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Mechanism of ionized calcium (iCa) in odontogenesis stunting children: Review article including a new theory for future studies on eruption rate in stunting children

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Abstract

Introduction: The normal development of the craniofacial complex can be predicted by the eruption rate. Delayed eruption is a condition that is associated with stunting. Stunting is caused by a decrease in extracellular serum iCa levels due to Environmental Enteric Dysfunction (EED), inadequate nutrition, and hormonal dysfunction. Calcium is 99 % of hydroxyapatite's composition. Dental Pulp Cells stem cell (DPCs), osteoblasts, and osteoclasts are all highly affected by extracellular calcium (iCa) levels, because there was calcium channels and receptors are found in their membranic. The aim of the review is to discuss how iCa influences the odontogenic process and the eruption pattern in stunting children.

Methodology: Literature review and theoretical approach using data from Sci-Direct, GoogleScholar, and PubMed, which have been extracted using the PRISMA technique for articles based on keywords.

Result: The procedure of searching for data using an online data base resulting obtained a total of 295 articles found from 2002–2022. At the feasibility stage, 295 articles have been screened and reviewed according to the exclusion and inclusion criteria, which are related to the keyword study of the literature in the search strategy. 26 articles were finally chosen to be analyzed.

Conclusion: iCa influences odontogenesis and eruption processes in Stunting Children. Serum iCa decreased in stunting children.

Keywords: Ionized Calcium (iCa); Stunting; Eruption Teeth

1. Introduction

Child growth and development, craniofacial complex growth, and the determination of the type of food for children are figure by the eruption time of the teeth. In pediatric dentistry, predicting the chronology and time of tooth eruption is important for analyzing the growth and development of children, predicting occlusion patterns, preventing malocclusion, and determining orthodontic treatment plans [1]. A potential indicator of pathologic conditions in maxilofacial development is delayed eruption [2]. Malnutrition conditions such as stunting are one of the causes of delayed eruption of teeth [3]. The prevalence of stunting in Southeast Asia is still the greatest in the world, at 34.4%, the equivalent of 1 in 3 children under 5 years of age [4]. Indonesia is one of the four Southeast Asian countries with the highest stunting prevalence [5].

Calcium is one of the ions that make up >99 percent of hydroxyapatite structures in bones and teeth. The majority of calcium metabolism mechanisms occur in teeth and bone cells, so inadequate intake or poor absorption of calcium

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causes impaired linear bone growth in children [6]. There are three types of calcium in the blood: free calcium (ionized calcium/iCa), binding calcium, and calcium complex [7]. iCa levels are important as secondary messengers and regulators of osteoblast and osteoclast activity. Low calcium levels can induce an increase in osteoclast activity as a homeostasis process, whereas high calcium levels can cause an increase in osteoblast proliferation and differentiation [8]. Lowering iCa levels can disrupt tooth eruption by affecting the regulatory activities of osteogenesis and odontogenesis [9]. The aim of the review is to discuss how iCa influences the odontogenic process and the eruption pattern in stunting children.

2. Material and methods

This type of research is a literature review. The theoretical approach of this study used secondary data. Online databases are used to find secondary data sources (GoogleScholar, SciDirect, and PubMed). Keywords and their correlations are used to search journals. The journal then proceeds through a three-stage selection process: 1) identification, 2) screening, and 3) eligibility.

This method entails searching or scooping up the information from the literature that is relevant to the proposed approach. The data collected from several literatures according to the inclusion an exclusion criteria is organized into a single document that is used to discuss the problems identified.

This journal is accepted to the following exclusion and inclusion criteria at each stage of the selection process:

Criteria for inclusion:

a) Information sources in English and Indonesian,
b) Articles in scientific journals, such as literature review journals, systematic reviews, and randomized controlled trials / RCTs,
c) Articles can be viewed in full text via search engines (Scidirect, PubMed, and GoogleScholar).
d) Textbook reference years in the range of 25 years (1996-2021) and
e) Scientific journal articles in the region of 10 years (2002-2021),
f) Use the keywords "Stunting," "Eruption of Primary Teeth," and "Ionized Calcium,
g) All citation components are complete. Exclusion criteria: a) case reports, b) the focus of the article is not connected with our topic.

3. Results

The process of searching data through online databases (PubMed, Google Scholar, SciDirect) based on keywords results in 525 articles from PubMed, 3,500 from Scidirect, and 3,952 from Google Scholar, for a total of 7,977 publications. There are 2,207 articles with restricted access, leaving 5,790 articles accessible. The search for articles continues with the identification stage by looking for articles that contain the relevancy of each keyword. The search resulted 16 articles (PubMed), 41 articles (Sci-Direct), and 232 articles (Google Scholar), for a total of 289 articles related to the keyword study of literature in the search technique. The searching was also performed manually, and 10 supportive articles were identified. After doing a literature review, 299 publications were identified a keyword correlation. Screening was carried out based on the abstract in the following stage, and there were 238 articles that did not support the purpose of the following literature study, leaving 61 articles for the feasibility stage.

61 publications were screened and reviewed according to the exclusion and inclusion criteria during the feasibility stage. 14 papers were inaccessible, with incomplete citations, and 21 articles did not discuss eruptions in stunted children. There have been 26 articles used as a source of literature in the creation of theories to support this literature review. All of the publications used were published between 2002-2022 and included literature reviews, systematic reviews, and research journals (RCT, in vitro, and *in vivo*).

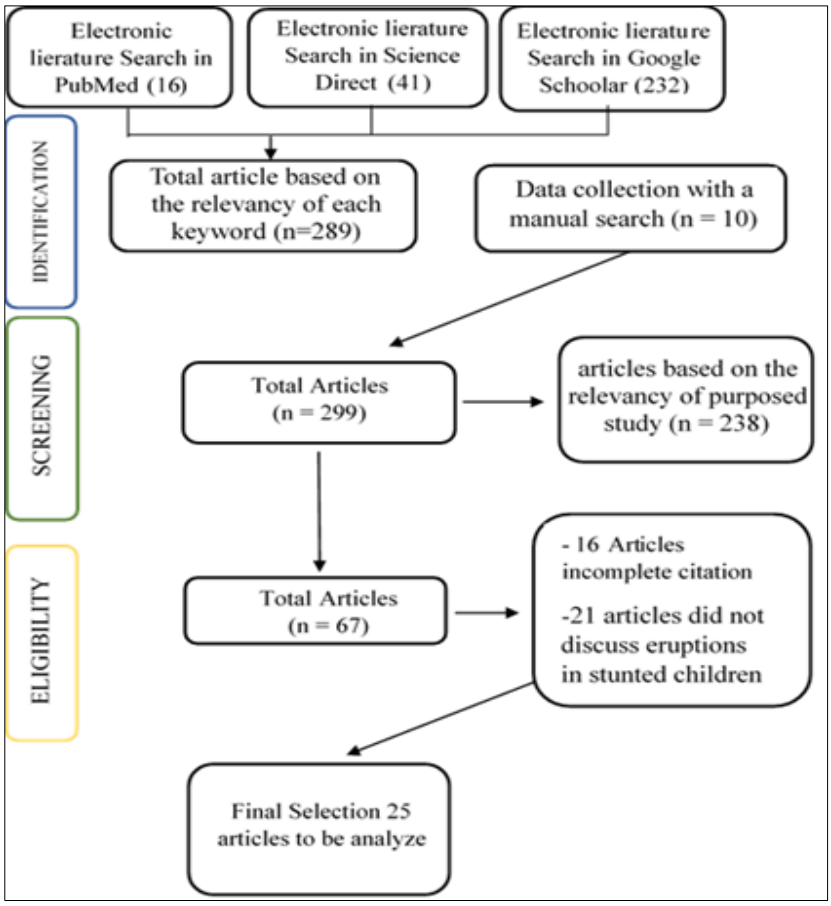

Figure 1 Search Schema for articles selection

4. Discussion

4.1. The role of calcium in stunting children

Stunting is a chronic malnutrition that causes short stature in children, which is measured by comparing height to age at periodic times with values less than -2 SD [10]. Stunting is caused by multifactorial such as: 1) nutritional deficiency, h [ormonal disorders (Insulin Growth Factor [IGF-1] resistance and disease-related syndrome), and 2) inadequate WASH (Water, Sanitation, and Hygiene) [10]. Hormonal abnormalities in stunting children are hypocalcemia, which is caused by calcium receptor resistance in cells, and also hypoparathyroidism and hypothyroidism, which are caused by decreased parathyroid and thyroid gland function. Decreasing thyroid hormone function causes a lowering secretion of growth hormones, such as Growth Hormone (GH), Thyroid Stimulating Hormone (TSH), Luteinizing hormone (LH), and Adrenocorticotropic hormone (ACTH), which have a role in the secretion of Insulin Growth Factor-1 (IGF-1).), whereas an abnormal parathyroid gland results in a decrease in Parathyroid Hormone (PTH), which can disturb the calcium homeostasis process and cause blood calcium levels to drop [11].

Environmental Enteric Disease is caused by poor WASH in stunted children (EED). Pro-inflammatory cytokines such as interleukin-1beta (IL-1), (IL-6), and tumor necrosis factor alpha (TNF-) are released as a result of systemic inflammatory conditions in EED. This increase in pro-inflammatory cytokines causes a drop in IGF-1 levels. EED can also result in reduced intestinal absorption / malabsorption, preventing the body from absorbing macronutrients and micronutrients, including calcium [11]. Calcium absorbed by the intestines is then distributed in the extracellular (blood and saliva) in the form of free calcium/ionized calcium (iCa/Ca2+), which amounts for 50% of total calcium, and a part of blood calcium is bound to blood proteins [12].

Stunting occurs because of bone growth processes such as indirect endochondral ossification, direct ossification by intramembranous bone formation, and bone mass expansion through apposition and deposition of bone matrix [13]. Growth hormone (GH), triiodothyronine (T3), androgen and estrogen hormones, and also vitamin D with parathyroid hormone, all contribute to endochondral ossification. IGF-1 secretion is stimulated by GH, TSH, androgens, and

estrogens. Thyroid Hormone Receptor (TR)-1 on IGF-1 is stimulated by TSH and T3. Androgen and estrogen hormones also have Estrogen Receptor (ER) on GH and IGF-1. Vitamin D has a direct influence on chondrocyte proliferation and stimulation through its receptors, or an indirect effect through increasing calcium absorption [11].

IGF-1 stimulates chondrocyte proliferation and differentiation of Fibroblast Growth Factor (FGF), including FGF18 and FGF19, through FGFR3, Epidermal Growth Factor (EGF), and Transforming Growth Factor (TGF)-Beta to initiate chondrogenesis [11]. Mesenchymal cell differentiation into chondrocyte cells then turns into perichondral cells, followed by apposition and maturation. IGF-1 stimulates chondrocyte proliferation and differentiation of Fibroblast Growth Factor (FGF), Transforming Growth Factor (TGF)-Beta, including FGF18 and FGF19, through FGFR3 and Epidermal Growth Factor (EGF) to initiate chondrogenesis. Mesenchymal cell differentiation into chondrocyte cell , which then mature into perichondral cells ini apposition and maturation process [14].

The binding of pro-inflammatory cytokines such as Interleukin-6 (IL-6), C-Reactive Protein (CRP), 1-Acid Glycoprotein (AGP), and CD 14 causes IGF-1 secretion to be suppressed under stunting situations [14]. Studied by Adriani et al., (2007) investigated the connection between increasing IGF-1 level with liner growt bone in stunting children [15]. Other supporting studies, like those published by Hossain et al. (2019) on stunted children aged 12-18 months, found that stunted children had lower levels of the growth hormone IGF-1, leptin, and gamma interferon (IFN-) than normal children. Stunted children's serum contains higher levels of proinflammatory cytokines such IL-6, IL-10, TNF-, and fecal alpha-1-antitrypsin (AAT) [16].

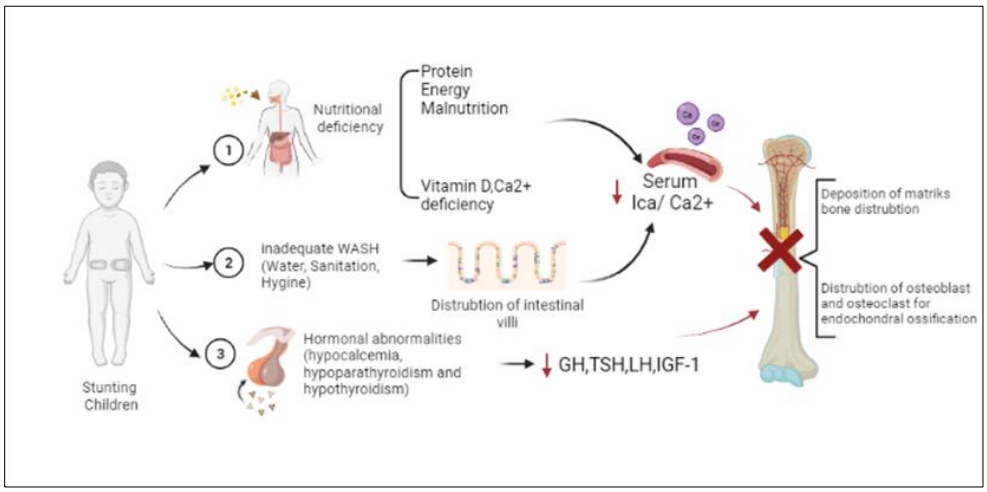

Figure 2 Illustrated Schema decreases iCa in stunting children

4.2. The role of calcium in odontogenesis

Dental pulp cells (DPCs), osteoblasts, and osteoclasts are all highly affected by extracellular calcium (iCa) levels. DPCs are mesenchymal-derived dental stem cells capable of differentiation and proliferation during the odontogenesis process. DPCs with plasma membrane calcium transport channels are sensitive to extracellular iCa levels. VGCC (*Voltage-Gated Ca^{2+} Channels)*, SOCE (*Store-Operated Ca^{2+} Entry Channels)*, and CaSR(*Extracellular Calcium Receptors)* are some of the most important calcium transport channels in DPCs cells, which play an important role in the eruption of teeth. Extracellular Ca2+ levels can act as first messengers in calcium channels that are depolarizing. The VGCC, SOCE, and CaSR channels are activated by an increase in extracellular Ca2+, allowing Ca2+ to enter intracellularly. Extracellular Ca2+ also acts as a second messenger by synthesizing intracellular protein signals [9]. The genetic coding in the calcium transport channel secretes proteins when Ca2+ passes through, causing the nucleus or ER to create specific protein signals through difference ways, such as: 1) The calcium channel secretes Cyclic Adenosine Monophosphate (CAMP)/ Protein Kinase (PKA) , c-Jun -Nterminal Kinase (JNK), and Extracellular Signal Regulated Kinase 1/2 when Ca2+ flows through VGCC (ERK 1/2) in the nucleus as a protein transcription factor. The calcium channel secretes ERK 1/2, a protein transcription factor in the nucleus, when Ca2+ flows through SOCE and CaSR [17]. 2) Intracellular Ca2+ can directly activate the ER pathway, causing protein signals to be released. Protein signals generated by the VGCC, SOCE, and CaSR pathways cause cells to proliferate and differentiate into odontoblasts, or secrete extracellular matrix proteins like FGF-1, OCN (*Osteocalcin)*, OPN(*Osteopontin)*, DSPP(*Dentin Sialophosphoprotein)*, and BMP-2 (*Dentin Sialophosphoprotein)*, which facilitate the processes of odontogenesis, cementogenesis, and root elongation with HERS activation, allowing the tooth to erupt [18]. 3) The calcium protein pathway, especially calmodulin (CaM), can be used to deliver intracellular second messenger signals to DPCs,

osteoblasts, and osteoclasts cells. In eukaryotic cells, CaM is a calcium-modulated protein that participates in calcium signal transduction. Ca2+ will bind to calmodulin on the EF-Hand when it enters the cell cytoplasm [19].

This CaM will pass through various protein interactions to produce certain signals. CaM kinase II (CaMKII) and c-fosexpression pathways, as well as the Runx2 gene, can promote cell differentiation and proliferation in osteoblasts. Growth signals like RANKl and M-CSF activate the process of osteoclastogenesis in osteoclasts. This signal will raise intracellular Ca2+ levels and activate calmodulin-dependent phosphatase/calcineurin via the nuclear factor of activated T cells, calcineurin dephosphorylater (NFAT). This CaM will pass through various protein interactions to produce certain signals. CaM kinase II (CaMKII) and c-fosexpression pathways, as well as the Runx2 gene, can promote cell differentiation and proliferation in osteoblasts [19].Growth signals like RANKl and M-CSF activate the process of osteoclastogenesis in osteoclasts. This signal will raise intracellular Ca2+ levels and activate calmodulin-dependent phosphatase/calcineurin via the nuclear factor of activated T cells, calcineurin dephosphorylater (NFAT) [20].

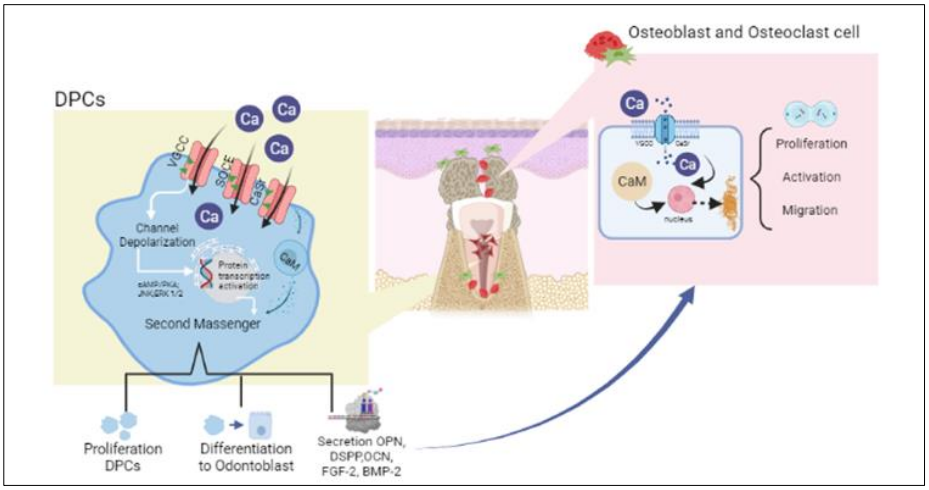

Figure 3 Illustrated Schema Distrubing Odontogenesis and Resulting Delayed Eruption

4.3. The pattern of tooth eruption of stunting children

Stunting children causes this process to be disturbed in a variety of ways. Calcium intake, EED, and hormonal anomalies in stunted children induce a drop in extracellular iCa levels in serum, resulting in the first pathway. The second mechanism involves vitamin D and hormone deprivation, which disrupts DPC and osteoblast cell receptors on the plasma membrane [21]. Stunting induces IGF-1 deficiency, which inhibits the function of osteoblasts and osteoclasts in the tooth eruption process [11].

In stunted children, the eruption of permanent teeth and deciduous teeth is typically delayed. Stunting and wasting are two kinds of malnutrition that commonly occur in children and cause delays in the eruption of permanent and deciduous teeth. PEM and other hormonal illnesses are frequently associated with malnutrition, resulting in failure of linear growth in children and delayed eruption [22].

Delayed tooth eruption in stunted children was confirmed in studies by Kaur et al., (2019) which showed delayed eruption of permanent teeth in malnourished children, with stunted children being the most affected [23]. Dimaisip-Nabuab et al., (2018) found that stunted children in three nations, Indonesia, Cambodia, and Laos, had a delay in the eruption of primary teeth [24]. Gaur and Kumar (2012) reported a link between linear bone growth delay and teeth eruption pattern in their study [25]. According to Psoter et al., (2008), stunted children had delayed primary tooth exfoliation and caries. Multifactorial factors contribute to delayed eruption in stunted children. Pro-inflammatory cytokines, hormonal changes, undernutrition, and a decrease in growth hormones like IGF-1 and CSF-1, all of which have been discussed previously, have an impact on bone and tooth growth [26].

5. Conclusion

iCa influences odontogenesis and eruption processes in Stunting Children. Serum iCa decreased in stunting children. Lower level iCa inhibiting mesencymal cell to bone cell (osteoblas, osteoclast) differentiation and lower level iCa distrubing eruption pathway. Lower iCa calcium poteintially causes delayed eruption.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that there is no conflit of interest regarding the publications of this document.

References

[1] H Poureslami *et al.*, Does Timing of Eruption in First Primary Tooth Correlate with that of First Permanent Tooth? A 9-years Cohort Study, *J. Dent. Res. Dent. Clin. Dent. Prospects*. 2015; 9(2): 79–85.

[2] C Un Lam *et al.* Influence of metabolic-linked early life factors on the eruption timing of the first primary tooth, *Clin. Oral Investig.* 2016; 20(8): 1871–1879.

[3] A Badruddin, IA Putri, MR dan Rahardjo.Factors associated with primary teeth eruption pattern in children under three years old in beji depok, west java.Journal of International Dental and Medical Research, 10(Specialissue). 2017; 10: 564–568.

[4] UNICEF., *Children , food and nutrition*:The State of the world's children*(SOWC);* Growing well in a Changing world.October 2019. ISBN:978-92-806-5003-7;36-60.

[5] FAO, *Asia and the Pacific. Regional overview of food security and nutrition: accelerating progress towards the SDGs.* 2018.Accelerating progress towards the SDGs. Bangkok. License: CC BY-NC-SA 3.0 IGO.Available at: http://www.fao.org/3/CA0950EN/CA0950en.pdf;11-25.

[6] M Zimmermann, PR Trumbo. Nutrient Information, *Am. Soc. Nutr.* 2013; 4(1): 262–264.

[7] GS Baird, Ionized calcium, *Clin. Chim. Acta*. 2011; 412(9–10): 696–701.

[8] SA Al-Dujaili *et al.* Calcium Sensing Receptor Function Supports Osteoblast Survival and Acts as a Co-Factor in PTH Anabolic Actions in Bone, *J. Cell. Biochem.* 2016; 117(7): 1556–1567.

[9] S An, The emerging role of extracellular Ca2+ in osteo/odontogenic differentiation and the involvement of intracellular Ca 2+ signaling: From osteoblastic cells to dental pulp cells and odontoblasts, *J. Cell. Physiol.* 2019; 234(3): 2169–2193.

[10] Aryu Candra, Epidemologi Stunting. Fakultas Kedokteran Diponegoro.2020.ISBN: 978-623-7222-63-7*(Epid);*15-37

[11] DJ Millward, Nutrition, infection and stunting: The roles of deficiencies of individual nutrients and foods, and of inflammation, as determinants of reduced linear growth of children, *Nutr. Res. Rev.* 2017; 30(1): 50–72.

[12] R. D. Gebreyohannes, A. Abdella, W. Ayele, and A. C. Eke, Association of dietary calcium intake, total and ionized serum calcium levels with preeclampsia in Ethiopia, *BMC Pregnancy Childbirth*. 2021; 21(1): 1–7.

[13] WCW Chan, Z Tan, MKT To, D Chan. Regulation and role of transcription factors in osteogenesis, *Int. J. Mol. Sci.* 2021; 22(11): 1–21.

[14] E Gabusi *et al.*, Extracellular calcium chronically induced human osteoblasts effects: Specific modulation of osteocalcin and collagen type XV, *J. Cell. Physiol.* 2012; 227(8): 3151–3161.

[15] M Adriani, B Wirjatmadi. The effect of adding zinc to vitamin A on IGF-1, bone age and linear growth in stunted children, *J. Trace Elem. Med. Biol.* 2014; 28(4): 431–435.

[16] M Hossain *et al.*, Serum adipokines, growth factors, and cytokines are independently associated with stunting in Bangladeshi children, *Nutrients*. 2019; 11(8): 1–16.

[17] B Xiang *et al.*, The osteoclasts attach to the bone surface where the extracellular calcium concentration decreases, *Cell Biochem. Biophys.* 2016; 74(4): 553–558.

[18] N. Fujiwara, MJ Tabata, M Endoh, K Ishizeki, T Nawa. Insulin-like growth factor-I stimulates cell proliferation in the outer layer of Hertwig's epithelial root sheath and elongation of the tooth root in mouse molars in vitro, *Cell Tissue Res.* 2005; 320(1): 69–75.

[19] M Zayzafoon, Calcium/calmodulin signaling controls osteoblast growth and differentiation, *J. Cell. Biochem.* 2006; 97(1): 56–70.

[20] C Choukroune, Tooth eruption disorders associated with systemic and genetic diseases: clinical guide, *J. Dentofac. Anomalies Orthod.* 2017; 20(4): 402.

[21] R Joy, Stunted Growth in Kids : Role of Vitamin D. Quaterly Medical review. Vol 71 No 2 April-june 2020;1-12

[22] R Almonaitiene, I Balciuniene, J Tutkuviene. Factors influencing permanent teeth eruption. Part one--general factors., *Stomatologija*. 2010; 12(3): 67–72.

[23] G Reddy *et al.*, Clinical and radiographic evaluation of autogenous dentin graft and demineralized freeze-dried bone allograft with chorion membrane in the treatment of Grade II and III furcation defects-: A randomized controlled trial, *Indian J. Dent. Sci.* 2019; 11(2): 83.

[24] J Dimaisip-Nabuab *et al.*, Nutritional status, dental caries and tooth eruption in children: A longitudinal study in Cambodia, Indonesia and Lao PDR 11 Medical and Health Sciences 1117 Public Health and Health Services 11 Medical and Health Sciences 1105 Dentistry, *BMC Pediatr.* 2018; 18(1): 1–11.

[25] R Gaur, P Kumar. Effect of undernutrition on deciduous tooth emergence among Rajput children of Shimla District of Himachal Pradesh, India, *Am. J. Phys. Anthropol.* 2012; 148(1): 54–61.

[26] W Psoter, B Gebrian, S Prophete, B Reid, R Katz. Effect of early childhood malnutrition on tooth eruption in Haitian adolescents, *Community Dent. Oral Epidemiol.* 2008; 36(2): 179–189.