Growth Hormone Deficiency for Oral-Health

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Growth hormone (GH) is involved in the regulation of the postnatal dental and skeletal growth, but its effects on oral health have not been clearly defined. This paper aims to provide a review of current clinical knowledge of dental caries, tooth wear, developmental enamel defects, craniofacial growth and morphology, dental maturation, and tooth eruption in growth hormone deficient (GHD) children. A systematic review was carried out using Scopus, MEDLINE-EbscoHost and Web of Science from 2000 to May 2021.

growth hormone deficiency children caries dental maturation craniofacial growth/morphology tooth wear enamel defects

1. Introduction

Growth hormone (GH) is a critical regulator of the growth process in children. Both, cell sensitivity to GH and the site of GH action are closely coordinated and affect the odontogenesis. When the new matrix begins to form, GH receptors are expressed in tooth tissues and mediate local growth responses. However, cementocytes and mature odontoblasts in later stages of tooth development do not display expression, which suggests that they become insensitive [1].

Recent studies have shown that IGF-I and its receptor are expressed in both dental epithelial and mesenchymal tissues of tooth germs, increasing the size of bioengineered tooth germs. In vitro IGF-I signaling promotes cell proliferation, differentiation, and matrix secretion in mouse tooth germs, and so it can be hypothesized that IGF-I regulates tooth morphogenesis [2][3].

Oyanagi et al. [3] showed that the combination of IGF-I and BMP2 promotes odontoblast differentiation and the expression of the ameloblastin enamel matrix gene (*Ambn*) in mice. Their research demonstrated that the expression of *Ambn* is directly enhanced by IGF-I in dental epithelial cells, so *Ambn* may play an essential role in normal ameloblast differentiation. It is interesting that at least a hundred genes have been recognized as being expressed during different stages of amelogenesis; this total includes genes that codify sex hormone receptors and growth hormone receptors [4]. Estrogen plays an essential role during tooth formation by influencing the process of enamel and dentin mineralization. An animal model of estrogen deficiency showed a significant reduction in enamel microhardness [4]. The results reported by Arid et al. [4] in humans have demonstrated that genetic polymorphism in estrogen receptors (rs12154178) and in GH receptors (rs1509460) is associated with alterations in ameloblast function and developmental defects of enamel (DDE). It must be remembered that disturbances in enamel

formation are associated with poor esthetics and the higher susceptibility of teeth to harmful local factors. Developmental enamel defects increase the risk of dental caries and noncarious tooth surface loss, which affect long-term dental health [5][6]. The posteruptive onset of the caries process takes part for as long as three years after permanent tooth eruption [7]. Caries in primary teeth shows a rapid course, due to the specific morphological structure and a lower degree of mineralization. Effective prevention and treatment, especially in the case of primary dentition, can considerably extend the time that a tooth remains in the oral cavity, thus preventing the consequences of its premature loss. In patients with growth hormone deficiencies, missing teeth and tooth-bone discrepancies become risk factors for masticatory organ disorders.

Data from the literature confirm that dental age is delayed with respect to chronological age by up to two years in growth hormone-deficient (GHD) children [8]. It has been reported that tooth eruption, defined as the mucosal penetration of any visible part of a tooth into the oral cavity, is delayed in both primary and permanent dentition [8][9]. The relationship between the maturation of the skeletal system and the formation of permanent dentition has been confirmed in several studies [10][11]. There is a relationship between mineralization of the canine and the MP3 stage—one of the stages of ossification of the middle phalanx of the third finger in the development of bones of the wrist [10]. Moreover, the relationship between dental age and maturity in the cervical vertebrae is also determined. A significant association has been confirmed between cervical vertebral maturation (CMV) classification and the development of canine and second premolar teeth [12]. At the same time, it should be remembered that the time for emergence of permanent premolars and canines can be modified by the activity of caries in primary teeth. Several studies have concluded that early extraction of second primary molar or caries in primary molars can accelerate the clinical eruption of permanent second molars [13].

2. Analysis on Results

After duplicates were manually eliminated, our systematic search of the three medical databases yielded a total of 62 publications meeting the search criteria. An initial selection of these was made using their titles and abstracts.

A total of fifty one articles were excluded because they focused on topics other than dental status, they did not study pediatric GHD patients, or they were reviews. Based on the full text, ten publications were qualified for further analysis; two of these concerned the mineralized tissues of the tooth–dental caries [14][15], two dealt with dental maturity [9][16], two with malocclusion [9][17], and six with craniofacial growth or morphology [18][9][19][20][21][22].

Two articles worked with the same group of patients [14][15]; for this reason, some results were considered only once.

The publications describe patients living in North America, Asia, and Europe [18][9][14][15][16][17][19][20][21][22]. All the studies involved patients from 5 to 18 years of age, covering a total of 465 GHD and 51 ISS (idiopathic short stature) individuals. Patients with ISS, as described by Choi et al. [21], Hodge et al. [17] and Kim et al. [19], were not considered in our analysis. Two studies (by Segal et al. [22] and Hodge et al. [17]) provided no information on the sex of the patients. One study by Kjellberg et al. [9] dealt only with male patients. Except for the articles of Segal et

al. [20], Hodge et al. [17], Choi et al. [21], and Kim et al. [19], the studies all described only GHD and untreated GHD patients. In Segal et al. [22], eleven patients had multiple pituitary hormone deficiencies. The control groups in the studies included healthy children [16][19][21] or relatives [22], reference materials [18][9][20], medical records [17], and study groups divided into subgroups [14][15][21][22]. In five articles the researchers were dentists or dental hygienists [9][14][15][19][21]. Two papers [14][15] included analysis of vitamin D levels. Other vitamin and mineral deficiencies were not assessed.

2.1. Hard Mineralized Tissue Pathology

Dental caries was examined in two publications presenting the same patient cohort [14][15]. The dental examinations were carried out in line with World Health Organization (WHO) criteria for epidemiological studies. The severity of dental caries was assessed using the DMFT index, which identifies those teeth (T) which have cavities (D); are missing (M); or have been filled (F) as a result of caries. A statistically significant effect of vitamin D3 concentration on the DMFT index and its component DT was found among children from rural areas, where an increase in vitamin D3 concentration by ten units resulted in a decrease in the value of DMFT by 0.82 and a decrease in the value of DT component by 0.66. The percentage of these children with active caries was higher than in urban areas, but not statistically significantly [14]. A positive and statistically significant correlation between the duration of GH therapy and DMFT index was, however, observed in patients from urban areas [15]. There was no healthy control group in this study.

2.2. Dental Maturity and Malocclusion

Two of the papers we considered describe the prevalence of malocclusion in GHD children [9][17]. Both used the relations of first permanent molars (Angle's classification) to detect deviations from Angle's Class I occlusion, where the mesiobuccal cusp of maxillary first molar occludes in the buccal groove of the mandibular first molar. In the study of Kjellberg et al. [9], 29% of the boys in the study group showed Angle's Class II malocclusion, while the remainder were Angle's Class I. Dental crowding of at least 2 mm was recorded in 44% of patients. A large overjet (>6 mm) was seen in 14%, and a large overbite (>5 mm) in 5%.

Hodge et al. [17] observed Angle's Class II in 31% and Angle's Class III in 6% of patients. Increased overjet and deep overbite were each found in up to 37% of subjects, which is a significantly greater prevalence than in Kjellberg et al. [9]. However, these discrepancies are probably due to differences in methodology and definitions. In the study of Hodge et al. [17], an overjet greater than 2 mm and an overbite greater than 3 mm were considered abnormal, while Kjellberg et al. [9] noted only more extreme abnormalities. Unlike Hodge et al. [17], Kjellberg et al. [9] used radiographs and plaster models to record relations between the jaws.

Dental maturity was evaluated in two studies by Kjellberg et al. [9] and Partyka et al. [16]. Each investigator used a different method: the method of Demirjian was employed by Kjellberg and the method of Matiegka and Lukasova by Partyka; both of which were validated. Kjellberg et al. [9] defined dental maturity on the basis of tooth formation

recorded on orthopantomograms. The sum of scores for each individual was converted into a dental age in accordance with the instructions given by Demirjian. The method of Matiegka and Lukasova established dental age by identifying the most recently erupted full group of teeth, including incomplete groups. From Matiegka's table for boys and Lukasova's for girls, age corresponding with the number of teeth can be found, giving a result for a specific patient [16]. Both studies showed statistically significant differences between birth age and dental age between the GHD and non-GHD patients and control groups [9], and between birth age and dental age in patients starting treatment [16]. In Kjellberg et al. [9], dental maturity was delayed about one year in both the non-GHD and GHD boys. Partyka et al. [16] reported a delay of 18.82 and 2.70 months (for the group starting treatment and that undergoing treatment, respectively).

2.3. Craniofacial Growth/Morphology

Six articles on craniofacial growth and morphology were included in the systematic review [18][9][19][20][21][22]. Five publications used lateral cephalograms to measure the results [18][9][19][20][21]. The number of landmarks and the linear and angular measurements differ between the studies, and three articles mentioned the methods used: Kjellberg et al. [9] used the Bjork method, Choi et al. [21] used Pancherz's method, and Segal et al. [22] used the triangulation methods developed by Bookstein. Anterior cranial base length was found to be significantly reduced by Preda et al. [20], Kim et al. [19], and Choi et al. [21], while the posterior cranial base length was shorter in Kjellberg et al. [9], Preda et al. [20], Choi et al. [21], and Kim et al. [19]. Total cranial base length was significantly less in Preda et al. [20] and Kim et al. [19]. Lower anterior facial height was significantly smaller among boys and girls prior to and during treatment in Funatsu et al. [18]. Segal et al. [22] also found smaller vertical proportions, suggesting a deficiency in the lower face. Both mandibular ramus height and corpus length were shorter in boys prior to treatment in Choi et al. [21]. Smaller mandibular corpus lengths were noted by Preda et al. [20] among boys and girls, and prior to and during treatment in Funatsu et al. [18], while mandibular ramus lengths were shorted in untreated boys in Kim et al. [19]. The measured angles referred to the mandible's and maxilla's retroposition [9][19][20]. Significant differences between the studied group were also apparent in the angle between the maxillary and mandibular planes, which was larger than normal [19][20][21].

2.4. Quality Assessment and Risk of Bias

All studies were classified in accordance with the Cochrane collaboration guidelines [23]. A control group was used in all publications, although its size and structure was not always consistent. While only three groups were gender-paired [18][9][21], most of them were similar to the study group in terms of age [18][9][14][15][17][19][20].

The control group in the study by Kjellberg et al. [9], Segal et al. [22], Hodge et al. [17], and Preda et al. [20] consisted of children from previous studies. None of the publications described the blindness of examiners. Intrarater and interrater reliability were calculated in Kjellberg et al. [9] and Choi et al. [21] All papers performed statistical analysis, although not all aspects were statistically analyzed in one of the studies [9].

The publications on malocclusion [9][10] were found to be at medium risk of bias. Two articles on dental caries describe the same cohort of children and present similar conclusions [14][15]. One of them was classified as a good

quality study, since it additionally included a sample size calculation [15]. One publication on craniofacial characteristics [20] was at medium risk, and five [18][9][19][21][22] were at low risk. One publication on dental maturity [16] was at medium, one at low risk [9].

3. Current Insights

There is very little in the literature on oral cavity status in patients with GHD. Our systematic review has shown that some dental topics have not yet been discussed. There has been little to evaluate dental conditions like tooth wear and enamel defects, although we can assume that the effect of growth hormone on the dentition and facial bones is complex [1][24]. Publications on dental status and craniofacial growth in children with GHD are somewhat confined, and their results are not always concordant [25].

The size, growth, and osseous maturity of the jaw also play a role in the process of tooth eruption. A strong correlation has been shown between eruption time and dental maturity. The teeth typically erupt when they have reached a 2/3 root length [26], but individual correlation between chronological age and eruption time is inconsistent [26][27]. Research has demonstrated that, in GHD patients, dental age (maturity) is significantly delayed [9][16]. This is consistent with the results of Cantu et al. [8], which indicated a mean delay in dental age of close to one year. Furthermore, they observed no significant effect of GH treatment on dental maturation. The lack of a subsequent therapeutic response would indicate that dental age is less affected by GH than craniofacial growth.

The studies involved in our systematic review report that not only the height of GHD children, but also their craniofacial morphology and growth, are affected [19]. These studies support the previously demonstrated idea that the linear growth of the body is strongly correlated with jaw growth [28], and that the growth of craniofacial skeletal structures is poor in periods of slow longitudinal growth [18][9][19][20][21][22].

Birth age does not reflect fully the physiological development of a child. In order to closely evaluate the process of growth, it is necessary to use other criteria, such as dental age and skeletal age. These parameters are essential for dental providers to provide diagnoses and to plan therapy. In clinical practice, evaluation of both dental and skeletal age would be valuable in all children undergoing dental treatment, especially in those with GHD.

4. Conclusions

The available studies indicate that children with GHD showed abnormal craniofacial morphology with reduced mandibular dimensions, with a resulting tendency to Angle's Class II occlusion, which affected up to 31% of the patients. Dental age has been shown to be delayed in GHD patients by about 1 to 2 years. Moreover, the risk of dental caries in children with GHD decreases with increasing levels of vitamin D. The data are scarce and further studies would be valuable in evaluating the risk of various oral health problems and in organizing targeted dental care for this vulnerable group.

To gain more of an insight into the effects of this disease and its treatment on oral health and craniofacial structures, data need to be collected both before and after GH administration. Such longitudinal studies could help us to understand the complex endocrine mechanisms regulating the stomatognathic system's development and functions, in order to provide the optimal treatment of GHD-related disturbances.

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