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EVALUATION OF THE EFFECT OF MEDICATIONS USED IN CHILDREN WITH RHEUMATIC DISEASES ON DENTAL MATURATION

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ABSTRACT

The study's main objective is to compare dental maturation in healthy children and those with rheumatic diseases. It also aims to estimate the dental age (DA) of children with Pediatric Rheumatic Diseases (PRD); specifically focusing on comparing those receiving medical treatment to those who are not, and to differentiate between biological and non-biological medication recipients, to identify potential differences.

This observational cross-sectional study was conducted to assess the dental maturation stages in a cohort of 278 children (126 boys, 152 girls) aged between 6 and 14 years between September 2021 and December 2023. The study population included individuals with PRD requiring dental treatment and systemically healthy children. Digital panoramic radiographs were utilized for the evaluation of dental maturation in both groups.

A statistically perfect agreement was found among the DA estimated by the researchers (Interclass correlation coefficient (ICC)=1.000; $p<0.01$). A statistically perfect level of agreement was found between the chronological age (CA) of the cases and the DA estimated using Willems method (ICC=0.921; $p<0.01$). It was found that the difference between the estimated DA and CA was higher in girls and boys in the PRD group who were taking medication.

No significant differences were found in DA estimated based on gender and treatment status among individuals with PRD. Willems method tended to underestimate the age of girls receiving biological treatment while overestimating the age in all other groups.

KEYWORDS: dental age estimation; Willems method; pediatric rheumatic diseases.

INTRODUCTION

Determining the stage of tooth development is essential across various branches of dentistry and forensic science. This method, which leverages the progressive stages of tooth development, serves to estimate an individual's biological age based on dental characteristics. The progressive maturation of human dentition facilitates this process. The degree of maturity provides valuable information for several dental treatment planning processes, such as the management of dental trauma, caries risk assessment, and orthodontic therapies in pediatric dentistry [1, 2].

The most commonly used indicators of maturity are morphological parameters (body weight and height), secondary sexual characteristics, and skeletal and dental ages [1, 3]. Dental radiographs and hand/wrist X-rays are highly reliable for age estimation, making them preferred methods due to their accuracy [4, 5]. Age assessment primarily relies on analyzing teeth, with various techniques focusing on differentiating between the crown and root in children [5]. Despite tooth eruption being affected by environmental factors like impaction and spacing in the jaw, stages of tooth development are favored for dental age estimation because they're less influenced by external conditions [6]. Orthopantomograms and cephalometric radiographs are the most common tools for visualizing dental development for this purpose [6, 7].

Dental and skeletal immaturity deviations have been linked to a variety of medical conditions. Patients with cleft lip/palate [8] children with chronic renal failure [9] cystic fibrosis [10] are reported to have a delayed. Patients with hypopituitarism typically experience a delayed onset of dental maturation, albeit with less consistent occurrence and to a lesser extent than growth in the skeleton or stature [11]. PRD, on the other hand, are autoimmune or autoinflammatory-natured disorders that affect the bones, skin, and muscles, and they contribute to a significant burden of chronic illnesses in children worldwide [12]. Juvenile idiopathic arthritis (JIA), systemic JIA (sJIA), Kawasaki disease (KD), Henoch-Schonlein purpura (HSP), systemic lupus erythematosus (SLE), chronic uveitis, Takayasu arteritis (TA), and juvenile dermatomyositis (JDM) are among the rheumatological diseases that are commonly observed in children. Symptoms begin at a young age and last throughout maximum growth potential in these children. Long-term consequences usually follow delayed diagnosis and contribute to increasing disease burden, joint damage, deformity, and delayed growth and development [13].

An impairment in bone growth (delay) is a well-recognized complication in children suffering from JIA [14]. The majority of children diagnosed with JIA reportedly exhibit facial growth abnormalities, such as restricted openings and abnormalities in the size of their mandibles and maxillae. Patients with JIA may exhibit a minor advance in skeletal age before the age of 10, followed by retardation in age between 10 and 15 years; the bone age of JIA children varies with CA [15].

Recent advances in the treatment of rheumatic diseases mitigate growth impairments in children. This may be due to the ability to achieve early and better control of disease activity, the use of low-dose glucocorticoids, or a combination of both. The recent update of the American College of Rheumatology on the treatment of systemic arthritis recommends initial monotherapy with biologics as a treatment option. With the increasing use of biologics, it may be more possible to decrease steroid exposure in

young children, thereby preventing growth impairments [16]. Biologics use a more focused approach than conventional disease-modifying antirheumatic medications, concentrating on certain molecules or receptors to limit their effects and lessen inflammation. For this specific characteristic, their general side effects are less than conventional treatments, such as anti-inflammatory, immunosuppressive, or cytotoxic drugs. These medications, such as tumor necrosis factor (TNF) inhibitors, interleukin (IL)-6 inhibitors, and IL-1 inhibitors, have demonstrated remarkable efficacy in controlling disease activity, reducing symptoms, and improving long-term outcomes [12].

However, there is a scarcity of research that specifically examines the potential impact of this disease on the process of dental maturation in children who are affected, as opposed to those who are unaffected [17, 18]. The main objective of this study is to compare dental maturation in healthy children and children with rheumatic diseases. Additionally, to estimate the age of children with PRD, with a specific focus on comparing those who get medical treatment with those who do not, and to identify any differences between biological medication and non-biological medication recipients.

MATERIALS AND METHODS

This observational cross-sectional study was conducted to assess the dental maturation stages in a cohort of 278 children (126 boys, 152 girls) aged between 6 and 14 years between September 2021 and December 2023. The study population included individuals with PRD requiring dental treatment, who were attending the Umraniye Training and Research Hospital, Department of Pediatric Rheumatology. Additionally, systemically healthy children were recruited from the Department of Pediatric Dentistry at Marmara University Dentistry Faculty. Digital panoramic radiographs were utilized for the evaluation of dental maturation in both groups. Written informed consent was obtained from all parents and participants before the study. No compensation was provided for participation. The study protocol was approved by the Ethics Committee of Umraniye Training and Research Hospital, Istanbul, Turkey (2021-243) and registered at ClinicalTrials.gov (NCT05832359).

The sample size calculation for the study was conducted using G*Power version 3.1.9.2. Based on the results of a previous study titled "Dental age estimation in children affected by juvenile rheumatoid arthritis," considering the effect size of 0.3 calculated from the differences in mean ages estimated using Willems method between the groups, a one-way t-test was performed with 80% power and a 5% Type I error rate. The appropriate sample size for this study was determined to be n=278 (139 samples in each group).

Study population

A total of 278 participants, with panoramic radiographs dated between 2021 and 2023, were enrolled in the study. The inclusion criteria consisted of 139 children diagnosed with PRD aged 6-14 years, receiving biological therapy and non-biological therapy for more than 1 year and 139 systemically healthy subjects with no bilateral congenital absence of lower teeth during intraoral and/or radiographic examinations and the missing tooth in the left mandibular quadrant must be present in the right mandibular quadrant. The exclusion criteria were as follows patients with panoramic films showing asymmetry and magnification errors, where anatomical structures cannot be clearly visualized, with significant tooth loss due to trauma or disease, those who underwent root canal

treatment, or those with pathological tooth structure, with a history of chronic diseases not related to the assessment.

Radiographic evaluation and dental age estimation

139 panoramic radiographs of the PRD group were obtained as part of the standard procedure for setting the preliminary dental diagnosis and treatment plan at Marmara University Faculty of Dentistry with the use of protective lead aprons and thyroid protective equipment. The radiographs of the HC group were collected retrospectively from the digital database of the Department of Pediatric Dentistry, Marmara University Faculty of Dentistry following the obtained permissions. All radiographs were obtained using Planmeca Promax, performed at 66e70 kV, 11e14 mA, 6.2 s exposure time, and pulse X-ray. The evaluation of dental maturation on panoramic radiographs was performed by two researchers. Both were blinded to all other dental and medical information. Subsequently, inter-observer agreement was assessed through the interclass correlation test.

DA was estimated from panoramic radiographs of individuals in the PRD and HC groups using Willems method. The DA was recorded based on the stages of development of the left mandibular seven teeth according to the calcification stages (from A to H) developed by Demirjian [7] *(Fig 1)* and scored according to gender-specific tables revised by Willems et al. [6]

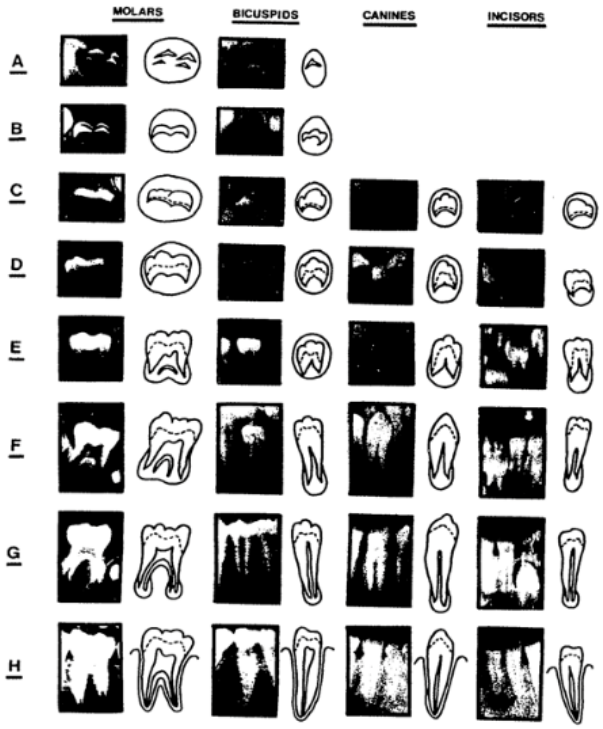

Fig 1 *(Developmental stages of the permanent dentition.)*

(Table 1-2). If any tooth in the left mandible was missing, the contra-lateral tooth in the right mandible was used as a substitute. Stages were converted into scores based on the tables provided. The obtained total maturity score was equivalent to the DA [6].

Table 1 *(Tooth mineralization scores of left seven mandibular teeth for boys according to Willems method corresponding to Demirjian's developmental tooth stages.)*

Tooth	A	B	C	D	E	F	G	H
Central incisor	…	…	1.68	1.49	1.5	1.86	2.07	2.19
Lateral incisor	…	…	0.55	0.63	0.74	1.08	1.32	1.64
Canine	…	…	…	0.04	0.31	0.47	1.09	1.9
First bicuspid	0.15	0.56	0.75	1.11	1.48	2.03	2.43	2.83
Second bicuspid	0.08	0.05	0.12	0.27	0.33	0.45	0.4	1.15
First molar	…	…	…	0.69	1.14	1.6	1.95	2.15
Second molar	0.18	0.48	0.71	0.8	1.31	2	2.48	4.17

Table 2 *(Tooth mineralization scores of left seven mandibular teeth for girls according to Willems method corresponding to Demirjian's developmental tooth stages.)*

Tooth	A	B	C	D	E	F	G	H
Central incisor	…	…	1.83	2.19	2.34	2.82	3.19	3.14
Lateral incisor	…	…	…	0.29	0.32	0.49	0.79	0.7
Canine	…	…	0.6	0.54	0.62	1.08	1.72	2
First bicuspid	-0.95	-0.15	0.16	0.41	0.6	1.27	1.58	2.19
Second bicuspid	-0.19	0.01	0.27	0.17	0.35	0.35	0.55	1.51
First molar	…	…	…	0.62	0.9	1.56	1.82	2.21
Second molar	0.14	0.11	0.21	0.32	0.66	1.28	2.09	4.04

By deducting the children's birthdate from the radiograph date, the CA for each child in the research was determined.

Statistical analysis

When evaluating the findings obtained in the study, the SPSS 26 (Statistical Package for the Social Sciences) program was used for statistical analysis. Descriptive statistical methods such as mean, standard deviation, median, minimum, and maximum values were used to evaluate the study data for quantitative variables, while frequencies and percentages were used for qualitative variables. The normality of the data was assessed using the Shapiro-Wilk test and Box Plot graphs. For quantitative variables showing a normal distribution, the Student's t-test was used for comparisons between the two groups. In evaluating the relationships between variables, Pearson correlation analysis and the Interclass Correlation Test were used based on the distribution. The results were evaluated at a 95% confidence interval with a significance level of $p<0.05$.

RESULTS

Demographic findings

The demographic data of the population presented in *Table 3* consisted of a total of 278 cases, of which 126 were boys and 152 were girls. The ages of the cases ranged from 6 to 14, with a mean of 9.94±2.42. When the age groups were examined, it was observed that 41 were between 6 and 6.99, 40 were between 7 and 7.99, 26 were between 8 and 8.99, 25 were between 9 and 9.99, 34 were between 10 and 10.99, 38 were between 11 and 11.99, 42 were between 12 and 12.99, and 32 were between 13 and 14 years old. 63 boys and 76 girls had PRD; 39 of them had autoinflammatory and 100 had autoimmune diseases. It was noted that medication was being used in 102 of the instances. Of the individuals taking medication, 26 used biological medication and 76 used non-biological ones.

Table 3 *(Distribution of Descriptive Characteristics.)*

		n
Gender	**Boys**	126
	Girls	152
Years	*Mean±SD*	9,94±2,42
	Median(Min-Max)	10,16 (6-14)
	6-9,99	41
	7-7,99	40
	8-8,99	26

	9-9,99	25
	10-10,99	34
	11-11,99	38
	12-12,99	42
	13-14	32
Disease Type	Otoinflammatory	39
	Autoimmune	100
Medication Use	**No**	37
	Yes	102
	Biological	26
	Non-biological	76

Using Willems method, the first researcher estimated DA ranging from 4.5 to 16.58 with a mean of 10.59±2.83, while the second researcher used the same procedure to determine DA ranging from 4.5 to 16.58 with a mean of 10.59±2.84.

There was a statistically perfect agreement between the DA estimated by the first and second researchers using Willems method (Interclass correlation coefficient (ICC)=1.000 (95% CI: 1.000 - 1.000; p=0.001; p<0.01).

Table 4 shows that perfect levels of concordance were observed between the CA of girls and boys and the DA was estimated using Willems method in all groups. The ICC value is above 0.9 for all cases in both the PRD and HC groups.

Table 4 *(Concordance between CA and DA estimated using Willems Method.)*

	PRD (n=63)		HC (n=63)	
	CA-DA	***p***	**CA-DA**	***p***
	ICC (%95 CI)		**ICC (%95 CI)**	

All cases	0,917 (0,886-0,940)	***0,001****	0,921 (0,892-0,943)	***0,001****
Boys	0,928 (0,884 – 0,956)	***0,001****	0,948 (0,916 – 0,968)	***0,001****
Girls	0,913 (0,881 – 0,951)	***0,001****	0,911 (0,863-0,943)	***0,001****

*aStudent-t Test. dPaired Samples-t Test. **p<0,01*

As shown in *Table 5*, the difference between DA and CA, regardless of gender, was found to be higher in the PRD group compared to the HC group.

Table 5 *(The comparison of DA and CA of boys and girls in the PRD and HC groups.)*

			PRD	**HC**	**^{a}p**
Boys	**CA**	*Mean±SD*	9,77±2,39	9,89±2,53	***0,269***
		Median (Min-Max)	10,2 (6-14)	10,1 (6-13,4)	
	DA	*Mean±SD*	10,85±2,74	10,88±2,77	***0,060***
		Median (Min-Max)	10,7 (4,5-16,6)	10,6 (5,2-16,6)	
		^{d}p	***0,001****	***0,001****	
	Difference	*Mean±SD*	1,06±0,97	0,99±0,85	
Girls	**CA**	*Mean±SD*	10,39±2,43	9,67±2,30	***0,064***
		Median (Min-Max)	10,4 (6-14)	9,9 (6-13,3)	
	DA	*Mean±SD*	10,77±3,02	9,97±2,72	***0,089***

		Median (Min-Max)	10,9 (5-15,8)	10,1 (5,5-15,8)
		[d]p	***0,001****	***0,001****
	Difference	*Mean±SD*	0,39±1,07	0,30±1,06

*aStudent-t Test. dPaired Samples-t Test. **p<0,01*

Upon comparing the DA with the CA, it was discovered that the mean for boys in the PRD group was overestimated by 1.06±0.97 years, the mean for boys not taking medication was overestimated by 0.99±0.82 years, and the mean for boys taking medication was overestimated by 1.11±0.78 years. For girls in the PRD group, the DA was overestimated by 0.39±1.07 years, for girls not using a medication, the mean was overestimated by 0.30±1.06 years, for girls using a medication, the mean was overestimated by 0.44±0.94 years *(Table 5,6)*. The group receiving medicine had a greater difference, independent of gender, between DA and CA.

Table 6 *(The comparison of DA and CA of boys and girls in the PRD group based on medication usage.)*

			Medication use		
			No	**Yes**	***[a]p***
Boys	**CA**	*Mean±SD*	9,32±2,27	9,93±2,43	***0,388***
		Median (Min-Max)	8,8 (6,3-13,3)	10,3 (6-14)	
	DA	*Mean±SD*	10,44±2,26	10,99±2,89	***0,492***
		Median (Min-Max)	9,8 (6,5-14,9)	10,8 (4,5-16,6)	
		[d]p	***0,001****	***0,001****	
	Difference	*Mean±SD*	0,99±0,82	1,11±0,78	
Girls	**CA**	*Mean±SD*	11,17±2,36	10,09±2,41	***0,082***
		Median (Min-Max)	11 (6,4-14)	10,2 (6-14)	

	DA	*Mean±SD*	11,61±2,80	10,46±3,07	***0,138***
		Median (Min-Max)	11,3 (5,7-15,8)	10,4 (5-15,8)	
		[d]p	***0,001****	***0,001****	
	Difference	*Mean±SD*	0,30±1,06	0,44±0,94	

*[a]Student-t Test. [d]Paired Samples-t Test.**p<0,01*

The differences between DA and CA varied from -0.43 to 1.48 years. It was the mean difference that was compared between the two groups *(Table 7)*. The mean difference between DA and CA was not significantly different between the PRD and HC groups.

Table 7 (The comparison of DA and CA of boys and girls in the PRD group based on the type of medication they have used.)

			Type of medication		
			Biological	Non-Biological	***[e]p***
Boys	**CA**	*Mean±SD*	10,54±2,50	9,74±2,42	***0,346***
		Median (Min-Max)	10,6 (7-13,8)	9,8 (6-14)	
	DA	*Mean±SD*	12,02±2,95	10,67±2,84	***0,179***
		Median (Min-Max)	11,6 (7,4-16,6)	10,4 (4,5-16,6)	
		[d]p	***0,001****	***0,001****	
	Difference	*Mean±SD*	1,48±0,97	0,93±1,04	
Girls	**CA**	*Mean±SD*	9,51±2,38	10,30±2,41	***0,277***
		Median (Min-Max)	9,5 (6-13,3)	10,5 (6-14)	
	DA	*Mean±SD*	9,07±2,86	10,97±3,02	***0,059***

	Median (Min-Max)	9,4 (5-13,8)	11 (6,2-15,8)
	[d]p	***0,001*****	***0,001*****
Difference	*Mean±SD*	-0,43±0,85	0,67±1,07

aStudent-t Test. dPaired Samples-t Test.**p<0,01

Willems method tended to overestimate the dental age of boys in the PRD group who were using non-biological medication by an average of 0.93±1.04 years, while it tended to overestimate the age of those using biological medication by an average of 1.48±0.97 years. The approach underestimated the dental age of girls using biological medication by 0.43±0.85 years while overestimating the age of girls using non-biological medication by an average of 0.67±1.07 years *(Table 7)*. Three of the patients using biological medication were also receiving steroid treatment simultaneously.

In our study, it was found that the difference between DA and CA was higher in girls and boys in the PRD group who were taking medication; however, this difference was not significant. The presence of disease, medication use, and the type of medication used did not affect the estimations (p>0.05).

DISCUSSION

The estimation of DA in children and young adults constitutes a critical technique that provides essential information within forensic science, anthropological studies, pediatric dentistry, endocrinology, and orthodontic practice. This methodology involves synthesizing information derived from detailed assessments of developing dentition, achievable through both direct clinical evaluations and radiographic analysis [19]. The objective of our study was to examine the effect of PRD, the influence of medication usage, and the specific type of medication on DA. Additionally, we researched the validity of Willems method for age estimation in the Turkish population and attempted to determine whether other methods should be developed in this regard.

Growth-related dental problems, such as malocclusion, delayed tooth eruption, and discrepancies in jaw growth, can significantly impact an individual's oral health, function, and aesthetics (20). Traditionally, skeletal maturity assessment is determined through hand-wrist radiographs. While primarily used to assess dental conditions, panoramic radiographs can also provide valuable insights into skeletal maturity. The degree of root development of certain teeth, like the second molars, correlates with skeletal development stages. Hand-wrist radiographs, although highly reliable, require additional radiographic exposure and are considered more invasive compared to panoramic radiographs. Panoramic radiographs offer a less invasive alternative that can be used to gather essential information on a patient's developmental stage, especially useful in orthodontic settings where panoramic radiographs are routinely taken for dental evaluation. In addition, the interpretation of hand-wrist radiographs is complicated by factors such as polymorphism and sexual dimorphism that can lead to variability in assessing skeletal maturity. By providing a safer, less variable, and potentially more informative approach to evaluating growth and maturity, panoramic radiographs can significantly

enhance the accuracy and efficacy of dental treatment planning, ensuring interventions are timely and aligned with the patient's growth patterns [21].

Demirjian, Cameriere European Formula, and Willems are the major radiographic methods for measuring tooth development in the first seven left-sided permanent mandibular teeth. Demirjian method has been used to estimate DA in individuals with unilateral complete cleft lip and palate, neurofibromatosis type 1, Down syndrome, and cleidocranial dysplasia. This method tends to overestimate DA and its accuracy is influenced by ethnic variations. Many investigations across many groups have shown the accuracy and reliability of Willems method and Cameriere European formula for age estimation. This validation led us to use these approaches for children with PRD for dental age estimation [21]. To the best of our knowledge, this study is the first to employ the Willems method for assessing DA in individuals affected by PRD, including those treated with biological therapies as well as those without such treatment. Therefore, no data from other investigations are available for comparing our findings. The findings of Altan et al., who investigated the efficacy and precision of the Willems method among Southern Turkish children, align with our results, particularly noting higher accuracy in girls [22]. Similarly, Koc et al. determined through their study, which compared the London Atlas, Willems method, and the Nolla method, that Willems method was the most appropriate for estimating DA in Eastern Turkish children [23]. Furthermore, research by Apaydin and Yasar, which assessed Demirjian method, Willems method, and Cameriere formula, concluded that Willems method was the most reliable for Turkish children. [24] Conversely, Ozveren et al.'s studies suggested that while Cameriere method showed marginally superior performance, both Cameriere and Willems methods are viable for dental age estimation in the Turkish population, offering a slight contrast to the uniform preference for the Willems method seen in other studies [25].

The first findings of this research emphasize the consistency in the assessments conducted by the researchers. The ICC values for all cases in the PRD and HC groups were found to be 1.00, indicating a very high degree of agreement between CA and DA across the entire sample. This high degree of concordance suggests that Willems method is a reliable tool for estimating CA based on DA in pediatric populations, with similar effectiveness observed regardless of gender. The gender-specific analyses reveal slightly higher concordance for boys compared to girls. Furthermore, existing literature on dental age estimation suggests that methods based on assigning developmental stages may be superior to those involving direct measurements. Consistent with this perspective, the methodology employed in our study avoided measurement-based approaches, in favor of stage allocation, thereby replacing continuous variables with categorical ones [26].

The scientific literature supports the inclusion of control groups in observational studies to enable comparable and more reliable outcomes. Ratios above 1:2 (case: control) are recommended to detect potential alterations in case groups, with the control group providing proper statistical support to identify these changes [21]. In the current study, a control group of healthy children was established, noting that there was no statistical difference between the average CA of the children included in the PRD and the HC group. More specifically, the CA of boys in the PRD group had a mean age of 9.77 ±2.39 compared to the HC group, which had a mean of 9.89±2.53 years, indicating no statistically significant difference. The DA for boys in the PRD group had a mean of 10.85, slightly differing from the HC group's

mean of 10.88, again showing no significant difference. For girls, the PRD group reported a mean CA of 10.39 years, while the HC group was slightly lower at 9.67 years.

Willems method has been found to overestimate the DA of a healthy population [27, 28]. In our study, parallel to these results, regardless of the group, boys tend to exhibit a DA that is significantly advanced compared to their CA. The difference between DA and CA is less pronounced in girls than in boys but still indicates that DA is slightly ahead of CA in both groups.

Lehtinen and colleagues estimated the DA of children using Demirjian method in a study conducted on Finnish children. The groups consisted of both healthy and JIA children. The study also investigated the effect of cortisone usage on DA. As a result, the method tended to overestimate the dental age of children in both the JIA and healthy groups. In the group receiving corticosteroid treatment DA was estimated to be advanced, but no significant difference was found [17]. Pinchi and colleagues have also used Demirjian method in addition to Willems method, which we have used in our study. In the study aiming to examine age estimation in children with and without JIA treatment and compare it with healthy individuals, it was found that Willems method tended to underestimate age, while Demirjian method tended to overestimate age. It was observed that the use of steroids and the presence of the disease did not have an impact on the tooth calcification process. [18]. The different outcomes might be explained by the sample's origin, which depicts a different population. In our study, we used Willems method, which we deemed to be a reliable method for dental age estimation in Turkish children. [23-25]

A vast amount of literature exists that describes how and how much skeletal growth is affected, by nutritional and even socioeconomic conditions, congenital chromosomic and metabolic anomalies, and systemic illnesses [29-31]. The pathogenesis of growth disorders is multifactorial and includes the role of chronic inflammation, long-term use of supra-physiological doses of corticosteroids, undernutrition, altered body composition with lean mass reduction, physical inactivity, delays of pubertal onset or slow pubertal progression. Also, the degree, extent, and duration of disease activity are important, like the age at onset of the disease. These factors can exert a systemic effect on the GH-IGF-1 axis, or a local influence on the growth plate homeostasis and function. Growth suppression in children on prolonged corticosteroid therapy has long been recognized: a combination of neuroendocrine disturbance, including reduced growth hormone level, and a direct effect on bone and connective tissue metabolism is the major mechanism. Further, the type of steroid, the administration regimen, and the treatment period have been considered important regarding the severity of tissue damage [32]. It is noted that biological treatments may reduce systemic inflammation and have a corticosteroid-sparing effect. Many studies have reported that anti-TNF treatments, the most widely used biologics, improve growth in patients with JIA [33].

There are very few studies that test the influence of systemic disorders on the dental mineralization process. Generally, the dental development process is considered unaffected by severe illnesses such as syndromic pathologies. Therefore, the process of dental mineralization is regarded as very stable and unaffected by changes in overall growth. However, specific literature exists regarding pathological conditions that can affect tooth calcification [18]. A deeper look at the dental maturation in children under medication or not and with and without biological treatment was taken and provided another outcome of this study. Although the differences in DA and CA were statistically significant in both groups

in the study, the comparison between the two groups (medication use vs. no medication use) did not show a statistically significant difference in the acceleration of DA. Besides, the dental maturation comparisons between biological and non-biological medication users for both DA and CA among boys and girls were performed. The findings hint at distinct effects of biological and non-biological medications on dental development, with biological medications appearing to accelerate DA in boys but potentially delay it in girls. This divergence suggests that the impact of medication on dental development might be influenced by biological sex, the nature of the medication, and perhaps the underlying condition being treated. This result may be related to the fact that biological medications that modulate immune responses might influence the timing of tooth eruption or dental development in complex ways [34]. The contrasting findings between boys and girls, especially with biological medications, could be due to differences in hormonal influences, medication dosages, or the diseases being treated. Some studies have suggested that gender can play a role in the pharmacokinetics and pharmacodynamics of drugs, potentially leading to differing outcomes in drug effects [35]. The results of this study should be interpreted with caution, primarily because of the relatively small number of patients having biological therapy. Therefore, there is a possibility that the deviations in dental maturity from CA would be different between genders having biological treatment and those without this condition if the sample contained a larger number of patients.

Our study is subject to several potential limitations. Firstly, the inability to categorize patients with PRD into specific subgroups (for instance, JIA, Thalassemia, etc.) due to the reliance on cross-sectional data precluded us from identifying any variances in dental development attributable to different childhood rheumatic disease etiologies and functional statuses. Secondly, the relatively small cohort of childhood rheumatic disease patients who underwent biological therapy might also limit the generalizability of our findings. Despite these constraints, it is important to highlight that, this study marks the first attempt to employ Willems method for estimating DA in children with childhood rheumatic diseases undergoing biological treatment.

Another finding that can be drawn from this study, despite being based on a small sample, is that the Willems method tends to overestimate DA in both healthy children and children with PRD.

CONCLUSION

No significant differences in estimates emerged between the gender and the treated and non-treated subjects affected by PRD. Willems method tended to underestimate the age of girls undergoing biological treatment, while it tended to overestimate the age of all other groups. However, further studies are required to ascertain whether accelerated dental development in children with PRD is inherent to the disorder itself or a consequence of the treatment, including the medication administered.

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REFERENCES

1. Maber M, Liversidge H, Hector M. Accuracy of age estimation of radiographic methods using developing teeth. Forensic science international. 2006;159:S68-S73.
2. Tunc ES, Koyuturk AE. Dental age assessment using Demirjian's method on northern Turkish children. Forensic science international. 2008;175(1):23-6.
3. Cameron N. Can maturity indicators be used to estimate chronological age in children? Annals of human biology. 2015;42(4):302-7.
4. Cameriere R, Ferrante L. Age estimation in children by measurement of carpals and epiphyses of radius and ulna and open apices in teeth: a pilot study. Forensic science international. 2008;174(1):60-3.
5. Cameriere R, Ferrante L, Cingolani M. Age estimation in children by measurement of open apices in teeth. International journal of legal medicine. 2006;120:49-52.
6. Willems G, Van Olmen A, Spiessens B, Carels C. Dental age estimation in Belgian children: Demirjian's technique revisited. Journal of forensic sciences. 2001;46(4):893-5.
7. Demirjian A, Goldstein H, Tanner JM. A new system of dental age assessment. Human biology. 1973:211-27.
8. Harris E, Hullings J. Delayed dental development in children with isolated cleft lip and palate. Archives of oral biology. 1990;35(6):469-73.
9. Jaffe EC, Roberts G, Chantler C, Carter J. Dental maturity in children with chronic renal failure assessed from dental panoramic tomographs. J Int Assoc Dent Child. 1990;20(2):54-8.
10. Mahaney M. Delayed dental development and pulmonary disease severity in children with cystic fibrosis. Archives of Oral Biology. 1986;31(6):363-7.
11. MYLLÄRNIEMI S, LENKO HL, PERHEENTUPA J. Dental maturity in hypopituitarism, and dental response to substitution treatment. European Journal of Oral Sciences. 1978;86(5):307-12.
12. Sterba Y, Ilowite N. Biologics in Pediatric Rheumatology: Quo Vadis? Curr Rheumatol Rep. 2016;18(7):45.
13. Pilania RK, Singh S. Rheumatology Panel in Pediatric Practice. Indian Pediatrics. 2019;56:407-14.
14. Spradley MK. Metric methods for the biological profile in forensic anthropology: sex, ancestry, and stature. Academic forensic pathology. 2016;6(3):391-9.
15. Laaksonen A-L. A prognostic study of juvenile rheumatoid arthritis. Analysis of 544 cases. Acta Paediatrica Scandinavica. 1966:1-163.
16. Bhattad S, Mohite RS, Singh N. Growth and development in children with rheumatic diseases: Maintaining a balance between drugs and disease activity. Indian Journal of Rheumatology. 2023;18(Suppl 1):S38-S43.
17. Lehtinen A, Oksa T, Helenius H, Rönning O. Advanced dental maturity in children with juvenile rheumatoid arthritis. European Journal of Oral Sciences. 2000;108(3):184-8.

18. Pinchi V, Bianchi I, Pradella F, Vitale G, Focardi M, Tonni I, et al. Dental age estimation in children affected by juvenile rheumatoid arthritis. International Journal of Legal Medicine. 2021;135:619-29.
19. Liversidge HM. The assessment and interpretation of Demirjian, Goldstein and Tanner's dental maturity. Annals of human biology. 2012;39(5):412-31.
20. Marinelli A, Giuntini V, Franchi L, Tollaro I, Baccetti T, Defraia E. Dental anomalies in the primary dentition and their repetition in the permanent dentition: a diagnostic performance study. Odontology. 2012;100:22-7.
21. Marinkovic N, Zelic K, Milovanovic P, Milutinovic J, Djuric M, Nikodijevic Latinovic A, et al. Dental age and skeletal maturity assessment in patients with cerebral palsy. European Journal of Oral Sciences. 2021;129(3):e12780.
22. Altan HO, Altan A, Bilgiç F, Sözer ÖA, Damlar I. The applicability of Willems' method for age estimation in southern Turkish children: A preliminary study. Journal of forensic and legal medicine. 2016;38:24-7.
23. Koç A, Özlek E, Öner Talmaç AG. Accuracy of the London atlas, Willems, and Nolla methods for dental age estimation: a cross-sectional study on Eastern Turkish children. Clinical Oral Investigations. 2021:1-8.
24. Apaydin B, Yasar F. Accuracy of the demirjian, willems and cameriere methods of estimating dental age on turkish children. Nigerian journal of clinical practice. 2018;21(3):257-63.
25. Ozveren N, Serindere G, Meric P, Cameriere R. A comparison of the accuracy of Willems' and Cameriere's methods based on panoramic radiography. Forensic science international. 2019;302:109912.
26. Gabardo G, Maciel JVB, Franco A, de Lima AAS, da Costa TRF, Fernandes Â. Radiographic analysis of dental maturation in children with amelogenesis imperfecta: A case-control study. Special Care in Dentistry. 2020;40(3):267-72.
27. Wang J, Ji F, Zhai Y, Park H, Tao J. Is Willems method universal for age estimation: A systematic review and meta-analysis. Journal of Forensic and Legal Medicine. 2017;52:130-6.
28. Paz Cortés MM, Rojo R, Alía García E, Mourelle Martínez MR. Accuracy assessment of dental age estimation with the Willems, Demirjian and Nolla methods in Spanish children: Comparative cross-sectional study. BMC pediatrics. 2020;20:1-9.
29. Guzman J, Kerr T, Ward LM, Ma J, Oen K, Rosenberg AM, et al. Growth and weight gain in children with juvenile idiopathic arthritis: results from the ReACCh-Out cohort. Pediatric Rheumatology. 2017;15:1-11.
30. MacRae V, Wong S, Farquharson C, Ahmed S. Cytokine actions in growth disorders associated with pediatric chronic inflammatory diseases. International Journal of Molecular Medicine. 2006;18(6):1011-8.
31. McErlane F, Carrasco R, Kearsley-Fleet L, Baildam EM, Wedderburn LR, Foster HE, et al., editors. Growth patterns in early juvenile idiopathic arthritis: Results from the Childhood Arthritis Prospective Study (CAPS). Seminars in Arthritis and rheumatism; 2018: Elsevier.

32. Wang S-J, Yang Y-H, Lin Y-T, Yang C-M, Chiang B-L. Attained adult height in juvenile rheumatoid arthritis with or without corticosteroid treatment. Clinical rheumatology. 2002;21:363-8.
33. d'Angelo DM, Di Donato G, Breda L, Chiarelli F. Growth and puberty in children with juvenile idiopathic arthritis. Pediatric Rheumatology. 2021;19:1-13.
34. Marks Jr SC, Schroeder HE. Tooth eruption: theories and facts. The Anatomical Record: An Official Publication of the American Association of Anatomists. 1996;245(2):374-93.
35. Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. Clinical pharmacokinetics. 2009;48(3):143-57.