on medical treatment to correct dental calcification problems, but should instead institute prophylactic procedures early to prevent dental abscesses (Seow 1984; Seow and Latham 1986; Seow et al. 1989). These include occlusal coverage of teeth with adhesive resins and stainless steel crowns using very conservative restorative measures.

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Abe K, Ooshima T, Tong SM, Yasufuku Y, Sobue S: Structural deformities of deciduous teeth in patients with hypophosphatemic vitamin D-resistent rickets. Oral Surg 65:191–98, 1988.

Alon U, Chan JCM: Effects of hydrochlorothiazide and amiloride in renal hypophosphatemic rickets. Pediatrics 75:754–63, 1985.

Archard HO, Witkop CJ: Hereditary hypophosphatemia (vitamin D-resistent rickets) presenting primary dental manifestations. Oral Surg 22:184–93, 1966.

Chesney RW, Mazess RB, Rose P, Hamstra AJ, DeLuca HF, Breed AL: Long-term influence of calcitriol (1,25-dihydroxyvitamin D) and supplemental phosphate in X-linked hypophosphatemic rickets. Pediatrics 71:559–67, 1983.

Drezner MK: Understanding the pathogenesis of X-linked hypophosphatemic rickets: a requisite for successful therapy. In: A CPC series: Cases in Metabolic Bone Disease. Vol 2. New York: Triclinica Communications, 1987, pp 1–11.

Fraser D, Scriver CR: Familial forms of vitamin D-resistant rickets revisited. X-linked hypophosphatemic and autosomal recessive vitamin D dependency. Am J Clin Nutr 29:1315–29, 1976.

Glorieux FH, Scriver CR, Reade TM, Goldman H, Roseborough A: Use of phosphate and vitamin D to prevent dwarfism and rickets in X-linked hypophosphatemia. N Engl J Med 287:481–87, 1972.

Harrell RM, Lyles KW, Harrelson JM, Friedman NE, Drezner MK: Healing of bone disease in X-linked hypophosphatemic rickets/osteomalacia: induction and maintenance with phosphorus and calcitriol. J Clin Invest 75: 1858–68, 1985.

Harris R, Sullivan HR: Dental sequelae in deciduous dentition in vitamin D resistant rickets. Case report. Aust Dent J 5:200–203, 1960.

Harrison HE, Harrison HC: Hereditary metabolic bone diseases. Clin Orthop 33:147–63, 1964.

Howard CP, Huse DM, Hayles AB, Stickler GB: Growth in patients with familial hypophosphatemic rickets treated with large doses of phosphate. Pediatr Res 13:380 (Abstr 326), 1979.

Lunt RC, Law DB: A review of the chronology of calcification of deciduous teeth. J Am Dent Assoc 89:599–606, 1974.

Marks SC, Lindahl RL, Bawden JW: Dental and cephalometric findings in vitamin D resistant rickets. ASDC J Dent Child 32:259–65, 1965.

McNair SL, Stickler GB: Growth in familial hypophosphatemic vitamin D-resistant rickets. N Engl J Med 281:511–16, 1969.

Risnes S: Enamel apposition rate and the prism periodicity in human teeth. Scand J Dent Res 94:394–404, 1986.

Schour I, Poncher HG: Rate of apposition of enamel and dentin measured by the effect of acute fluorosis. Am J Dis Child 54:757–76, 1937.

Seeto E, Seow WK: Scanning electron microscopic analysis of dentin in vitamin D-resistant rickets — assessment of mineralization and correlation with clinical findings. Pediatr Dent 13: 43–48, 1991.

Seow WK: X-linked hypophosphataemic vitamin D-resistant rickets. Aust Dent J 29:371–77, 1984.

Seow WK, Latham SC: The spectrum of dental menifestations in vitamin D-resistant rickets: implications for management. Pediatr Dent 8:245–50, 1986.

Seow WK, Romaniuk K, Sclavos S: Micromorphologic features of dentin in vitamin D-resistant rickets: correlation with clinical grading of severity. Pediatr Dent 11:203–8, 1989.

Stickler GB, Jowsey J, Bianco AJ Jr: Possible detrimental effect of large doses of vitamin D in familial hypophosphataemic vitamin D-resistant rickets. J Pediatr 79:68–71, 1971.

Stickler GB, Morgenstern BZ: Hypophosphatemic rickets: final height and clinical symptoms in adults. Lancet ii:902–5, 1989.

Tsuru N, Chan JCM, Chinchilli VM: Renal hypophosphatemic rickets: growth and mineral metabolism after treatment with calcitriol (1,25-dihydroxyvitamin D_3) and phosphate supplementation. Am J Dis Child 141:108–10, 1987.