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Elevated Serum 25(OH)-Vitamin D Levels Are Negatively Correlated with Molar-Incisor Hypomineralization

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Abstract

To date, the precise etiology of molar-incisor hypomineralization (MIH) is uncertain. Vitamin D plays a key role in hard tissue formation. Therefore, this study aimed to analyze the relationship between serum 25-hydroxy-vitamin D (25(OH)D) status and dental health data obtained from 1,048 children in a 10-year follow-up of the Munich GINIplus and LISAplus birth cohorts. The dental examination included the diagnosis of MIH and recording of (non-)cavitated caries lesions in primary and permanent teeth. Serum 25(OH)D concentrations were taken from blood samples of the 10-year investigation and measured with a fully automated, modular system. Different logistic regression and Poisson hurdle models were calculated. MIH was diagnosed in 13.6% of the study population. Approximately 16.4% of the children demonstrated caries-related defects (D3-4MFS > 0). The mean season-adjusted concentration of 25(OH)D was 75.8 nmol/l (standard deviation 22.0 nmol/l). After adjusting for sex, age, body mass index, parental education, equivalent income, and television/personal computer (TV/PC) viewing hours, a 10 nmol/l increase in serum 25(OH)D concentrations was significantly associated with a lower odds ratio of having MIH (OR = 0.89; $P = 0.006$). Furthermore, higher 25(OH)D values were associated with a lower number of caries-affected permanent teeth. It is concluded that elevated serum 25(OH)D concentrations were associated with better dental health parameters.

Keywords: birth cohort study, epidemiology, prevention, dental enamel, developmental defect, caries

Introduction

The etiology of molar-incisor hypomineralization (MIH) has not yet been determined, and there is little information in the literature regarding preventive agents and strategies because of the lack of understanding of the condition (Crombie et al. 2009; Alaluusua 2010). As ameloblasts and odontoblasts are target cells for vitamin D or its metabolites, they play key

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roles in enamel and dentin formation (Berdal et al. 1995; Berdal et al. 2000). Therefore, it is plausible that vitamin D deficiency is linked to developmental disorders in enamel (e.g., vitamin D-dependent rickets) (Foster et al. 2014).

The endogenous synthesis of vitamin D3 (cholecalciferol) following skin exposure to UVB radiation from sunlight and exogenous attainment from diet and supplementation are understood to be the two main sources of vitamin D. Despite seasonal variations, it is estimated that the endogenous metabolism synthesizes up to 90% of the body's vitamin D (Macdonald 2013). The contribution of nutritional vitamin D intake to the overall vitamin D supply is small. Therefore, oral supplementation is considered, particularly for groups with potential vitamin D deficiency (e.g., individuals without adequate sun exposure) (Balasubramanian et al. 2013; Braegger et al. 2013; Płudowski et al. 2013). Vitamin D3 is hydroxylated in the liver into 25-hydroxy-vitamin D3 and in the kidney into the active metabolite 1,25-hydroxy-vitamin D3. In the circulatory system, vitamin D metabolites are bound to vitamin D binding proteins, and actions are mediated by vitamin D receptors or by vitamin D-dependent molecules in target organs and cells (Berdal 1995; Lips 2006; Macdonald 2013). Regarding tooth development, it is mainly suggested that 1,25(OH)2D acts by controlling serum calcium or phosphate and gene expression (Berdal 1995; Papagerakis et al. 2003). The serum concentration of 25-hydroxy-vitamin D (25(OH)D) is an established biomarker that reflects both endogenous synthesis and vitamin D intake.

Because of its key role in the endocrine system, serum 25(OH)D concentration has been considered to be an important biomarker in numerous individual- or population-based studies. In dentistry, a recently published meta-analysis identified vitamin D as a promising caries-preventive agent (Hujoel 2013). When analyzing the few available studies that have investigated serum 25(OH)D concentration in relation to dental health variables, the same trend was observed. In young children, Schroth et al. (2013) reported a significant association between low serum 25(OH)D levels and severe early childhood caries; the authors argued that children with severe early childhood caries were likely malnourished, as they displayed significantly lower levels of calcium and serum albumin as well as higher levels of parathyroid hormone as compared with the control group. Another recently published study suggested that higher serum 25OHD concentrations are independently associated with a lower risk of tooth loss in 50-year-old adults (Zhan et al. 2014).

Regarding the unknown etiology of MIH and the influential role of 25(OH)D in tooth development, our cross-sectional analysis aimed to analyze this relationship. The tested null hypothesis was that there is no association between 25(OH)D at 10 years of age and MIH. In addition, the association between 25(OH)D and caries was analyzed in 10-year-olds.

Materials and Methods

The GINIplus and LISAplus protocols were approved by the ethics committee at the Bavarian General Medical Council, and written consent was obtained from all participating children and their guardians. The recommendations of the STROBE guidelines for observational studies (von Elm et al. 2008) were applied.

Study Population

The German infant study on the Influence of Nutrition Intervention plus air pollution and genetics on allergy development (GINIplus) and study on Lifestyle factors on development of the Immune System and Allergies in East and West Germany plus air pollution and genetics on allergy development (LISAplus) are ongoing birth cohort studies that were initiated in the 1990s to prospectively investigate a broad spectrum of determinants of common chronic diseases in childhood, with a specific focus on respiratory health. Healthy term newborns (GINIplus: n = 2,949; LISAplus: n = 1,467) from parents who were born in Germany and have a German nationality were recruited between September 1995 and January 1999 in Munich, Germany. Neonates fulfilling at least one of the following criteria were excluded from this study: premature birth (maturity at <37 gestational weeks); low birth weight (<2000 g); congenital malformation; symptomatic neonatal infection, antibiotic medication; hospitalization or intensive medical care during the neonatal period; immune-related diseases of the mother, such as autoimmune disorders; diabetes; hepatitis B; long-term medication use; or abuse of drugs or alcohol. Follow-ups were conducted at the ages of 6 mo (LISAplus only), 1y, 18 mo (LISAplus only), 2 y, 4 y, 6 y and 10 y. At the 2- or 4-, 6-, and 10-y follow-ups, the children were clinically examined by a pediatrician, and the parents completed several age-related questionnaires regarding their children's medical, nutritional, behavioral and socioeconomic characteristics. Details concerning the study background, representative recruitment strategy, inclusion and exclusion criteria and protocols have been extensively described elsewhere (Heinrich et al. 2002; Zutavern et al. 2006, von Berg et al. 2013). Almost 50% of subjects were lost to follow-up during the first 10 y due to various circumstances, including withdrawals, the inability to trace the participants, and waning interest. Therefore, the representativeness of the study population may be limited because the drop-out was not random. Higher drop-out rates of children from families with lower parental educational levels existed.

At the 10-y follow-up visit, a dental examination was performed in 1,148 children (GINIplus: n = 693; LISAplus: n = 455) to collect detailed information regarding each subject's oral health status (Heitmüller et al. 2013; Kühnisch

et al. 2014). Additionally, the serum 25(OH)D concentrations were available for 1048 children of these children (538 boys and 510 girls; average age, 10.2 y; SD, 0.2 y).

Dental Examination

Prior to the clinical examination, each participant brushed their teeth. A halogen lamp was used to illuminate the oral cavity (Ri-Magic; Rudolf Riester GmbH, Jungingen, Germany), a blunt CPI probe (CP-11.5B6; Hu-Friedy, Chicago, IL), a dental mirror, and cotton rolls for drying teeth were used to improve the clinical detection of demarcated hypomineralization and caries. Each child was screened for MIH according to the criteria of the European Academy of Pediatric Dentistry (Lygidakis et al. 2010). In general, hypomineralization with a diameter <1 mm was not documented. Other enamel disturbances, e.g., hypoplastic defects, fluorosis (diffuse hypomineralization), amelogenesis imperfecta, and dentinogenesis imperfecta, were distinguished from MIH-related hypomineralization and were not scored. Children with at least one affected first permanent molar were considered to have MIH (Lygidakis et al. 2010; Kühnisch et al. 2014). The caries status was determined using the surface-related DMF index for the permanent dentition ($D_{3\text{-}4}$MFS) and the primary dentition ($d_{3\text{-}4}$mfs) using WHO standard methodology (World Health Organization 1997). A $D_{3\text{-}4}/d_{3\text{-}4}$ lesion was recorded when the surface showed an unmistakable cavity, undermined enamel, or a detectably softened floor or wall. Non-cavitated caries lesions ($D_{1\text{-}2}$S) were recorded on a surface-related level in the permanent dentition, according to the ICDAS criteria (Pitts 2009) and the Universal Visual Scoring System (Kühnisch et al. 2011). First visible signs, established caries lesions, and microcavities without dentin exposure were summarized as non-cavitated caries lesions.

Before beginning the study, all dentists (Jan Kühnisch, Daniela Heitmüller, and Claudia Neumann) underwent extensive calibration training. Detailed information on training and intra- and inter-examiner reproducibility data were published recently (Heitmüller et al. 2013).

Serum 25(OH)D Concentration Measurements at the Age of 10 Years

The total vitamin D serum concentration was determined by Roche's vitamin D laboratory test using the fully automated Modular system (E170; Roche Diagnostics, Mannheim, Germany). The specificity was reported by the manufacturer as $25(OH)D_2$ = 81%; $25(OH)D_3$ = 98%; $1,25(OH)_2D_2$ = 6%; $1,25(OH)_2D_3$ = 5%; $24,25(OH)_2$ = 121%, and the lower detection limit was 3 ng/ml. The intra-assay coefficient of variation was 2.2% to 6.8% for sera with levels between 8.35 and 69.6 ng/ml; the inter-assay coefficient of variation, as provided by the manufacturer, was 3.4% to 13.1% for the levels between 8.35 and 69.6 ng/ml.

Statistical Analysis

All descriptive and explorative analyses were performed using the statistical software R 2.15.3 (R Core Team 2013). Using generalized additive models with thin plate regression splines, the 25(OH)D levels were corrected for sampling date to normalize for seasonal variability, as implemented in the R package "mgcv" (Wood 2003). Oral health parameters showed a right-skewed distribution (i.e., many participants had no caries or MIH, whereas a small number of participants had high indices). Such a zero-inflated distribution requires an appropriate statistical analysis method (Preisser et al. 2012). Therefore, two-part models were used to analyze the association between the oral health parameters and serum 25(OH)D concentrations as a continuous predictor. The first part of this model used logistic regression for the probability of a non-zero count, which refers to the disease prevalence; odds ratios (OR) were calculated. The second part of the model used Poisson regression for the mean count among the subsets with a non-zero count, which refers to disease severity. Relative risks (RR) were determined (Zeileis et al. 2008; Preisser et al. 2012). Poisson hurdle models were used, as implemented in the R package "pscl" (Jackman 2012). These models were appropriate for analyzing the count data with excess zeros and consist of two components. In cases where an insufficient number of affected subjects was used to estimate the Poisson analysis, only the logistic part of the model was evaluated.

Results

General information and the dental health parameters of the study population can be seen in Tables 1 and 2. MIH was identified in 13.6% (143/1048) of all 10-year-old participants (Table 2). In investigating the relationship between MIH and serum 25(OH)D levels, significant associations were found throughout all types of regression models after adjusting for potential confounding factors; higher serum 25(OH)D concentrations were associated with a lower probability of having MIH (Table 3). After adjusting for sex, age, body mass index (BMI), parental education, equivalent income, and time spent in front of the television/personal computer (TV/PC) during the winter and summer seasons (Table 3), a significantly lower OR of having MIH (OR = 0.89; $P = 0.006$) was found per 10 nmol/l increase in serum 25(OH)D concentration. However, no association was found with having a lower number of hypomineralized molars among children with MIH (RR = 1.00; $P = 0.999$). Nevertheless, a lower number of hypomineralized teeth was observed in subjects with higher 25(OH)D levels (OR =

Table 1. Characterization of the Children from the GINIplus and LISAplus Cohorts at the 10-y Follow-up (*n* = 1,048).

Study Population of 1,048 Children	%	Mean (SD)	n
GINIplus study	61.2		641
LISAplus study	38.8		407
Male sex	51.3		538
Age, y		10.2 (0.2)	
Body mass index		17.1 (2.3)	
Parental education			
Low <10 y	4.8		50
Medium 10 y	17.8		187
High >10 y	77.3		810
Missing	0.1		1
Equivalent income			
<€1,406	30.6		321
€1,406–€2,103	29.4		308
>€2,103	32.9		345
Missing	7.1		74
Time spent in front of TV/PC during the winter season			
<1 h	41.8		438
1-2 h	51.0		535
>2 h	6.3		66
Missing	0.9		9
Time spent in front of TV/PC during the summer season			
<1 h	74.0		775
1–2 h	23.0		241
> 2 h	1.8		19
Missing	1.2		13
Serum 25(OH)D concentration, nmol/l		75.8 (22.0)	

TV/PC, television/personal computer.

Table 2. Dental Health Parameters of All Included Children from the GINIplus and LISAplus Cohorts at the 10-y Follow-up (*n* = 1,048).

	Permanent Dentition		Primary Dentition	
Dental Health	%	n	%	n
MIH	13.6	143	—	—
$D_{1-2}S$	48.2	505	—	—
$D_{3-4}MFS/d_{3-4}mfs$	16.4	172	41.6	436
$D_{3-4}S/d_{3-4}S$	2.4	25	17.9	188
FS/fs	15.2	159	35.8	375
All participants, mean (SD)				
Hypomineralized molars	0.3 (0.8)		—	
Hypomineralized teeth	0.8 (1.5)		—	
D_{1-2}	1.4 (2.2)		—	
$D_{3-4}MFS/d_{3-4}mfs$	0.4 (1.1)		2.3 (4.0)	
$D_{3-4}S/d_{3-4}S$	0.0 (0.2)		0.5 (1.5)	
FS/fs	0.3 (1.0)		1.8 (3.6)	
Affected participants, geometric mean (SD)				
Hypomineralized molars	1.7 (1.7)			
Hypomineralized teeth	1.9 (1.9)		—	
$D_{1-2}S$	2.3 (2.0)		—	
$D_{3-4}MFS/d_{3-4}mfs$	1.9 (1.9)		4.1 (2.3)	
$D_{3-4}S/d_{3-4}S$	1.2 (1.5)		2.2 (2.0)	
FS/fs	1.9 (1.9)		3.7 (2.2)	

All dental health parameters were calculated for those subjects with at least one diseased tooth in each category.

Table 3. Poisson Hurdle Models and Logistic Regression (for $D_{3-4}S$) for Investigating the Association between 25(OH)D Serum Concentrations and Molar-Incisor Hypomineralization (MIH) and Caries in 1,048 Children Aged 10 Years.

		Disease Prevalence		Disease Severity	
	Model	OR (CI)	*P* Value	RR (CI)	*P* Value
Hypomineralized molars	1/ Hurdle	**0.90 (0.83–0.97)**	**0.008**	0.99 (0.91–1.06)	0.704
	2/ Hurdle	**0.90 (0.83–0.97)**	**0.006**	1.00 (0.92–1.08)	0.965
	3/ Hurdle	**0.89 (0.82–0.97)**	**0.006**	1.00 (0.92–1.08)	0.999
Hypomineralized teeth	1/ Hurdle	0.96 (0.91–1.01)	0.154	**0.96 (0.92–0.99)**	**0.013**
	2/ Hurdle	0.96 (0.91–1.01)	0.149	**0.96 (0.92–0.99)**	**0.020**
	3/ Hurdle	0.96 (0.91–1.02)	0.163	**0.96 (0.92–0.99)**	**0.015**
$D_{1-2}S$	1/ Hurdle	0.96 (0.91–1.01)	0.145	1.01 (0.98–1.04)	0.494
	2/ Hurdle	0.96 (0.91–1.02)	0.152	1.01 (0.98–1.04)	0.539
	3/ Hurdle	0.95 (0.90–1.00)	0.051	1.00 (0.97–1.02)	0.677
$D_{3-4}MFS$	1/ Hurdle	0.96 (0.89–1.04)	0.370	**0.93 (0.88–0.99)**	**0.032**
	2/ Hurdle	0.96 (0.89–1.04)	0.359	**0.93 (0.87–0.99)**	**0.023**
	3/ Hurdle	0.96 (0.90–1.03)	0.273	**0.94 (0.89–0.99)**	**0.019**
$d_{3-4}mfs$	1/ Hurdle	0.99 (0.95–1.04)	0.829	1.00 (0.98–1.01)	0.661
	2/ Hurdle	1.00 (0.95–1.05)	0.877	1.00 (0.98–1.01)	0.718
	3/ Hurdle	1.00 (0.95–1.05)	0.877	1.00 (0.98–1.01)	0.718
$D_{3-4}S$	1/ Logistic	1.02 (0.85–1.22)	0.870	—	—
	2/ Logistic	1.01 (0.84–1.22)	0.884	—	—
	3/ Logistic	0.93 (0.78–1.11)	0.403	—	—
$d_{3-4}S$	1/ Hurdle	1.03 (0.97–1.10)	0.318	**0.95 (0.91–0.99)**	**0.021**
	2/ Hurdle	1.03 (0.97–1.09)	0.376	0.96 (0.92–1.01)	0.109
	3/ Hurdle	1.03 (0.97–1.09)	0.376	0.96 (0.92–1.01)	0.109
FS	1/ Hurdle	0.97 (0.89–1.05)	0.424	**0.91 (0.85–0.97)**	**0.006**
	2/ Hurdle	0.97 (0.89–1.05)	0.429	**0.91 (0.84–0.97)**	**0.005**
	3/ Hurdle	0.96 (0.90–1.04)	0.304	**0.93 (0.88–0.98)**	**0.012**
Fs	1/ Hurdle	0.99 (0.94–1.04)	0.578	1.01 (0.99–1.03)	0.570
	2/ Hurdle	0.99 (0.94–1.04)	0.640	1.01 (0.99–1.03)	0.622
	3/ Hurdle	0.99 (0.94–1.04)	0.640	1.01 (0.99–1.03)	0.622

Effect estimates are displayed per 10 nmol/l increase in seasonally adjusted serum 25(OH)D concentrations. Model 1 is adjusted for study, sex, age, and body mass index. Model 2 is a Model 1 adjustment plus socioeconomic factors (parental education, equivalized income). Model 3 is a Model 2 adjustment plus time spent in front of TV/PC in winter and summer. Boldface indicates significance.
Hurdle, Poisson hurdle model; OR, odds ratio; CI, confidence interval; RR, relative risk.

0.96 per 10 nmol/l; $P = 0.015$). Furthermore, significantly fewer caries-related restorations (FS component) were found in children with higher serum 25(OH)D concentrations; this result also affects the $D_{3-4}MFS$ value (Table 3).

Discussion

The major finding was that higher serum 25(OH)D concentrations were significantly associated with a lower proportion of 10-year-olds with MIH and fewer hypomineralized teeth (Table 3). In addition, significantly fewer caries-related restorations (FS) were observed in children with increased serum 25(OH)D levels (Table 3). Given that MIH most likely occurs in the first year of life and dental caries is frequently a progressive disease, it is an interesting finding that the serum 25(OH)D concentration at 10 years of age was significantly related to these two conditions.

Whereas the association with MIH has not been previously investigated, the case-control study by Schroth et al. (2013) showed the same association for the appearance of caries lesions. The authors found that preschool children with caries appeared to have significantly greater odds for having low vitamin D status compared with caries-free controls. This finding aligns with a recently published review (Grant 2011) and meta-analysis (Hujoel 2013) that highlighted the caries preventive influence of UVB exposure and vitamin D supplementation. The meta-analysis of controlled clinical trials suggested that supplemental vitamin D in early life was associated with a 47% to 54% reduced risk of caries (Hujoel 2013). Although the included trials demonstrated the consistent preventive effects of vitamin D against caries regardless of the vehicle or method of administration, they failed to explain the reasons for this apparent preventive effect (Hujoel 2013). The same conclusion can

be drawn for the significant association between lower serum 25(OH)D concentration and the higher ORs observed for the development of MIH. The regression models demonstrated a significant association (Table 3); however, a concrete metabolic pathway is missing. It can be speculated that vitamin D-dependent mineralization processes are affected and, therefore, should be analyzed in future studies. The same finding may be revealed when investigating sunlight exposure, vitamin D fortification of food, and the use of supplements in relation to MIH and dental caries, as these factors might also demonstrate a preventive effect (Grant 2011).

Uniquely, this study investigated how MIH correlates with a child's serum 25(OH)D status, as no previous study has analyzed this potential association. Another unique feature of this study was the adjustment for important influencing factors on serum 25(OH)D concentration, e.g., seasonal variations, individual outdoor/indoor activities, and indicators of socioeconomic status, which resulted in the normalization of the ratios from regression models. Furthermore, the Poisson models followed the latest recommendations for epidemiological studies, as the included indices frequently contained low or even zero counts (Preisser et al. 2012).

When considering limiting factors, it must be mentioned that the shown associations are based on cross-sectional data from the 10-year follow-up. Unfortunately, the serum 25(OH)D concentrations were not measured during earlier time points in both of the included cohorts, particularly not during the period of tooth development in early life. The availability of such data would allow considerations for 1) the association of serum 25(OH)D concentrations during hard tissue mineralization and the clinical status after later tooth eruption, 2) the longitudinal analysis of the consistency of serum 25(OH)D levels and, 3) the countercheck of the registered results in the same population at other time points. Unfortunately, our own data or comparable results from other investigations are unavailable and, therefore, cannot be used for interpretation. Additionally, there is only scarce information published about longitudinal changes in serum 25(OH)D concentrations in children or in young adolescents, which hinders any interpretations so far. Besides this, the observed associations might also be confounded by comorbid systemic diseases. With respect to these limitations, it should be acknowledged that an unidentified confounding factor could also be affecting these associations.

Conclusion

Based on the results of this study, it can be concluded that lower vitamin D serum concentrations were associated with a higher probability for MIH- and caries-related restorations in 10-year-old children. Vice versa, it can be argued that higher vitamin D levels were related to better oral health outcomes. With respect to this remarkable finding and the limited number of studies and data, it seems necessary to investigate the role of vitamin D from different perspectives in future studies before generalizing this finding.

Author Contributions

J. Kühnisch, contributed to conception, design, data acquisition, and interpretation, drafted and critically revised the manuscript; E. Thiering, contributed to conception, data analysis and interpretation, drafted and critically revised the manuscript; J. Kratzsch, R. Heinrich-Weltzien, R. Hickel, contributed to conception and data interpretation, drafted and critically revised the manuscript; J. Heinrich, contributed to conception, design, data acquisition, analysis, and interpretation, drafted and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work.

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