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ORIGINAL ARTICLE

Implications of Vitamin D Status for Children's Bone Health: A Data Mining Analyses of Observational Studies

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ABSTRACT

Objective: To investigate associations/correlations between bone alterations and vitamin D status in children through data mining analyses based on observational studies. **Material and Methods:** Searches in PubMed, Scopus, Web of Science, and Embase databases were performed to recover studies, published until October 2022, with healthy children, which investigated the vitamin D status, related or not to undesirable bone alterations linked to bone quality (bone mineral density and bone mineral content), fracture or anthropometry. Country, study design, area of expertise (medicine, nutrition, dentistry, others), bone outcome, 25-hydroxyvitamin D data (serum or intake levels), the exams for bone diagnosis, and the results were analyzed in the VantagePoint™ software. **Results:** Of 20,583 studies, 27 were included. The USA (n=9; 33.3%) had the highest number of publications. Cross-sectional (n=11; 40.7%), case-control (n=9; 33.3%), and cohort studies (n=7; 25.9%) contemplated the medicine and nutritional areas without any study in dentistry. Studies about bone quality (n=21; 77.8%), analyzed through dual-energy X-ray absorptiometry (DXA; n=14; 51.8%), with association (n=16; 59.2%) between the low serum levels of 25-hydroxyvitamin D and undesirable bone alterations (n=14; 51.8%) were the most prevalent. **Conclusion:** Most studies were conducted in the medical area and showed an association between low bone quality and low levels of 25-hydroxyvitamin D, verified through DXA.

Keywords: Bibliometrics; Vitamin D; Bone Density; Child.

Introduction

Vitamin D, also known as "solar vitamin," is a secosteroid [1] produced in an endogenous form by the skin tissues after solar exposure. It can also be purchased by ingesting specific foods or supplementation [1,2]. Vitamin D goes through two activation stages, one in the liver and the other in the kidneys. Vitamin D is converted in the liver into hydroxyvitamin D, which is transformed into 1,25-di-hydroxyvitamin D in the kidneys to be metabolically active. Thus, the liver and kidneys are vital in vitamin D activation [3].

One of the main functions of vitamin D is to regulate the amount of calcium and phosphorus in the organism [4-8], allowing good bone mineralization during early childhood and adolescence, which leads the individual to have stronger bones throughout life [9]. In cases of low levels of vitamin D, primarily due to mild hypocalcemia, secondary hyperparathyroidism, osteomalacia, and rickets disease, there is an increase in bone remodeling, with loss of trabecular bone and narrowing of the cortical bone and, therefore, increases the risk of bone deformities and fractures due to minor traumas [4].

Considering the harmful effects of low levels of 25-hydroxyvitamin D in children, a significant amount of research has been published concerning its bone effects. Thereby, it is interesting and helpful to researchers in various areas of health, such as medicine, nutrition, and dentistry, to trace a descriptive overview of the observational studies published about the levels of 25-hydroxyvitamin D. This, in turn, enables the design of robust research on what is necessary to advance to obtain scientific evidence on the effect of low 25-hydroxyvitamin D levels on undesirable bone alterations in children.

Therefore, the study aimed to employ data mining and descriptive analyses to provide a quantitative profile of the publications' methods and results on possible associations between vitamin D status in healthy children and undesirable bone alterations involving the medicine, dentistry, and nutritional areas.

Material and Methods

This is a data mining and descriptive analysis of the observational studies published in the literature that were retrieved from a systematic search in electronic databases. Through a quantitative approach, it aimed to provide information to organize and classify some characteristics of the publications, besides identifying patterns and the knowledge of state-of-the-art related to vitamin D status in healthy children associated or not associated with undesirable bone alterations. The study protocol was registered in the Open Science Framework (OSF) database under the DOI 10.17605/OSF.IO/EUA5D.

Search Strategy

Extensive bibliographic research was carried out independently by two researchers (BFA and LJ), assisted by a librarian with experience in systematic searches (DM), who guided the search strategies in the following electronic databases: PubMed, Scopus, Web of Science and Embase in October 2022. We completed the search within the same day to avoid any bias caused by database updates. The search strategy included MeSH terms, synonyms, and accessible terms related to the subject of this review, adapted for each database, without language, date, or publication status restrictions. Thus, keywords were used to search for "observational studies" (S) related to "child" (P), which verified "vitamin D" status (E), associated or not with the "frequency of any diseases" (O). The Boolean operators "AND" and "OR" were applied to combine the terms (Table 1).

Table 1. A search strategy is applied according to each electronic database.

Database	Strategy
PubMed	((Vitamin D[Mesh] OR Vitamin D[Tiab] OR Cholecalciferol[Mesh]) OR Cholecalciferol[Tiab] OR Vitamin D3[Tiab] OR Ergocalciferols[Mesh] OR Ergocalciferol*[Tiab] OR Calcitriol[Mesh] OR Calcitriol[Tiab] OR "dihydroxyvitamin D" AND (child[mesh] OR child*[tiab] OR Child, Preschool[Mesh] OR Infant[mesh] OR Infant*[tiab] OR pre-school*[tiab] OR preschool*[tiab])) AND (observational[tiab] OR Prospective studies[Mesh] OR prospective study[tiab] OR cohort studies[Mesh] OR cohort[tiab] OR follow-up studies[Mesh] OR follow-up study[tiab] OR case-control studies[Mesh] OR case control[tiab] OR retrospective studies[Mesh] OR cross-sectional studies[Mesh] OR cross-sectional[tiab] OR "Disease Frequency"[tiab] OR "prevalence study"[tiab])
Scopus	(((TITLE-ABS-KEY ("Vitamin D") OR TITLE-ABS-KEY ("dihydroxyvitamin D") OR TITLE-ABS-KEY (cholecalciferol) OR TITLE-ABS-KEY ("Vitamin D3") OR TITLE-ABS-KEY (ergocalciferols) OR TITLE-ABS-KEY (calcitriol))) AND ((TITLE-ABS-KEY (child*) OR TITLE-ABS-KEY (preschool*) OR TITLE-ABS-KEY (pre-school*) OR TITLE-ABS-KEY (infant*)))) AND ((TITLE-ABS-KEY (observational) OR TITLE-ABS-KEY ("prospective study") OR TITLE-ABS-KEY (cohort) OR TITLE-ABS-KEY ("follow-up study") OR TITLE-ABS-KEY ("case control") OR TITLE-ABS-KEY ("retrospective study") OR TITLE-ABS-KEY ("cross-sectional") OR TITLE-ABS-KEY ("Disease Frequency") OR TITLE-ABS-KEY ("prevalence study")))
Web of Science	((TS=(((((("Vitamin D") OR ("dihydroxyvitamin D")) OR (cholecalciferol)) OR ("Vitamin D3")) OR (ergocalciferol)) OR (calcitriol))) AND (TS=((((child*) OR (preschool*)) OR (pre-school*)) OR (infant*)))) AND (TS=(((((((((observational) OR ("prospective study")) OR (cohort)) OR ("follow-up study")) OR ("case-control")) OR ("retrospective study")) OR ("cross-sectional")) OR ("Disease Frequency")) OR ("prevalence study")))
Embase	('vitamin d':ti,ab,kw OR 'dihydroxyvitamin d':ti,ab,kw OR cholecalciferol:ti,ab,kw OR 'vitamin d3':ti,ab,kw OR ergocalciferols:ti,ab,kw OR calcitriol:ti,ab,kw) AND (child*:ti,ab,kw OR 'preschool*':ti,ab,kw OR infant*:ti,ab,kw) AND (observational:ti,ab,kw OR 'prospective study':ti,ab,kw OR cohort:ti,ab,kw OR 'follow up':ti,ab,kw OR 'case control':ti,ab,kw OR 'retrospective study':ti,ab,kw OR 'cross-sectional':ti,ab,kw OR 'disease frequency':ti,ab,kw OR 'prevalence study':ti,ab,kw)

Study Selection

The inclusion criteria were predefined to include only observational studies (cross-sectional, case-control, and cohort studies) about low nutritional and serum 25-hydroxyvitamin D levels in healthy children (0-10 years) [10] - characterized by the absence of clinical signs/symptoms related to diseases, associated or not to undesirable bone alterations (low bone mineral density, fractures and altered anthropometric measurements). Systematic reviews, case reports, letters to the editor; books and book chapters; clinical trials; studies with adolescents, adults, and the elderly; studies with children with neurological, cognitive, systemic, or chronic diseases; studies that investigated non-osseous outcomes; animal studies, *in vitro* and *in situ* studies were excluded. A manual search was also performed in the reference lists of the included studies.

After the searches, all identified studies were imported into a tech-mining and data analysis software (VantagePoint™, version 13.0; Search Technology, Inc.) to remove duplicates. Three independent examiners (BFA, MLM, and LJ) selected the studies by reading the titles and abstracts, applying the eligibility criteria. Studies with insufficient data in the title and abstract were selected for full reading. If the requested information was still not found, the examiners contacted the authors through e-mail. The article was only deleted after five unsuccessful attempts to obtain the missing information. Any disagreement about eligibility was resolved by two experienced researchers (AF and MAV).

Data Extraction and Analyses

The studies were imported into VantagePoint™, and the following variables were assessed in the software itself and also in Microsoft Excel (Microsoft, USA): country (mentioned in the study referring to the first author), authors, journals, area of expertise (medicine, nutrition, dentistry, others), type of study, bone outcome (bone quality – bone mineral density and bone mineral content, fracture and anthropometry), obtaining vitamin D (by ingestion or 25-hydroxyvitamin D serum levels), type of examination performed for bone diagnosis (dual-energy X-ray absorptiometry - DXA, radiography, computed tomography, ultrasound) and results (whether or not there was an association between bone outcome and vitamin D status).

Considering the variable 'country,' all countries of the United Kingdom were counted as a single group, being represented on a world map. A frequency graph also represented countries that included two or more studies. The metrics of the most productive authors (with two or more publications) were represented by a correlation map, which also shows their collaboration (common publications). In addition, a graph was created to represent journals with two or more publications considered the present study's main journals.

Correlation analyses were used for the variables related to the area of expertise and the results of each study. The results were represented by nonlinear graphs (cluster maps), displaying information in 'nodes' linked to each other, creating a cluster. These 'nodes,' represented by small circles, reveal the number of items in a given research group. When two subjects connect to the same node, it means that the studies correlate with the cross-subject. A graph was created to show the results of possible associations between vitamin D status and the type of studies.

Data about the author, the publishing year, the investigated undesirable bone alterations, the performed exams, and the association results of the studies were descriptively presented. In addition, correlation analyses between the undesirable bone alterations and type of examination, results, and means of obtaining vitamin D status were also performed.

Results

The search of the databases initially resulted in 20,583 identified studies, and 9461 duplicates were excluded. After title, abstract, and full-text evaluation, 27 studies were included in this review (Figure 1) [11-37], with general characteristics exemplified in Table 2.

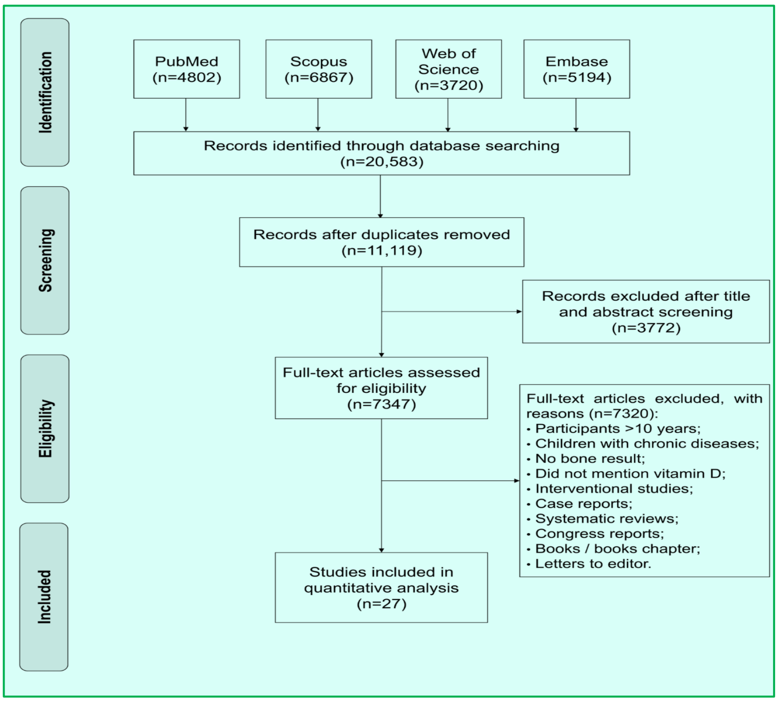

Figure 1. Flowchart of the review.

Table 2. Authors and the relationship between vitamin D and the variables investigated in the included studies (n=27).

Authors	Outcome			Vitamin D		Exams						Results
	Bone Quality	Bone Fracture	Anthropometric Measures	Serum levels*	Intake levels	Dual-Energy X-ray Absorptiometry	Radiograph	Peripheral Quantitative Computed Tomography	Ultrasound	No images		Association (Positive or Negative)
Al-Ghamdi et al. [11]	+			+		+			+			°
Breen et al.[12]	+		+	+		+						•
Das et al. [13]			+		+							•
El-Sakka et al. [14]	+		+	+	+	+						°
Filteau et al. [15]	+		+	+					+	•		°
Fu et al. [16]	+			+								°
Garcia et al. [17]	+			+		+						°
Herrmann et al. [18]	+		+	+					+			-
James et al. [19]		+		+						+		+
Mäyränpää et al. [20]	+	+		+		+						+
McVey et al. [21]			+	+		+						-
Mercy et al. [22]			+		+				+			+
Minkowitz et al. [23]		+		+						+		+
Nguyen et al. [24]		+	+	+		+						-
Oladosu et al. [25]		+		+						+		+
Rajakumar et al. [26]	+		+	+	+					+		-
Ren et al. [27]	+	+	+		+	+						+
Ryan et al. [28]	+	+	+	+	+	+						+
Ryan et al. [29]	+	+		+	+	+						-
Ryan et al.[30]	+	+		+		+						-
Ryan et al. [31]	+	+		+		+						+
Sakamoto et al. [32]	+			+			+					+
Sayers et al. [33]	+			+				+				+
Sharawat at al. [34]	+		+	+		+						+
Videhult et al. [35]	+			+	+	+						-
White et al. [36]	+			+		+						-
Yorifuji et al. [37]	+		+	+			+					-

*25-hydroxyvitamin D; +With association; -Without association.

The included studies were conducted in 22 different countries (Figure 2A). The United States of America (n=9; 33.3%) is the country that is most studied on vitamin D and undesirable bone alterations. One multicentric study included different populations (Belgium, Estonia, Germany, Hungary, Italy, Spain, Sweden, and Cyprus). Countries with a more significant number of publications are shown in Figure 2B.

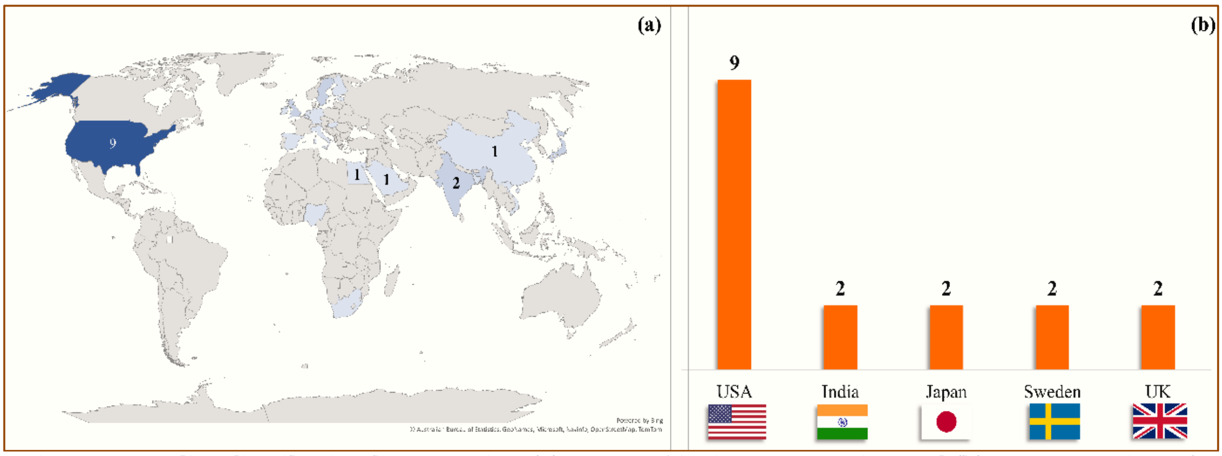

Figure 2. Studies distribution by countries: (a) geographical representation and (b) representation of countries with two or more studies published.

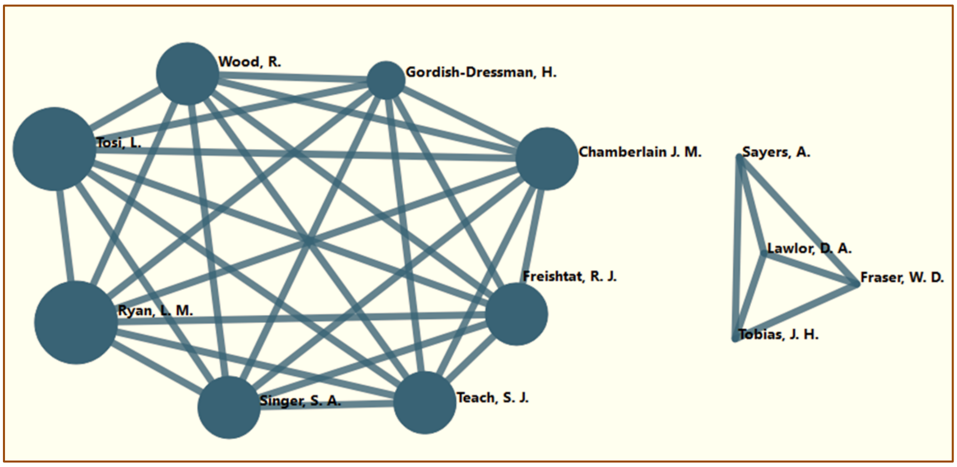

Figure 3. Authors who published the most studies on the association between low levels of 25-hydroxyvitamin D and undesirable bone alterations in healthy children.

Authors, Publishing Year, and Journals

A total of 185 authors were associated with the 27 included studies published between 2002 and 2022. Considering the first authors of the studies with two or more publications, *Ryan L. M.* and *Tosi, L.* were the ones who most published (n=4, for each; 14.8%), followed by *Chamberlain J. M.*, *Freishtat R. J.*, *Singer S. A.*, *Teach S. J.* and *Wood R.* (n=3, for each). *Ryan L. M.*, in his four publications, sought associations between fractures in African American children's forearms and low levels of 25-hydroxyvitamin D (serum level ≤20 ng / mL), with the collaboration of 7 authors for publishing these studies. A cooperation network between the authors can be seen in Figure 3, demonstrating the correlation between the authors and the largest number of publications. The *Journal of Investigative Medicine* (Impact Factor=3.235) owns 3 of the four studies published by *Ryan L. M.* (Table 3).

Table 3. Frequency of journals with observational studies published about the impact of vitamin D status on children's bone health over the years.

Journal	Years		Total	IF*
	2002-2010	2011-2022		
Journal of Investigative Medicine	0	3	3	3.235
Archives of Osteoporosis	0	2	2	3.236
Journal of Pediatric Orthopaedics	0	2	2	2.537

Journal of Clinical Endocrinology and Metabolism	1	1	2	4.756
Archives of Disease in Childhood: Fetal and Neonatal Edition	1	0	1	6.643
BMJ Open	0	1	1	3.007
Bone	0	1	1	4.626
Calcified Tissue International	0	1	1	4.227
Current Pediatric Research	0	1	1	2.05
European Journal of Pediatrics	0	1	1	3.860
Food and Nutrition Bulletin	0	1	1	2.751
Food and Nutrition Research	0	1	1	3.894
International Journal of Pediatrics	0	1	1	-
Journal of Bone and Mineral Research	0	1	1	6.390
Journal of Clinical and Diagnostic Research	0	1	1	1.148
Nutrients	0	1	1	7.185
Oncotarget	0	1	1	2.678
Osteoporosis International	0	1	1	4.507
Pediatrics	0	1	1	7.124
Pediatrics International	0	1	1	1.617
Public Health Nutrition	0	1	1	4.022
The Lancet Diabetes and Endocrinology	0	1	1	44.867

*IF: Impact Factor; The International Journal of Pediatrics doesn't have an IF classification.

Area of Expertise, Type of Study, and Found Associations/Correlations

Of the 27 observational studies included, 16 (59.2%) were from the medical area, 1 (3.7%) was from the nutritional research, and 10 (37.0%) covered both areas. Of the 16 medicine studies, 11 (40.7%) demonstrated an association, and 5 (18.5%) did not demonstrate an association between vitamin D status and the bone undesirable alterations investigated. The nutritional article did not show an association between the nutritional status of vitamin D and bone alterations. Of the ten studies that contemplated both areas, 5 (50%) demonstrated association, and 5 (50%) had no association, considering the same parameters.

Among the studies, 11 (40.7%) are cross-sectional, 9 (33.3%) are case-control, and 7 (25.9%) are cohort studies. Of the 11 cross-sectional studies, 7 (63.3%) demonstrated an association, and 4 (36.4%) had no association between the investigated bone outcomes and vitamin D status. Of the nine case-controls, 6 (66.7%) demonstrated association, and 3 (33.3%) had no association; and of the seven cohorts research, 3 (42.9%) demonstrated association, and 4 (57.1%) were not associated (Figure 4).

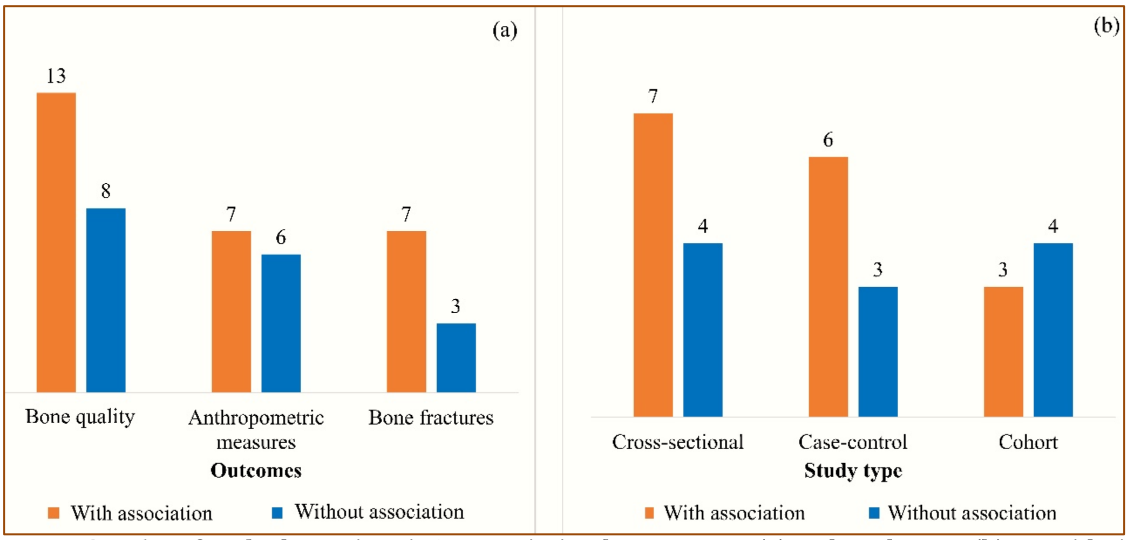

Figure 4. Results of 25-hydroxyvitamin D association by outcomes (a) and study type (b), considering the 27 included studies. The same study could be classified into more than one outcome.

Type of Bone Outcome, 25-hydroxyvitamin D Data, and the Exams' Type

Among the included studies, 21 (77.8%) analyzed the children's bone quality, of which 12 (57.1%) presented association results between low levels of 25-hydroxyvitamin D and impaired bone quality. Ten studies (37.0%) analyzed bone fracture, of which 7 (70.0%) presented association, demonstrating that low levels of 25-hydroxyvitamin D favors bone fractures. Fourteen (51.8%) studies analyzed anthropometry, of which 7 (50.0%) presented association results between low levels of 25-hydroxyvitamin D and altered anthropometry. It is noteworthy that among the studies, 16 (59.2 %) evaluated more than one bone outcome (Table 2), and two of them evaluated the three investigated outcomes (bone quality, fracture, and anthropometry).

The 25-hydroxyvitamin D data were reported through serum levels in 20 (74.1%) studies and by vitamin D intake through a food consumption frequency questionnaire or dietary recall in only 3 (11.1%). The remaining studies (n=4; 14.8%) investigated serum levels and vitamin D intake using nutritional data.

Of the 14 (51.8%) studies that investigated bone mineral density (BMD) and bone mineral content (BMC) using DXA, total body measurements (excluding the head), lumbar spine (L1-L4), proximal femur, and distal radius were considered. Radiographs were used in two (7.4%) studies to evaluate the association between low levels of 25-hydroxyvitamin D and the child's growth and fracture, performed on the lower limbs (total length), hands, wrist, and ankle. One study chose peripheral quantitative computed tomography (pQCT) to investigate BMD and BMC in the cortical bone of the tibia, measuring bone area and thickness. Quantitative ultrasound (QUS) was used in 4 (14.8%) studies to investigate bone stiffness and BMD of the distal radius, calcaneus, and middle tibia. The studies that did not perform imaging tests (n=6; 22.2%) used questionnaires (n=3; 11.1%) and medical records (n=3; 11.1%) to collect data on the history of patients with fractures (n=4; 14.8%); in addition to anthropometric measurements such as body mass index value (n=2; 7.4%) for growth evaluation.

Discussion

The history of vitamin D began to be investigated in the mid-17th century with the Industrial Revolution. The buildings were made very close to each other, preventing the passage of sunlight and soot from the burning of coal, which polluted the air [2]. Consequently, bone deformities were observed as the main characteristic in children who lived at this time, such as arched legs, pelvic deformation, asymmetric skull, visible appearance of the ends of the ribs next to the sternum bone, spinal deformities, deformations, or delay in the formation of weak and flaccid teeth and legs [6]. These effects persisted throughout adulthood, impairing these individuals' quality of life [2]. Precisely because vitamin D is essential for bone metabolism, influencing children's growth, we sought to quantitatively present data from studies investigating possible associations between low 25-hydroxyvitamin D levels and undesirable bone alterations in healthy children. As far as we know, this is the first article that addresses a bibliometric analysis of studies presenting associations between vitamin D status in healthy children with impaired bone quality, fractures, and altered anthropometric measurements.

It was observed that the two main authors who publish on the subject are directly connected through their institutional research groups, with few associations between authors from different institutions. This indicates that the lack of multicenter studies may be a limitation in understanding the results in various populations. The authors of the present study also observed a few studies from developing countries, which may indicate a need for more resources or investment for research in this area. In addition, most studies have been conducted in low-temperature countries, where residents probably do not frequently remain exposed to the sun.

In general, 90% to 95% of most people's vitamin D needs are met by frequent exposure to sunlight. Thus, the interest of these countries in studying the association between low 25-hydroxyvitamin D levels and bone complications is justified [2].

About 50 to 100% of European and American children are likely to have vitamin D deficiency, and 97% of African Americans have insufficient serum levels of 25-hydroxyvitamin D [2]. These data may explain the author Ryan L. M.'s interest in the association between fractures of African American children and low levels of 25-hydroxyvitamin D in their studies [28-31]. It is also emphasized that dark pigmentation of the skin is considered a risk factor for low levels of 25-hydroxyvitamin D due to a reduced ability to produce this vitamin in the skin [38]. In addition, African American children also have a low diet in vitamin D-rich foods when compared to other ethnic groups [39], which may be associated with socioeconomic factors. Nonetheless, regarding the literature, Asians also presented low levels of 25-hydroxyvitamin D [39]. This can be explained by the sun's zenith angle, as during the winter, people who live further north and south on Earth in relation to the equator are generally unable to produce vitamin D in their skin for up to 6 months of the year [40]. Furthermore, these vitamin deficiencies can have multifactorial causes, including diet, genetic, environmental, and economic factors. Therefore, it is necessary to study the status of vitamin D in all individuals in order to seek a balance between diet, sun exposure, and other related factors, regardless of country and season.

The investigated bone outcomes in most studies were bone quality measured through BMD. During early childhood to late adolescence, skeletal mass is continuously accumulated, and around 18 years, 90–95% of bone accumulation seems complete [41,42]. However, 80% of bone mineral density is genetically determined [42], leaving 20% to be influenced by environmental factors, such as exercise and calcium food intake; low levels of 25-hydroxyvitamin D directly affect skeleton mineralization due to the reduction of the efficiency of intestinal calcium absorption [42]. BMD was the most prevalent measure to evaluate bone quality in studies because it is the most accurate evaluation method [43,44].

The authors add that they chose not to specify the type of alterations or diseases in the search strategy so as not to miss any potential study that has investigated some other health condition as the main theme but also reported some bone condition as a secondary outcome.

In this study, it was observed that bone fracture was the outcome of great importance for most authors since 50% of the studies showed an association between low levels of 25-hydroxyvitamin D and bone fracture. Skeletal fractures are responsible for a significant proportion of childhood injuries [45,46] and result in substantial health costs [47,48], in addition to the acute consequences of these lesions, including pain and functional limitation [49]. Some studies suggest that the high risk of fractures in healthy children stems from lower bone mineralization associated with environmental factors, including low 25-hydroxyvitamin D status (serum level <20 nmol/L) [26], malnutrition such as low calcium intake, low milk intake [50] and high body mass index (BMI) [51,52], physical inactivity, obesity [53,54] and genetics [55]. Therefore, the lack of food micronutrients, such as vitamin D, could negatively impact the child's bone mineralization process and may lead to future osteoporosis [56].

Different tests, such as dual-energy X-ray absorptiometry (DXA), peripheral quantitative computed tomography (pQCT), and quantitative ultrasound (QUS), allow the evaluation of bone mineral density. The results of the present study revealed that the use of DXA was more prevalent (51.8%) concerning other types of imaging exams. This result was probably found because it is an examination that uses two X-ray beams of two different energies to measure bone loss. It is considered the gold standard method for estimating BMD and the risk condition of a bone disease [57]. In addition, DXA can represent several regions, such as the entire body, spine, and femur regions. This test is used to diagnose osteoporosis and assess the risk of fracture. It is also used to monitor a given bone therapy [57]. However, besides being considered a high-cost test, this method emits a high dose of ionizing radiation to the patient. Especially in children and adolescents, the biological effects caused by ionizing radiation are more present, so the concern with the conscious use of tests that emit radiation is increasingly discussed [58], and a criterion when indicating such examination for this age group is recommended.

Peripheral quantitative computed (pQCT) is an imaging technique that uses computerized X-ray attenuation processing to acquire sectional images like a conventional tomography computer. From the cuts is the production of a high-quality model in three dimensions [59]. Its use for medical purposes has accelerated in recent years, being used for biological materials studies such as teeth, implants, bones, and, more recently, cartilage. However, it is still practically restricted to scientific research because it is expensive [60]. Due to this limitation, we observed that only one study in developed countries used pQCT.

Two-dimensional tests, when compared to tomographic exams, emit a lower radiation dose to the patient [60] and, in certain situations, are sufficient to elucidate the diagnosis. Changes in bone microarchitecture or quality caused by low levels of 25-hydroxyvitamin D alter X-ray and thus modify image density and texture [61]. Therefore, an X-ray becomes a good alternative, being of low cost, easy execution, and fast processing for routine examinations. The authors of the present study also observed that quantitative ultrasound (QUS) was used to determine bone stiffness (14.8%), being a cheaper device with more significant space savings compared to DXA or quantitative computed tomography and does not require the use of ionizing radiation [62]. Moreover, QUS is not only a cheap substitute for measuring BMD, but it can also provide additional information about bone resistance, primarily used to estimate fracture risk [62].

The data about 25-hydroxyvitamin D was investigated through serum levels in most studies, and insufficient or deficient vitamin D intake was investigated through food frequency questionnaires (FFQ) [63] or dietary recalls. The authors of the present study believe that the investigation of vitamin D status through laboratory tests, where serum levels report the results, is more accurate and reliable since, through diet questionnaires, the results depend mainly on the collaboration of the person responsible for the customary investigation of the child's food intake, which can lead to errors or omissions. One reason for these errors is the sex difference that interferes with the reproducibility of FFQs [64], suggesting that women have a more stable memory than men [65]. This finding is probably explained by the fact that women pay more attention to food intake or because they cook more frequently [66]. In addition, children eat meals at school [67,68], and in some cases, parents are not aware of the intake of certain foods. According to the literature, the report of parents together with children is more accurate than just the individual responses of the parents, emphasizing the value of the child's contribution [69]. In this type of evaluation, whose data should be accurate to obtain greater internal validity of the results, using a questionnaire with photos representing the size/quantity of the consumed portion of the food would be interesting. According to some studies, questionnaires with limited categories of answers, provision of memory tips, and evaluation of frequencies or size of the portion through photos make the instrument more accessible and more understandable, resulting in greater data validity [70,71].

Only observational studies, which are subject to reverse causality, were selected for the present review. However, this does not represent a problem since this type of study was chosen for evaluating association/correlation measures rather than the cause-effect relationship. The adopted age range (0-10 years old) was established according to the WHO definition for the group of children [10]. Several studies were excluded by this criterion, which limited the final number of studies in the present review. However, we limited it to children to reduce variability between studies.

This study presents some limitations, such as no information on exposure to sunlight and sociodemographic data, which could better characterize the sample studied if they were present in the recovered studies. In addition, some studies needed to provide complete information about the collected data, especially those that used medical records information. With this, it was impossible to describe some critical parameters such as the analysis software used, the accuracy of the selected areas in each image, the different regions of the body, and even the type of examination performed to investigate the bone outcome.

In the present review, no study involving healthy children was recovered that investigated a possible association between low 25-hydroxyvitamin D levels and changes in facial bones involving the dentistry area or any other area. This data serves as a warning to dentists since several alterations can affect those bones, affecting the entire stomatognathic system and, consequently, the quality of life of the affected individual due to the increased risk of fracture in the face of a low-impact trauma.

Conclusion

Studies that evaluated a possible association between low 25-hydroxyvitamin D levels and changes in bone quality, fractures, and modified anthropometry in healthy children have been published frequently in recent years, mainly by authors from developed countries. No article on the investigated subject was found in Dentistry. Low 25-hydroxyvitamin D levels were reported by most studies that observed fractures, anthropometric changes, and impaired bone quality in healthy children, who were mainly submitted to dual-energy X-ray absorptiometry for bone evaluation.

Authors' Contributions

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All authors declare that they contributed to a critical review of intellectual content and approval of the final version to be published.

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Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

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