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ORIGINAL ARTICLE

Vitamin D deficiency is a risk factor for delayed tooth eruption associated with persistent primary tooth

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ABSTRACT

Objective: To verify the association between 25(OH)D level and polymorphisms in the vitamin D receptor gene (*VDR*) with the disturbance in the dental development and eruption.
Design: A total of 183 children from two datasets were evaluated. The first dataset was a case–control (15:15) designed to assess if persistent primary tooth (PPT) is associate with serum 25(OH)D level and with genetic polymorphisms in *VDR*. The second dataset of genomic DNA samples from 54 children with delayed tooth eruption (DTE) and 99 controls were analysed to verify if genetic polymorphisms in *VDR* (rs2228570 and rs739837) are associated with DTE. The 25(OH)D and the genotyping/allele distribution were analysed using the *T*-test and chi-square test, respectively.
Results: The level of 25(OH)D in the PPT group (24.9 ± 6.4 mg/mL) was significantly lower than the control (30.0 ± 7.0 mg/mL) (p=.047). Our data show that children with 25(OH)D deficiency are more likely to present PPT (OR = 2.36; 95%CI: 1.51, 3.70). The rs739837 and rs2228570 polymorphisms were not associated with DTE (OR = 1.44; 95%CI: 0.87, 2.39 and OR = 0.80; 95%CI: 0.45, 1.44, respectively).
Conclusions: Vitamin D deficiency is a risk factor for PPT.

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25-Hydroxyvitamin D; vitamin D deficiency; tooth eruption; single nucleotide polymorphism

Introduction

Vitamin D represents a group of fat-soluble secosteroids [1] obtained mainly through skin exposure to UVB irradiation by sunlight [2,3]. The 7-dehydrocholesterol present in the skin is converted to previtamin D_3 [2,4], and, in the liver, it is converted to 25-hydroxyvitamin D_3 (25(OH)D_3), the best serum indicator of vitamin D status. In the kidney, 25(OH)D_3 undergoes hydroxylation and becomes 1,25-dihydroxy vitamin D (1,25(OH)$_2$$D_3$), the biologically active form that activates vitamin D receptor (*VDR*) [4,5]. *VDR* is a transcription factor that binds to DNA and regulates hundreds of gene expression [2], mediating the vitamin D activities and other processes including cell proliferation, differentiation, angiogenesis and apoptosis [6]. Previous studies have analysed the DNA sequence variations of *VDR*, known as genetic polymorphisms [7,8], which are frequently observed in the population [9].

Vitamin D has an essential role in phosphate and calcium metabolism and, therefore, in bone homeostasis [1,3,4,10]. It can stimulate both formation and resorption of bone [11] and can also influence host immune responses. Previous studies have shown that vitamin D deficiency increases the incidence of periodontal disease [12] and that inadequate level of vitamin D has been associated with increased susceptibility to dental caries [13] and maternal periodontal diseases during pregnancy [14]. Genetic studies provided excellent opportunities to link molecular insights with epidemiological data and, therefore, gain much interest.

Genetic polymorphisms in *VDR* have been associated with external apical root resorption [15], periodontal disease [16], dentinogenesis imperfecta [17], chronic periodontitis [18] and dental caries [8,9]. Although many genetic polymorphisms in *VDR* have been described and associated with the aetiology of several pathological conditions, the influence of genetic polymorphisms in *VDR* on *VDR* protein function is not entirely understood. Two genetic polymorphisms in *VDR* are rs2228570 (also known as the Fok1 polymorphism) and rs739837 (also known as the Bms1 polymorphism), have been frequently studied [9]. Studies have shown that rs2228570 can change the structure and stability of the *VDR* and the binding energy of its ligand [18,20]. Likewise, rs739837 could cause differences in RNA translation's stability and efficiency [21].

Tooth development [22] and eruption [23] are complex processes that also involve alveolar bone resorption and an

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eruption pathway formation [23]. Disturbances in dental development can lead to a persistent primary tooth (PPT) and delayed tooth eruption (DTE). PPT occurs when a primary tooth is retained beyond the regular exfoliation time. PPT can cause malocclusions, periodontitis, ankylosis [24] and a severe impact on patient dissatisfaction [25]. The molecular mechanism underlying PPT occurrence has not been fully explained, but it is known that PPT can lead to DTE of the permanent tooth [26]. DTE is the emergence of a tooth into the oral cavity at a delayed time than expected according to sex and ethnic differences [27]. The failure of dental emergence in the oral cavity influences the paediatric and orthodontic treatment plan, impacting a patient's oral health [27,28].

DTE is commonly associated with PPT. However, DTE can occur in the absence of PPT. Considering that vitamin D can stimulate both formation and resorption of bone and that PPT and DTE are common findings in dental practice, there is a lack of information in the literature concerning the vitamin D level or genetic polymorphisms *VDR* associations with alterations in the permanent tooth eruption process. Thus, this study aimed to investigate whether impaired vitamin D signalling could lead to dental development and eruption disturbances inducing PPT and DTE.

Materials and methods

Ethics

The Ethics Committee of the School of Dentistry of Ribeirão Preto, University of São Paulo, Brazil, approved the study (register numbers 44249415.0.00005419 and 35323314.7.0000.5419). All parents and caregivers were appropriately clarified about this research and signed informed consent.

Subjects of the study

This study evaluated 183 children from two datasets from the School of Dentistry of Ribeirão Preto, São Paulo, Brazil. Children of both sexes and aged between 6 and 13 years living in the Ribeirão Preto area were included in this study. A flow chart for patient selection and inclusion/exclusion criteria is presented in Figure 1. The fluctuation of 25(OH)D levels is not expected in Ribeirão Preto, as there is a small fluctuation in the total sunshine hour and UVB incidence over the year in this city. Thus, the patient recruitment and sample collection were not done in a specific season. The parents and caregivers answered the anamnesis before the oral examination and sample collection, which were performed on the same day.

The first dataset was a case–control consecutive sample designed to assess if PPT is associated with serum 25(OH)D levels and genetic polymorphisms in *VDR*. All children in dental treatment in 2015 were screened and examined by a paediatric dentist (TAX). According to the age and time of teeth exfoliation table published by The American Dental Association, children with primary teeth with the exfoliation time expired for more than 1 year [24,29], were included in the PPT group. All children from the PPT group presented the successor permanent teeth with at least half of the root formed and the primary teeth with a maximum of one-third of the root resorption identified in periapical radiographs (Figure 2). The same number of children with regular primary teeth exfoliation time, matching in age, was selected for the Control group. Children with the absence of the successor permanent teeth (tooth agenesis), ankylosis or indication of PPTs due to endodontic treatment or dental trauma were not included in this study. Children with systemic disease or syndrome were also excluded (Figure 1). Therefore, blood and genomic (gDNA) samples extracted from saliva from 15 children with PPT and 15 control children (without PPT) were evaluated in this part of the study.

The second dataset consists of a nested case–control designed from a cross-sectional sample to verify if genetic polymorphisms in *VDR* were associated with DTE in a more extensive selection. Regular tooth emergence and DTE were considered according to a chronological scale and the gender for Brazilian children from São Paulo state [30]. Children that presented at least one delayed permanent tooth eruption were selected for the DTE group. The paediatric dentist

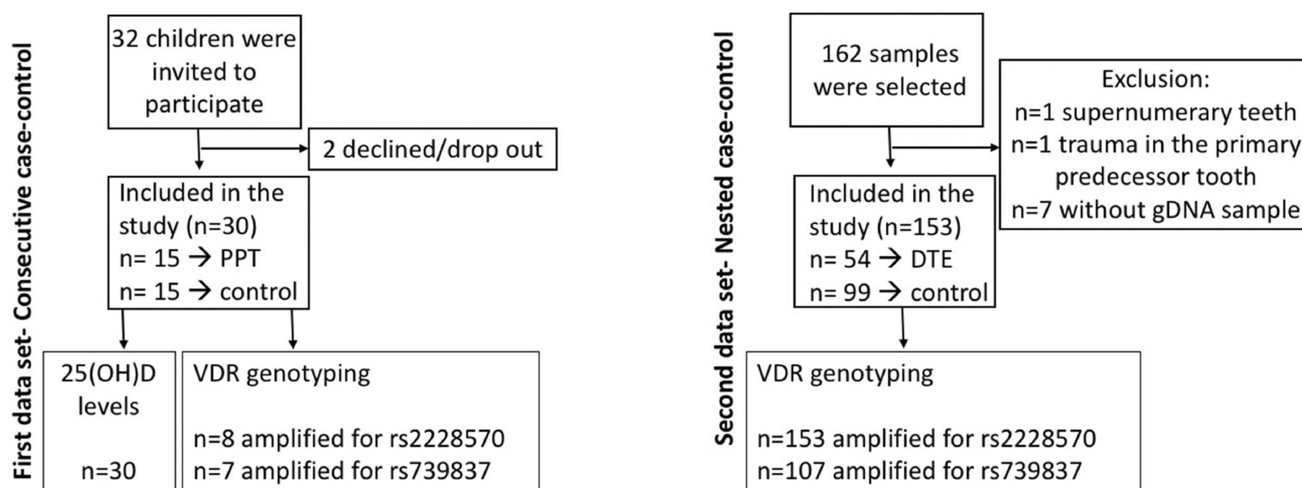

Figure 1. Flowchart of the two studied datasets.

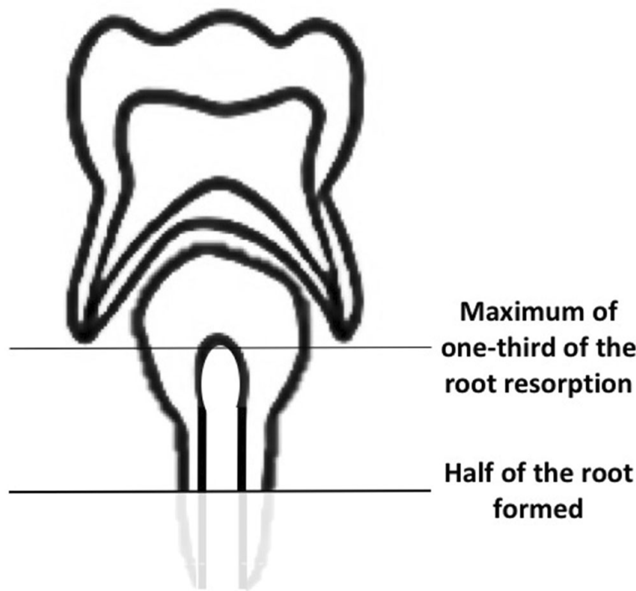

Figure 2. A representative illustration of the criteria used to determine PPT.

(ECK) performed periapical radiographic examinations to confirm the permanent tooth's presence. Once canines present a high impaction rate [31,32], the DTE of canines was excluded from this study. Children with odontomas, supernumerary teeth, dental trauma associated with DTE or with systemic diseases [27] were not included in the study (Figure 1). In this dataset, gDNA samples extracted from saliva from 54 children with DTE and 99 children without DTE were evaluated. This sample was previously described [33].

Serum concentrations of 25(OH)D

Blood samples were collected at the Clinical Analysis Service of School of Pharmaceutical Sciences of Ribeirão Preto, University of São Paulo, and serum 25(OH)D levels were measured by chemiluminescence, using a LIAISON® 25 OH Vitamin D TOTAL Assay (DiaSorin, Saluggia, Italy) kit according to the manufacturer's instructions. After the introduction of the samples into the LIAISON® Analyser, there was the first incubation. The 25(OH)D was dissociated from its binding protein and bound to the solid phase's antibody. At the end of 10 min, the vitamin D marker linked to an isoluminol derivative was added, and the unbound material was removed with a wash cycle. Subsequently, the initiator reagents were added, and the chemiluminescence reaction started. A photomultiplier measured the light signal as relative light units (RLUs), which is inversely proportional to 25(OH)D concentration.

Vitamin D deficiency [25(OH)D < 20 mg/mL] was determined according to the Brazilian Society of Paediatrics [34] and other published researchers' orientations [3,35].

Genotyping analysis

Children were instructed to rinse the mouth with 10 mL of saline, and the expectorating rinse was collected. Briefly, for gDNA isolation, we used an extraction solution (Tris–HCl 10 mM, pH 7.8; EDTA 5 mM; SDS 0.5%) containing proteinase K (100 mg/mL) (Invitrogen, Grand Island, NY), as previously reported [36]. The DNA was precipitated with isopropanol and resuspended and stored at −20 °C. The gDNA's concentration and purity were determined by spectrophotometer (Nanodrop 1000; Thermo Scientific, Wilmington, DE).

Two genetic polymorphisms in the *VDR* were selected. The rs2228570 (A > G/Met > Thr) is a missense variant, and the rs739837 (G > T) is located in an untranslated region. Their minor allele frequency should be higher than 30%. The genetic polymorphisms were blinded genotyped by real-time polymerase chain reaction (PCR), TaqMan assay (StepOnePlus Real-Time PCR System, Applied Biosystems, Foster City, CA) in a total volume of 3 μL (4 ng DNA/reaction, 1.5 μL Taqman PCR master mix, 0.125 SNP assay; Applied Biosystems, Foster City, CA). The cycling was carried out by 95 °C for 10 min, 40 cycles of 92 °C for 15 s, and 60 °C for 1 min.

Statistical analysis

For the 25(OH)D analysis, the D'Agostino-Pearson test was used to evaluate if 25(OH)D levels were distributed normally. The Student's *t*-test was applied to analyse the levels in PPT and control groups, and Welch's correction was applied to the Student's *t*-test if the variance between groups was different ($p<.05$). The level of vitamin D distribution, according to the *VDR* genotypes, was evaluated using ANOVA.

For the genotyping analysis, the chi-square test was used to compare genotype and allele distribution. The unadjusted odds ratio was used to calculate the relative risk among groups with DTE and control.

The study used GraphPad Prism version 5.0 (Graph-Pad, San Diego, CA), SPSS Statistics 20.0 (IBM™, Armonk, NY), and Epi Info 7 (Epi Info 7 Software, Atlanta, GA) for data analysis. A significance level of 5% ($p<.05$) was adopted.

Post hoc power analysis was conducted after the study had been completed using clinical.com. For the first dataset, the calculation used the mean level of 25(OH)D difference between the groups (6 mg/mL) and an error probability of 0.05, which indicated that a sample size of 15 children per group would present a power of 71.4%. For the second set of data, the calculation used the genotype frequency difference between the groups of 15% and an error probability of 0.05, which indicated that our sample would present a power of 58.9%.

Results

The characteristics of both datasets of participants are presented in Table 1. Gender, age and body mass index (BMI) were not statistically different between control and PPT groups or between control and DTE groups.

Analysis of vitamin D concentrations and VDR polymorphisms in persistent primary tooth group

We initially aimed to investigate whether vitamin D could be involved with dental development disturbances and primary teeth exfoliation. For this, we evaluated the serum level of 25(OH)D in participants with PPT. It is worthy of mentioning that this set of participants presented DTE associated with PPT.

The levels of 25(OH)D in control and PPT groups are shown in Figure 3. The PPT group exhibited significantly lower 25(OH)D levels (from 14.2 to 37.4 mg/mL) than control group (from 21.9 to 48.2 mg/mL) (p=.047). Interestingly, 26.7% of children from the PPT group presented vitamin D deficiency, while none (0%) in the control group presented vitamin D deficiency. Our data indicate that children with vitamin D deficiency have 2.36 times more chance to present PPT (OR = 2.36 [CI 95% 1.50, 3.70]).

Once our previous data suggested that vitamin D deficiency increases PPT's risk, we further evaluated if PPT incidence could also be associated with the genetic polymorphisms in *VDR*. Table 2 shows data related to the genotype and allele distributions between control and PPT groups. The difference between the control and PPT groups was not statistically significant (p>.05).

Moreover, our data show no association between genetic polymorphisms in *VDR* (rs2228570 and rs739837) and serum 25(OH)D levels (p>.05). However, the differences in the frequencies of genotypes and alleles in *VDR* suggested an association that was deeper explored.

Table 1. General characteristics of the participants.

	Control (n = 15)	PPT (n = 15)	p Value
Male sex, n (%)	8 (53.3)	9 (60.0)	.711
Female sex, n (%)	7 (46.7)	6 (40.0)	–
Age mean (SD)	9.4 (1.8)	9.5 (1.7)	.912
dmft/DMFT	2.53 (2.41)	2.22 (2.11)	.969
BMI mean (SD)	17.2 (4.2)	18 (3.2)	.394
	Control (n = 99)	**DTE (n = 54)**	**p Value**
Male sex, n (%)	48 (63.1)	28 (36.9)	.690
Female sex, n (%)	51 (66.2)	26 (33.8)	–
Age mean (SD)	8.6 (1.9)	9.3 (2.1)	.067
dmft/DMFT	4.88 (3.84)	4.12 (3.29)	.202
BMI mean (SD)	18.2 (3.2)	17.8 (3.5)	.398

None of them report vitamin D intake.
BMI: body mass index; dmft: decayed, missing and filled teeth in primary dentition; DMFT: decayed, missing and filled teeth in permanent dentition; PPT: persistent primary tooth; DTE: delayed tooth eruption.

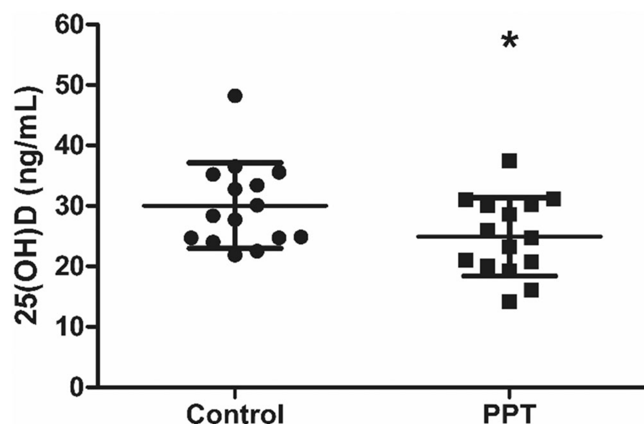

Figure 3. Concentrations of 25(OH)D in Control (n = 15) and PPT (n = 15) groups. Data are expressed as the mean ± SD. Statistical difference was determined by Student's t-test. *p=.047.

Analysis of VDR polymorphisms in delayed permanent tooth emergence group

To further assess if genetic polymorphisms in *VDR* were associated with DTE, an additional analysis in a larger sample size was performed in a set of a convenience sample of gDNA previously reported [33]. A total of 153 samples were analysed to assess if DTE would be associated with the genetic polymorphisms rs2228570 and rs739837 in *VDR*. Table 3 presents rs2228570 and rs739837 genotypes and alleles distributions in DTE and control groups. The data show that there was no association between DTE, rs2228570, and rs739837 polymorphisms.

Table 2. Genotype and allele distribution according to the Control (n = 15) and PPT (n = 15) groups.

Polymorphism	Group	Genotype n (%)			p Value	Allele n (%)		p Value	OR (95%CI)
rs2228570		AA	AG	GG	.274	A	G	.555	0.68 (0.19–2.42)
	Control	1 (7.69)	5 (38.46)	7 (53.85)		7 (26.92)	19 (73.08)		
	PPT	0 (0.0)	7 (70.0)	3 (30.0)		7 (35.0)	13 (65.0)		
rs739837		GG	GT	TT	.662	G	T	.507	1.50 (0.45–4.98)
	Control	3 (25.0)	6 (50.0)	3 (25.0)		12 (50.0)	12 (50.0)		
	PPT	1 (10.0)	6 (60.0)	3 (30.0)		8 (40.0)	12 (60.0)		

PPT: persistent primary tooth.

Table 3. Genotype and allele distribution according to the Control (n = 99) and DTE (n = 54) groups.

Polymorphism	Group	Genotype n(%)			p Value	Allele n(%)		p Value	OR (95%CI)
rs2228570		AA	AG	GG	.169	A	G	.148	1.44 (0.87–2.39)
	Control	14 (14.14)	47 (47.48)	38 (38.38)		75 (37.88)	123 (62.12)		
	DTE	7 (12.96)	18 (33.33)	29 (53.70)		32 (29.63)	76 (70.37)		
rs739837		GG	GT	TT	.107	G	T	.473	0.80 (0.45–1.44)
	Control	10 (14.08)	32 (45.07)	29 (40.85)		52 (36.62)	90 (63.38)		
	DTE	3 (8.33)	24 (66.67)	9 (25.00)		30 (41.67)	42 (58.33)		

DTE: delayed tooth eruption.

Discussion

In this study, we investigated if reduced vitamin D level and its signalling could be involved in dental development and eruption disturbances leading to PPT and DTE. Our results support that the level of vitamin D is involved in the time of primary tooth exfoliation.

Vitamin D is a hormone that plays an essential role in bone biology and is generally associated with high bone mass and reduced fracture risk [37]. Moreover, an adequate vitamin D level has also been associated with oral and dental health. Patients with vitamin D-dependent rickets present many oral manifestations including DTE [38], highlighting vitamin D as a crucial hormone for proper dentofacial development [39]. Although some studies on vitamin D and dental research, there is still a lack of data about this vitamin's role and its receptor in dental development and eruption.

The alveolar bone and primary teeth's root resorption observed during the permanent tooth's eruption involves an intricate resorption system. In some cases, primary teeth are retained beyond the regular time of exfoliation. It is frequently associated with the congenital absence (tooth agenesis) or impaction of the successor's teeth [24]. Nonetheless, some studies have shown that systemic disorders, such as hormonal deficiency and syndromes, can also be associated with PPT and, consequently, with DTE [40,41].

Disturbance in tooth eruption is a common finding in children [27], which can be aggravated by nutritional deficiency and genetic predisposition [27,42]. Therefore, this study investigated the possible association between vitamin D levels or genetic polymorphisms in *VDR* with dental development and tooth eruption disturbances.

Considering that different factors are involved in PPT and DTE's aetiology, we evaluated if vitamin D serum concentration was associated with PPT. Vitamin D deficiency is frequent in the world [1], and there is no consensus concerning the concentration of this hormone to be considered a deficiency [43]. This study was based on the Brazilian Society of Paediatrics [34] and other reviews [3,35], which considered concentrations lower than 20 mg/mL as vitamin D deficiency. We found that children with PPT presented lower vitamin D concentrations compared to control. Moreover, our data indicated that children with vitamin D deficiency had more risk of having PPT associated with DTE occurrence. This is the first study to report an association between low vitamin D levels and PPT occurrence to the best of our knowledge. The literature already stated that vitamin D deficiency causes secondary hyperparathyroidism, high bone turnover, bone loss, mineralization defects, hip and other fractures [44].

The previous study highlights the importance of maternal and neonatal vitamin D concentrations on primary dental development (formation and mineralization of primary teeth). The lower vitamin D level during mid-pregnancy or at birth was associated with delayed primary tooth eruption [45,46]. Also, vitamin D deficiency was associated with dental caries [47], and vitamin D-dependent rickets is related to enamel defects [38]. Here, we further show that vitamin D is associated with PPT. These new pieces of evidence bring essential information for the definition of the paediatric dentist treatment plan.

In dental research, genetic polymorphisms in *VDR* have already been associated with some clinical conditions, such as periodontal disease [16] and dental caries in permanent and primary teeth [7,8]. *VDR* is a nuclear receptor that mediates the cellular effects of 1,25-dihydroxy vitamin D_3 by binding to vitamin D response elements of target genes, resulting in gene transcription changes. Many of these target genes are crucial for tooth development and play an essential role in the different processes of tooth eruption and root resorption. A previous study in a Brazilian population demonstrated that apical root resorption of permanent teeth was associated with a genetic polymorphism in *VDR* [15]. Here, we show that the genetic polymorphisms rs2228570 and rs739837 in *VDR* are not associated with PPT or DTE.

In conclusion, our results support that vitamin D deficiency is a risk factor for PPT.

Disclosure statement

Erika Calvano Küchler, Sandra Yasuyo Fukada and Marcelo José Barbosa Silva conceived the ideas; Thaís Aparecida Xavier and Isabela Ribeiro Madalena collected the data; Erika Calvano Küchler, Marcelo José Barbosa Silva, Raquel Assed Bezerra da Silva, Léa Assed Bezerra da Silva and Andiara De Rossi analysed the data; Erika Calvano Küchler, Sandra Yasuyo Fukada, Thaís Aparecida Xavier and Isabela Ribeiro Madalena wrote the manuscript. All authors approved the final version of the manuscript.

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References

[1] Randev S, Kumar P, Guglani V. Vitamin D supplementation in childhood - a review of guidelines. Indian J Pediatr. 2018;85(3):194–201.
[2] Bikle DD. Vitamin D metabolism, mechanism of action, and clinical applications. Chem Biol. 2014;21(3):319–329.
[3] Bouillon R. Comparative analysis of nutritional guidelines for vitamin D. Nat Rev Endocrinol. 2017;13(8):466–479.
[4] Braegger C, Campoy C, Colomb V, et al. Vitamin D in the healthy European paediatric population. J Pediatr Gastroenterol Nutr. 2013;56(6):692–701.
[5] Haq A, Wimalawansa SJ, Pludowski P, et al. Clinical practice guidelines for vitamin D in the United Arab Emirates. J Steroid Biochem Mol Biol. 2018;175:4–11.
[6] Haddad S. Vitamin-D receptor (*VDR*) gene polymorphisms (Taq-I & Apa-I) in Syrian healthy population. Meta Gene. 2014;2:646–650.
[7] Kong YY, Zheng JM, Zhang WJ, et al. The relationship between vitamin D receptor gene polymorphism and deciduous tooth decay in Chinese children. BMC Oral Health. 2017;17(1):111.
[8] Yu M, Jiang QZ, Sun ZY, et al. association between single nucleotide polymorphisms in vitamin D receptor gene polymorphisms and permanent tooth caries susceptibility to permanent tooth caries in chinese adolescent. Biomed Res Int. 2017;2017:1–7.

[9] Uitterlinden AG, Fang Y, van Meurs JB, et al. Vitamin D receptor gene polymorphisms in relation to vitamin D related disease states. J Steroid Biochem Mol Biol. 2004;89–90(1–5):187–193.
[10] Elsori DH, Hammoud MS. Vitamin D deficiency in mothers, neonates and children. J Steroid Biochem Mol Biol. 2018;175: 195–199.
[11] Morris HA. Vitamin D activities for health outcomes. Ann Lab Med. 2014;34(3):181–186.
[12] Uwitonze AM, Murererehe J, Ineza MC, et al. Effects of vitamin D status on oral health. J Steroid Biochem Mol Biol. 2018;175: 190–194.
[13] Scardina GA, Messina P. Good oral health and diet. J Biomed Biotechnol. 2012;2012:1–8.
[14] Uwitonze AM, Uwambaye P, Isyagi M, et al. Periodontal diseases and adverse pregnancy outcomes: is there a role for vitamin D? J Steroid Biochem Mol Biol. 2018;180:65–72.
[15] Fontana ML, de Souza CM, Bernardino JF, et al. Association analysis of clinical aspects and vitamin D receptor gene polymorphism with external apical root resorption in orthodontic patients. Am J Orthod Dentofacial Orthop. 2012;142(3):339–347.
[16] Tanaka K, Miyake Y, Hanioka T, et al. *VDR* gene polymorphisms, interaction with smoking and risk of periodontal disease in Japanese women: the Kyushu Okinawa maternal and child health study. Scand J Immunol. 2013;78(4):371–377.
[17] Ulucan K, Akyüz S, Ozbay G, et al. Evaluation of vitamin D receptor (*VDR*) gene polymorphisms (FokI, TaqI and ApaI) in a family with dentinogenesis imperfecta. Tsitol Genet. 2013;47(5):28–32.
[18] El Jilani MM, Mohamed AA, Zeglam HB, et al. Association between vitamin D receptor gene polymorphisms and chronic periodontitis among Libyans. Libyan J Med. 2015;10(1):26771.
[19] Whitfield GK, Remus LS, Jurutka PW, et al. Are human vitamin D receptor polymorphisms functionally significant. In Norman AW, Bouillon R, Thomasset M, editors. Vitamin D endocrine system, structural, biological, genetic and clinical aspects. Riverside (CA): University of California; 2000. p. 817–823.
[20] Jia J, Tang Y, Shen C, et al. Vitamin D receptor polymorphism rs2228570 is significantly associated with risk of dyslipidemia and serum LDL levels in Chinese Han population. Lipids Health Dis. 2018;17(1):193.
[21] Zhang P, Li Q, Qi J, et al. Association between vitamin D receptor gene polymorphism and ankylosing spondylitis in Han Chinese. Int J Rheum Dis. 2017;20(10):1510–1516.
[22] Thesleff I. From understanding tooth development to bioengineering of teeth. Eur J Oral Sci. 2018;126(S1):67–71.
[23] Wise GE, Frazier-Bowers S, D'Souza RN. Cellular, molecular, and genetic determinants of tooth eruption. Crit Rev Oral Biol Med. 2002;13(4):323–334.
[24] Aktan AM, Kara I, Sener I, et al. An evaluation of factors associated with persistent primary teeth. Eur J Orthod. 2012;34(2): 208–212.
[25] Bin-Shuwaish MS. Ceramic veneers for esthetic restoration of retained primary teeth: a 4-year follow-up case report. Oper Dent. 2017;42(2):133–142.
[26] Parise GC, Schweigert Bona V, Pedrollo Lise D, et al. Esthetic rehabilitation of retained primary teeth- a conservative approach. J Prosthodont. 2019;28(1):e41–e44.
[27] Suri L, Gagari E, Vastardis H. Delayed tooth eruption: pathogenesis, diagnosis, and treatment. A literature review. Am J Orthod Dentofacial Orthop. 2004;126(4):432–445.
[28] Hua F, Zhang L, Chen Z. Trigger osteoclast formation and activation: molecular treatment strategy of delayed tooth eruption. Med Hypotheses. 2007;69(6):1222–1224.
[29] American Dental Association. Primary teeth eruption chart. 2012. [cited 2014 Dec 2]. Available from: http://www.mouthhealthy.org/en/az-topics/e/eruption-charts
[30] Marques GD, Guedes-Pinto AC, Abramowicz M. The eruption sequence of permanent teeth in children from the city of Sao Paolo. Rev Fac Odontol Sao Paulo. 1978;16(2):187–194.
[31] Yan B, Sun Z, Fields H, et al. Etiologic factors for buccal and palatal maxillary canine impaction: a perspective based on cone-beam computed tomography analyses. Am J Orthod Dentofacial Orthop. 2013;143(4):527–534.
[32] Uribe P, Ransjo M, Westerlund A. Clinical predictors of maxillary canine impaction: a novel approach using multivariate analysis. Eur J Orthod. 2017;39(2):153–160.
[33] Arid J, Xavier TA, da Silva RAB, et al. RANKL is associated with persistent primary teeth and delayed permanent tooth emergence. Int J Paediatr Dent. 2019;29(3):294–300. doi:.
[34] Sociedade Brasileira de Pediatria. Departamento de Nutrologia. Documentos científicos. Deficiência de vitamina D em crianças e adolescentes. [cited 2015 June 7]. Available from: http://www.sbp.com.br/src/uploads/2015/02/vitamina_d_dcnutrologia2014-2.pdf
[35] Misra M, Pacaud D, Petryk A, et al. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatrics. 2008;122(2):398–417.
[36] Küchler EC, Tannure PN, Falagan-Lotsch P, et al. Buccal cells DNA extraction to obtain high quality human genomic DNA suitable for polymorphism genotyping by PCR-RFLP and Real-Time PCR. J Appl Oral Sci. 2012;20(4):467–471.
[37] Turner AG, Hanrath MA, Morris HA, et al. The local production of $1,25(OH)_2D_3$ promotes osteoblast and osteocyte maturation. J Steroid Biochem Mol Biol. 2014;144:114–118.
[38] Zambrano M, Nikitakis NG, Sanchez-Quevedo MC, et al. 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(6):705–709.
[39] Tyszkowski M. Is There a relationship between nutrition, facial development, and crowding of the teeth? Int J Orthod Milwaukee. 2016;27(1):15–17.
[40] da Cunha LF, Caetano IM, Dalitz F, et al. Cleidocranial dysplasia case report: remodeling of teeth as aesthetic restorative treatment. Case Rep Dent. 2014;2014:1–5.
[41] Gupta R, Goel K, Solanki J, et al. Oral manifestations of hypothyroidism: a case report. J Clin Diagn Res. 2014;8(5):ZD20–ZD202.
[42] Peedikayil FC. Delayed tooth eruption. e-J Dent. 2011;1:81–86.
[43] Pludowski P, Holick MF, Grant WB, et al. Vitamin D supplementation guidelines. J Steroid Biochem Mol Biol. 2018;175:125–135.
[44] Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocr Rev. 2001;22(4):477–501.
[45] Dhamo B, Miliku K, Voortman T, et al. The associations of maternal and neonatal vitamin D with dental development in childhood. Curr Dev Nutr. 2019;3(4):nzy100.
[46] Jairam LS, Konde S, Raj NS, et al. Vitamin D deficiency as an etiological factor in delayed eruption of primary teeth: a cross-sectional study. J Indian Soc Pedod Prev Dent. 2020;38(3):211–215.
[47] Schroth RJ, Rabbani R, Loewen G, et al. Vitamin D and dental caries in children. J Dent Res. 2016;95(2):173–179.