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Dental age and tooth development in children with molar-incisor hypomineralization: A case-control study

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ABSTRACT

Objective: The aim of the study was to determine the dental age for the evaluation of tooth development in children with molar-incisor hypomineralization (MIH) by using the Willems method, Cameriere-European formula, and London Atlas.

Design: Panoramic radiographs of 308 children between the ages of 6–13 diagnosed with MIH and the same number of sex- and age-matched children without MIH were evaluated by two different examiners using the Willems method, Cameriere-European formula, and London Atlas. The mean difference between chronological age and dental age in both groups was calculated for each sex and age. The mean absolute error was used to determine the accuracies of the Willems method, Cameriere-European formula, and London Atlas.

Results: There was a statistically significant difference found only in Willems method in dental age estimation between the groups with and without MIH ($P = 0.001$). In the evaluation performed with Cameriere-European formula and London Atlas, which are more accurate methods for dental age estimation in both groups, no statistically significant difference was found in dental age estimation between the two groups ($P = 0.322$, $P = 0.290$, respectively). There was a statistically significant intense linear correlation for three methods in both groups ($P < 0.001$).

Conclusions: MIH, which is a developmental enamel defect, does not affect dental age and tooth development since there was no significant difference between groups with and without MIH according to the evaluations made with accurate dental age estimation methods.

1. Introduction

Age estimation methods have wide application areas in fields such as archeology, anthropology, forensic sciences, pediatric dentistry, and orthodontics (Bagattoni, D'Alessandro, Gatto, & Piana, 2019). Anthropometric parameters of individuals, sexual maturation status and hand-wrist or dental panoramic radiographs are used in age estimation. Although radiographical age estimation methods are often developed for populations with the same ethnicity, they should be evaluated across all populations to determine their forensic reliability (Cummaudo et al., 2021). In addition to evaluating the characteristics of teeth such as size, morphology, specific tooth wear and color, knowing the developmental characteristics of teeth at different ages makes it possible to use dental age estimation methods (Kirzioglu, Ceyhan, & Bayraktar, 2019). Dental age estimation research has focused on maximizing the accuracy of age estimation approaches in order to keep the frequency of amiss decisions in legal proceedings as low as possible (Gelbrich, Carl, & Gelbrich, 2020).

Different methods and approaches based on dental radiographs are used in dental age estimation and maturation. One of these methods is the Willems method (Willems, Van Olmen, Spiessens, & Carels, 2001), which is a modification of the Demirjian method (Demirjian, Goldstein, & Tanner, 1973) transformation steps and was first developed in 2001. In 2006, a novel method using the linear regression formula was developed (Cameriere, Ferrante, & Cingolani, 2006). It is a measuremental method based on the ratio between the open apices and the total length of teeth. This method was developed and tested over time, and the Cameriere-European formula that can be used for children in

Abbreviations: MIH, Molar-incisor hypomineralization.

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Table 1
The agreement between the dental age and the chronological age according to the sex and dental age estimation methods in children with and without MIH.

Sex	With MIH			Without MIH		
	ICC^{LA} (95% CI)	ICC^{CF} (95% CI)	ICC^{WM} (95% CI)	ICC^{LA} (95% CI)	ICC^{CF} (95% CI)	ICC^{WM} (95% CI)
Boy	0.94	0.93	0.93	0.98	0.95	0.96
Girl	0.94	0.95	0.92	0.97	0.95	0.96
Total	0.94	0.94	0.93	0.98	0.95	0.96

MIH: Molar-incisor hypomineralization; ICC: Intraclass correlation coefficient; LA: London Atlas; CF: Cameriere-European Formula; WM: Willems Method; CI: Confidence interval.

European countries was introduced in 2007 (Cameriere, De Angelis, Ferrante, Scarpino, & Cingolani, 2007). The London Atlas (AlQahtani, Hector, & Liversidge, 2010), developed in 2010, consists of a series of schematic images created for certain ages. By examining the reference images in the atlas which was developed based on evidence and available in many languages, the best-matched image to the individual's panoramic radiography is determined (Gelbrich et al., 2020).

Molar-incisor hypomineralization (MIH) was first described in 2001 as a developmental enamel defect in which at least one first permanent molar and often incisors are affected (Weerheijm, Jälevik, & Alaluusua, 2001). Although studies on MIH have increased in recent years, its etiology has not been fully clarified yet. It is thought that prenatal and perinatal factors, early childhood illnesses and the medications used in this period, long-term breastfeeding, environmental factors, along with genetic and epigenetic determinants may cause MIH (Silva, Scurrah, Craig, Manton, & Kilpatrick, 2016). It has been suggested that etiological factors linked to enamel forming genes or immune response-related genes have a role in the development of MIH (Hočevar, Kovač, Podkrajšek, Battelino, & Pavlič, 2020; Jeremias et al., 2013; Pang et al., 2020). Thus, defects can occur during amelogenesis when one or more components of dental or dento-skeletal development are compromised as a result of genetic and/or systemic factors (Thesleff, 2006). Given the uncertainty in the etiology of MIH, dental age and development may also be affected in individuals affected by MIH, as these defects may also be affected by genetic and/or systemic factors that may affect the individual's growth and development. In addition, while it can be assessed the dental age of children with normal tooth structure, it is unclear if dental age estimation methods can be obtained as a reliable outcome for children with MIH.

The aim of the study was to determine the dental age for the evaluation of tooth development in children with MIH by three different dental age estimation methods. The first null hypothesis tested was that there would be no difference between children with and without MIH on tooth development and dental age estimation, and the second null hypothesis tested was that Willems method, Cameriere-European formula, and London Atlas would predict the dental age with the same accuracy.

2. Materials and methods

2.1. Ethical approval and study population

This cross-sectional study was approved by the Çanakkale Onsekiz Mart University Faculty of Medicine Clinical Researches Ethical Committee (protocol no. 2020-05). For this study, panoramic radiographs from Turkish children (ages range from 6 to 13 years) who were diagnosed with MIH and in a group of sex- and age-matched without MIH, were selected from the archives of the Department of Pediatric Dentistry, School of Dentistry, Marmara University. Panoramic radiographs used in this study were taken between January 2018 and January 2020 for diagnosis and treatment planning within the appropriate indication. Radiographs of patients who came to the clinic with the complaint of any eruption issue or who had a local and/or systemic problem with eruption were not included in the study. The study group patients were determined by sex and age groups, and the control group patients were matched according to the distribution of these groups. The control group patients were randomly selected from the hospital archives in accordance with the inclusion criteria and matched with the study group patients in terms of age and sex.

2.2. Sample size calculation

The sample size was calculated based on a previous study conducted by Koç, Özlek, and Öner Talmaç (2021) using G*Power software (v.3.1.9.7, Universitat Kiel, Kiel, Germany) with the following assumptions: permissible error $\alpha = 0.05$, study power of 0.95, mean differences

Table 2
Comparison of dental age and chronological age for three different dental age estimation methods in both sexes and the total sample with and without MIH.

Sex	With MIH						Without MIH					
	CA mean (SD)	Methods	DA	DA-CA	MAE	*P*-value	CA mean (SD)	Methods	DA	DA-CA	MAE	*P*-value
Boy	9.16 (1.94)	**LA**	8.91 (2.06)	-0.26 (0.90)	0.75 (0.54)	**0.001**[b]		**LA**	9.16 (2.06)	0.02 (0.51)	0.34 (0.40)	0.666[b]
		CF	8.94 (1.76)	-0.22 (0.93)	0.69 (0.47)	**0.004**[b]	9.14 (1.93)	**CF**	9.28 (1.54)	0.14 (0.74)	0.37 (0.25)	**0.022**[b]
		WM	8.77 (2.12)	-0.39 (0.95)	0.77 (0.62)	**< 0.001**[a]		**WM**	9.60 (2.06)	0.46 (0.67)	0.58 (0.41)	**< 0.001**[b]
Girl	9.1 (1.73)	**LA**	9.17 (1.88)	0.07 (0.83)	0.57 (0.39)	0.289[b]		**LA**	9.24 (1.98)	0.15 (0.66)	0.48 (0.46)	**0.004**[b]
		CF	9.13 (1.86)	0.03 (0.80)	0.65 (0.47)	0.644[b]	9.09 (1.78)	**CF**	9.09 (1.53)	0.00 (0.70)	0.38 (0.36)	0.960[b]
		WM	9.02 (1.95)	-0.08 (1.02)	0.83 (0.65)	0.303[a]		**WM**	9.27 (1.85)	0.18 (0.68)	0.59 (0.43)	**0.001**[b]
Total	9.13 (1.83)	**LA**	9.04 (1.97)	-0.09 (0.88)	0.66 (0.47)	0.081[b]		**LA**	9.2 (2.02)	0.09 (0.60)	0.41 (0.43)	**0.010**[b]
		CF	9.04 (1.81)	-0.09 (0.87)	0.67 (0.47)	0.068[b]	9.11 (1.85)	**CF**	9.18 (1.53)	0.07 (0.72)	0.38 (0.31)	0.094[b]
		WM	8.90 (2.03)	-0.23 (1.00)	0.80 (0.64)	**< 0.001**[b]		**WM**	9.43 (1.95)	0.31 (0.69)	0.59 (0.42)	**< 0.001**[b]

DA: Dental age; CA: Chronological age; MIH: Molar-incisor hypomineralization; LA: London Atlas; CF: Cameriere-European Formula; WM: Willems Method; MAE: Mean absolute error; SD: Standard deviation.
All values marked in bold are statistically significant ($P < 0.05$).
[a] Paired *t*-test.
[b] Wilcoxon signed-rank test.

Table 3
Comparison of dental age and chronological age of different dental age estimation methods in children with and without MIH for different age groups for boys.

		With MIH						Without MIH					
Age	N* (%)	CA mean (SD)	Methods	DA	DA-CA	MAE	*P*-value	CA mean (SD)	Methods	DA	DA-CA	MAE	*P*-value
6–6.99	25 (16.9)	6.47 (0.31)	**LA**	6.34 (0.47)	-0.13 (0.47)	0.34 (0.33)	0.172[b]	6.48 (0.28)	**LA**	6.22 (0.54)	-0.26 (0.51)	0.43 (0.32)	**0.018**[b]
			CF	6.91 (0.45)	0.44 (0.38)	0.33 (0.31)	**< 0.001**[b]		**CF**	7.55 (0.18)	1.07 (0.29)	0.15 (0.10)	**< 0.001**[a]
			WM	5.99 (0.87)	-0.49 (0.74)	0.71 (0.49)	**0.003**[a]		**WM**	6.81 (0.73)	0.33 (0.60)	0.60 (0.38)	**0.011**[a]
7–7.99	22 (14.87)	7.53 (0.28)	**LA**	7.41 (0.75)	-0.12 (0.74)	0.50 (0.55)	0.443[b]	7.36 (0.29)	**LA**	7.50 (0.69)	0.15 (0.57)	0.46 (0.51)	0.245[b]
			CF	7.52 (0.45)	-0.02 (0.42)	0.37 (0.26)	0.852[a]		**CF**	7.72 (0.15)	0.36 (0.29)	0.12 (0.10)	**< 0.001**[a]
			WM	7.48 (0.54)	-0.05 (0.55)	0.41 (0.34)	0.648[a]		**WM**	7.90 (0.45)	0.55 (0.39)	0.30 (0.32)	**< 0.001**[a]
8–8.99	26 (17.57)	8.5 (0.31)	**LA**	8.19 (0.93)	-0.31 (0.91)	0.68 (0.62)	0.100[b]	8.46 (0.29)	**LA**	8.54 (0.53)	0.08 (0.60)	0.30 (0.43)	0.507[b]
			CF	8.34 (0.81)	-0.16 (0.74)	0.64 (0.48)	0.281[a]		**CF**	8.31 (0.61)	-0.15 (0.57)	0.52 (0.31)	0.187[a]
			WM	8.02 (1.02)	-0.48 (1.00)	0.64 (0.78)	**0.022**[b]		**WM**	8.88 (0.79)	0.42 (0.77)	0.57 (0.53)	**0.011**[b]
9–9.99	24 (16.21)	9.5 (0.28)	**LA**	9.08 (0.97)	-0.42 (0.91)	0.75 (0.60)	**0.033**[b]	9.65 (0.19)	**LA**	9.58 (0.28)	-0.06 (0.34)	0.15 (0.24)	0.366[b]
			CF	9.28 (0.99)	-0.23 (0.88)	0.86 (0.45)	0.223[b]		**CF**	10.11 (0.42)	0.46 (0.45)	0.35 (0.21)	**< 0.001**[b]
			WM	9.18 (0.93)	-0.32 (0.86)	0.75 (0.53)	0.080[a]		**WM**	10.16 (0.89)	0.51 (0.89)	0.75 (0.46)	**0.010**[a]
10–10.99	17 (11.49)	10.45 (0.3)	**LA**	10.26 (1.15)	-0.18 (1.16)	1.02 (0.47)	0.528[b]	10.46 (0.29)	**LA**	10.50 (0.71)	0.04 (0.55)	0.47 (0.52)	0.746[b]
			CF	9.89 (0.92)	-0.56 (0.92)	0.77 (0.47)	**0.024**[a]		**CF**	10.43 (0.27)	-0.03 (0.24)	0.16 (0.21)	0.662[b]
			WM	9.80 (0.91)	-0.64 (0.88)	0.71 (0.54)	**0.008**[a]		**WM**	11.11 (0.78)	0.65 (0.68)	0.66 (0.37)	**0.001**[a]
11–11.99	23 (15.54)	11.38 (0.28)	**LA**	11.11 (1.03)	-0.27 (1.04)	0.88 (0.51)	0.223[b]	11.35 (0.39)	**LA**	11.54 (0.47)	0.19 (0.33)	0.25 (0.40)	**0.012**[b]
			CF	10.81 (1.10)	-0.57 (1.08)	0.81 (0.72)	**0.019**[a]		**CF**	10.87 (0.58)	-0.49 (0.44)	0.36 (0.44)	**< 0.001**[b]
			WM	11.07 (1.27)	-0.31 (1.22)	1.06 (0.66)	0.229[a]		**WM**	11.89 (0.65)	0.54 (0.47)	0.43 (0.47)	**< 0.001**[a]
12–12.99	11 (7.43)	12.76 (0.43)	**LA**	12.32 (1.33)	-0.44 (1.21)	1.08 (0.70)	0.250[a]	12.56 (0.32)	**LA**	12.59 (0.54)	0.03 (0.57)	0.33 (0.41)	0.849[b]
			CF	11.75 (1.50)	-1.01 (1.56)	1.03 (0.62)	0.058[a]		**CF**	11.70 (1.07)	-0.85 (1.04)	0.96 (0.38)	**0.021**[b]
			WM	12.17 (1.57)	-0.60 (1.50)	1.14 (1.01)	0.215[b]		**WM**	12.70 (0.87)	0.14 (0.84)	0.75 (0.37)	0.582[b]

DA: Dental age; CA: Chronological age; MIH: Molar-incisor hypomineralization; LA: London Atlas; CF: Cameriere-European Formula; WM: Willems Method; MAE: Mean absolute error; SD: Standard deviation.
All values marked in bold are statistically significant ($P < 0.05$).
* The control group consisted of the same number of sex- and age-matched patients.
[a] Paired *t*-test
[b] Wilcoxon signed-rank test.

Table 4
Comparison of dental age and chronological age of different dental age estimation methods in children with and without MIH for different age groups for girls.

		With MIH						Without MIH					
Age	N* (%)	CA mean (SD)	Methods	DA	DA-CA	MAE	*P*-value	CA mean (SD)	Methods	DA	DA-CA	MAE	*P*-value
6–6.99	16 (10)	6.59 (0.3)	**LA**	6.69 (0.40)	0.10 (0.49)	0.31 (0.25)	0.447[b]	6.43 (0.27)	**LA**	6.38 (0.34)	-0.05 (0.39)	0.22 (0.26)	0.586[b]
			CF	6.97 (0.26)	0.38 (0.32)	0.19 (0.18)	**< 0.001**[b]		**CF**	7.36 (0.10)	0.93 (0.28)	0.07 (0.06)	**< 0.001**[b]
			WM	6.75 (1.40)	0.16 (1.34)	0.95 (1.01)	0.641[b]		**WM**	6.64 (0.64)	0.21 (0.50)	0.43 (0.46)	0.114[b]
7–7.99	35 (21.88)	7.51 (0.3)	**LA**	7.36 (0.65)	-0.15 (0.62)	0.49 (0.42)	0.156[b]	7.46 (0.27)	**LA**	7.53 (0.92)	0.07 (0.82)	0.62 (0.70)	0.611[b]
			CF	7.46 (0.56)	-0.05 (0.48)	0.37 (0.41)	0.516[b]		**CF**	7.53 (0.22)	0.07 (0.30)	0.16 (0.14)	0.175[a]
			WM	7.33 (0.79)	-0.18 (0.75)	0.62 (0.49)	0.178[a]		**WM**	7.67 (0.71)	0.21 (0.63)	0.58 (0.40)	0.052[a]
8–8.99	33 (20.63)	8.57 (0.31)	**LA**	8.77 (0.88)	0.20 (0.80)	0.69 (0.52)	0.156[b]	8.42 (0.26)	**LA**	8.50 (0.61)	0.08 (0.58)	0.30 (0.53)	0.437[b]
			CF	8.67 (1.05)	0.10 (0.93)	0.93 (0.47)	0.542[b]		**CF**	8.43 (0.68)	0.01 (0.55)	0.50 (0.45)	0.900[a]
			WM	8.67 (1.11)	0.11 (1.04)	0.91 (0.61)	0.565[a]		**WM**	8.68 (0.88)	0.26 (0.80)	0.68 (0.54)	0.069[a]
9–9.99	25 (15.63)	9.35 (0.25)	**LA**	9.74 (1.01)	0.39 (0.93)	0.79 (0.61)	**0.047**[b]	9.69 (0.22)	**LA**	9.94 (0.82)	0.25 (0.78)	0.67 (0.46)	0.117[b]
			CF	9.41 (0.96)	0.06 (0.87)	0.83 (0.45)	0.724[b]		**CF**	9.97 (0.50)	0.28 (0.52)	0.34 (0.36)	**0.013**[b]
			WM	9.32 (1.00)	-0.03 (0.99)	0.82 (0.55)	0.887[a]		**WM**	9.92 (0.77)	0.24 (0.75)	0.62 (0.44)	0.127[b]
10–10.99	28 (17.5)	10.47 (0.29)	**LA**	10.61 (1.26)	0.14 (1.19)	1.04 (0.67)	0.546[b]	10.46 (0.25)	**LA**	10.86 (0.62)	0.40 (0.60)	0.55 (0.57)	**0.002**[b]
			CF	10.33 (1.10)	-0.14 (0.98)	0.72 (0.81)	0.445[b]		**CF**	10.24 (0.63)	-0.23 (0.67)	0.28 (0.56)	0.085[b]
			WM	10.10 (1.26)	-0.37 (1.17)	0.96 (0.79)	0.108[a]		**WM**	10.57 (0.60)	0.10 (0.62)	0.48 (0.35)	0.381[a]
11–11.99	10 (6.25)	11.5 (0.24)	**LA**	11.60 (0.32)	0.10 (0.36)	0.18 (0.25)	0.422[b]	11.49 (0.29)	**LA**	11.70 (0.42)	0.21 (0.41)	0.32 (0.25)	0.142[b]
			CF	11.41 (1.13)	-0.10 (1.12)	0.92 (0.58)	0.792[b]		**CF**	10.84 (0.46)	-0.65 (0.30)	0.37 (0.25)	**< 0.001**[a]
			WM	11.38 (1.00)	-0.12 (1.02)	0.76 (0.60)	0.711[a]		**WM**	11.62 (0.58)	0.13 (0.42)	0.51 (0.23)	0.353[a]
12–12.99	13 (8.13)	12.52 (0.36)	**LA**	12.04 (0.52)	-0.48 (0.59)	0.50 (0.04)	**0.012**[b]	12.52 (0.4)	**LA**	12.58 (0.86)	0.06 (0.64)	0.71 (0.44)	0.754[b]
			CF	12.57 (0.74)	0.05 (0.68)	0.62 (0.37)	0.791[a]		**CF**	11.63 (1.19)	-0.89 (1.04)	0.93 (0.69)	**0.010**[a]
			WM	12.45 (0.95)	-0.08 (0.88)	0.77 (0.50)	0.763[a]		**WM**	12.43 (1.02)	-0.09 (0.91)	0.80 (0.59)	0.728[a]

DA: Dental age; CA: Chronological age; MIH: Molar-incisor hypomineralization; LA: London Atlas; CF: Cameriere-European Formula; WM: Willems Method; MAE: Mean absolute error; SD: Standard deviation.
All values marked in bold are statistically significant ($P < 0.05$).
* The control group consisted of the same number of sex- and age-matched patients.
[a] Paired *t*-test.
[b] Wilcoxon signed-rank test.

Table 5
Comparison of mean (SD) chronological age and dental age for both sexes and the total sample with and without MIH.

	Sex	With MIH	Without MIH	*P*-value
CA	**Boy**	9.16 (1.94)	9.14 (1.93)	0.906
	Girl	9.10 (1.73)	9.09 (1.78)	0.970
	Total	9.13 (1.83)	9.11 (1.85)	0.910
LA	**Boy**	8.91 (2.06)	9.16 (2.06)	0.297
	Girl	9.17 (1.88)	9.24 (1.98)	0.729
	Total	9.04 (1.97)	9.20 (2.02)	0.322
CF	**Boy**	8.94 (1.76)	9.28 (1.54)	0.083
	Girl	9.13 (1.86)	9.09 (1.53)	0.859
	Total	9.04 (1.81)	9.18 (1.53)	0.290
WM	**Boy**	8.77 (2.12)	9.60 (2.06)	**0.001**
	Girl	9.02 (1.95)	9.27 (1.85)	0.234
	Total	8.90 (2.03)	9.43 (1.95)	**0.001**

SD: Standard deviation; CA: Chronological age; MIH: Molar-incisor hypomineralization; LA: London Atlas; CF: Cameriere-European Formula; WM: Willems Method.
All values marked in bold are statistically significant ($P < 0.05$).

(dental age – chronological age) for the Willems method and London Atlas equal 0.80 and 0.83, standard deviations equal 1.02 and 1.07. The effect size was determined as 0.19. For paired *t*-tests, it was concluded that the sample size should be at least 298.

2.3. Sampling criteria

The children included in the study consisted of Turkish children residing in Istanbul and neighboring provinces. The intraoral examination was performed by a single trained examiner (BS) under the same dental unit and reflector, with a smooth-surfaced standard mouth mirror (#5) and tactile inspection with a standard dental probe (PCP11). Teeth affected by MIH were evaluated with the criteria approved by the European Academy of Paediatric Dentistry (EAPD) in 2015 (Ghanim, Elfrink, Weerheijm, Mariño, & Manton, 2015). These criteria include no visible enamel defects, enamel defects that are not associated with MIH, white/creamy and yellow/brown demarcated opacities, post-eruptive enamel breakdown, atypical MIH-specific restorations and caries, tooth loss due to MIH, and unscored conditions (Ghanim et al., 2015).

Children with and without MIH were selected from those without any systemic disease and/or syndrome. Patients with deep caries lesions reached the pulp, periapical or periodontal lesion, the presence of supernumerary teeth and tooth loss for any reason, a history of dental and/or orofacial trauma, previous endodontic and/or orthodontic treatment, and jaw bone pathologies (such as cyst and/or neoplasm) were excluded from the study.

2.4. Panoramic radiographs

Digital panoramic radiographs were taken with the Morita device (VeraView IC5, J. Morita MFG. Corp., Kyoto, Japan), used an exposure time of 8.8 s at 60–70 kV and 7.5 mA at the Oral and Maxillofacial Radiology Clinics, School of Dentistry, Marmara University.

The diagnostic quality of the panaromic radiographs obtained was evaluated according to the criteria of the UK National Radiological Protection Board (Public Health England (PHE) & Faculty of General Dental Practice (UK) (FGDP[UK]), 2020). Based on these criteria: 1 = diagnostically excellent, 2 = diagnostically acceptable, and 3 = diagnostically unacceptable. Grade 1 radiographs do not include exposure, positioning or processing errors. Grade 2 radiographs have some minor exposure, positioning, or processing errors. Grade 3 radiographs contain exposure, positioning, or processing errors and the situation makes it impossible to evaluate the radiograph. In addition, it has been stated that at least 70% of the radiographs should be grade 1 in terms of the validity of the evaluation (Public Health England (PHE) & Faculty of General Dental Practice (UK) (FGDP[UK]), 2020). In this context, only Grade 1 radiographs were evaluated in the study.

2.5. Chronological age calculation

Chronological age of the patients with and without MIH was calculated by using a formula ''[(the date that the panoramic radiograph was taken) − (the recorded birth date)]/365.25'' by Microsoft Excel 2013 (Microsoft, Redmond, WA, USA) in the decimal system.

2.6. Dental age estimation

2.6.1. Willems method

The schematic and radiographic imaging technique for dental age estimation created by Demirjian et al. (1973) was modified in 2001 by

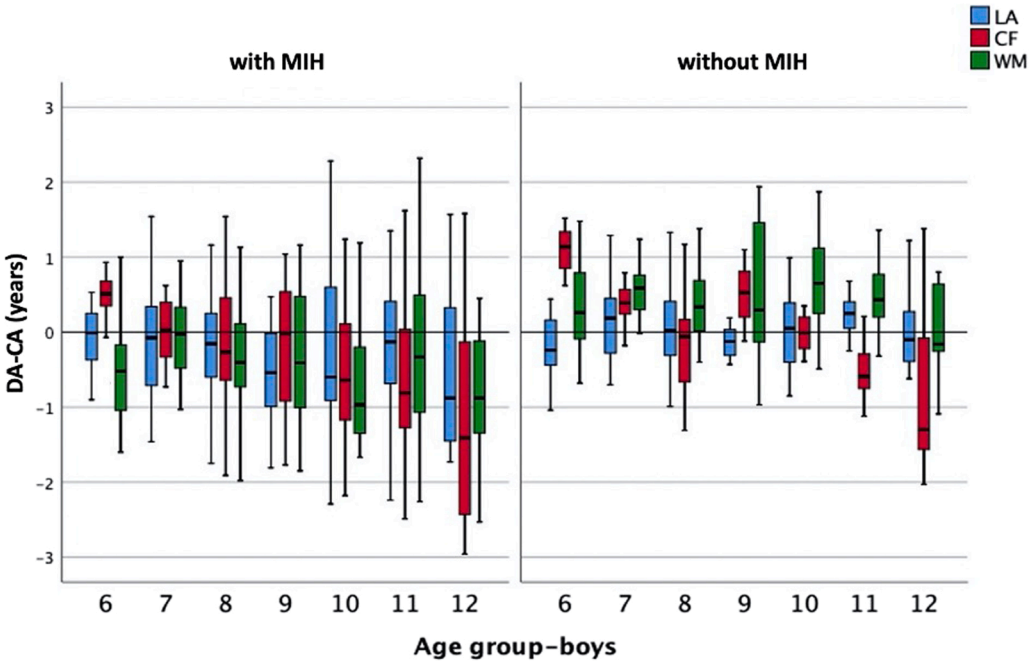


Fig. 1. Boxplots of the relationship between age groups and difference between dental age according to three dental age estimation methods and dental age – chronological age for boys with and without MIH *(DA: dental age; CA: chronological age; MIH: molar-incisor hypomineralization; LA: London Atlas; CF: Cameriere-European Formula; WM: Willems Method) (The interquartile range is represented by the box, the greatest and lowest values are represented by the whiskers, and the median is represented by the horizontal line in the middle.)*.

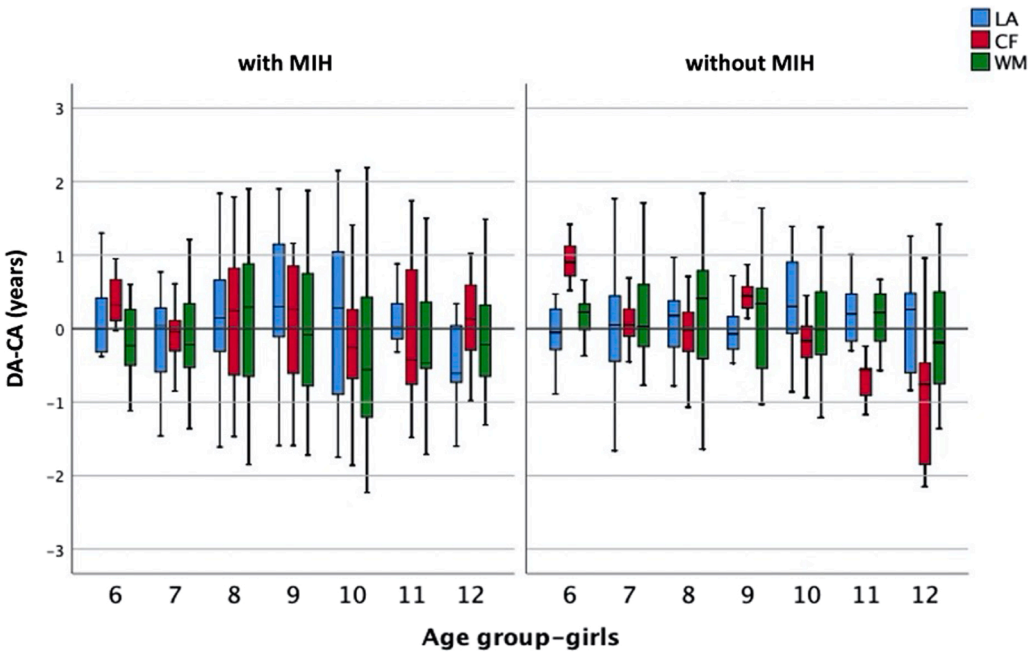


Fig. 2. Boxplots of the relationship between age groups and difference between dental age according to three dental age estimation methods and dental age – chronological age for girls with and without MIH *(DA: dental age; CA: chronological age; MIH: molar-incisor hypomineralization; LA: London Atlas; CF: Cameriere-European Formula; WM: Willems Method) (The interquartile range is represented by the box, the greatest and lowest values are represented by the whiskers, and the median is represented by the horizontal line in the middle.)*.

Willems et al. (2001). According to this method, each tooth in the left mandibular quadrant (except the third molar) was sex-specifically scored from A to H on the panoramic radiograph, and dental age was calculated by summing up the scores of these seven teeth.

2.6.2. Cameriere-European formula

Seven permanent teeth in the left mandibular quadrant were radiographically evaluated according to root development and apical aperture distance with the formula developed by Cameriere et al. (2007) for dental age estimation in European children. The radiographs were transferred to a computer-aided measurement program (ImageJ version 1.49v, U.S. National Institutes of Health, Bethesda, Maryland, USA). The number of teeth that have completed root development was coded as N_0. The distance between the inner faces of the apical opening was measured in teeth with one root with open apex (A_i, i = 1,.,5). For first and second molars, the distance between the inner faces of the two apical openings was measured and summed up (A_i, i = 6,7). The measurement for each tooth was divided by the total length of the tooth (L_i, i = 1,.,7) to normalize possible magnification and angulation differences between radiographs. x_5 is the value obtained by dividing the distance between the inner surfaces of the apical opening of the second premolar tooth by the length of the tooth. The dental age of the patient was calculated by placing the data obtained from all these calculations in the relevant places in the formula (Age = 8.387 + 0.282. g – 1.692. x_5 + 0.835. N_0 – 0.116. s – 0.139. s. N_0) where g is a variable, 1 for boys and 0 for girls. The s value represents the sum of the A_i/L_i ratios of teeth with open apex.

2.6.3. London Atlas

The London Atlas offers reference images for primary and permanent teeth starting from the *in-utero* period, at one-year intervals from the age of 1.5 (AlQahtani et al., 2010). In line with the images presented by the atlas, the examiners chose the image closest to the patient's panoramic radiograph. Root resorptions of primary teeth, and positions in jaws, degrees of root formation, and mineralization of permanent teeth were examined in detail during the evaluation of the images. The age represented by the reference image chosen by the examiners was determined as the dental age of the individual according to the atlas.

2.7. Statistical analyses

The data obtained from all three dental age estimation methods were evaluated separately and collectively for each sex and age group in children with and without MIH. The Kolmogorov-Smirnov test was used to test the normality of age differences between groups with and without MIH in both sexes, the total sample, and each age group. In different dental age estimation methods, the differences between dental age and chronological age were evaluated with the parametric test (paired *t*-test) if they showed normal distribution, and with the non-parametric test (Wilcoxon signed-rank test) if they did not show normal distribution. The mean difference between chronological age and dental age in both groups was calculated for each sex and age. The mean absolute error was used to determine the accuracies of the Willems method, Cameriere-European formula, and London Atlas.

For both sexes in both groups, the Spearman's rank correlation coefficient was used to examine the correlation between chronological age and dental age. The absolute value of the dental age – chronological age and its percentage according to chronological age were calculated to determine the accuracy of all three methods over a one-year period. All statistical analyses were conducted using SPSS Version 20.0 (IBM Corp., Chicago, IL, USA) and *P*-values of less than 0.05 were considered to indicate statistical significance.

The examiner who diagnosed MIH (BS) has been trained and conducted studies on MIH during his postgraduate education period. In addition, he was trained on MIH and other developmental enamel defects with intraoral photographs obtained from thirty patients. The radiographs from these patients were not added to the main study data. This pilot study allowed the calibration of examiner for the assessment and diagnosis of MIH using EAPD criteria (Ghanim et al., 2015). To assess the reproducibility of these criteria, 20% of the patients were re-examined.

Dental age estimations using three different methods were made by two different well-trained examiners (BS, BÇ). Six weeks after the initial evaluation, for the purpose of calibration for examiners and methods, 100 randomly chosen panoramic radiographs were scored twice, two weeks apart, by examiners. Reproducibility measurements and statistics were evaluated with the intraclass correlation coefficient. Intra-examiner reliability was assessed with Cohen's Kappa test.

3. Results

The intra-examiner Kappa values of the examiner that diagnosed to MIH ranged from 0.83 to 0.89. The high degree of agreement was retained during the pilot study process and re-examination periods.

In the radiographic evaluation made based on different dental age estimation methods, the intra- and inter-examiner agreements had intraclass correlation coefficient values of 0.98 and 0.95, respectively. There was no statistically significant difference, the intraclass correlation coefficient values were found to be remarkably strong and reliable.

There were 356 children diagnosed with MIH on clinical examination. Eight children were excluded due to any systemic disease and/or syndrome, 11 due to the presence of periapical and/or periodontal lesion, 3 due to the presence of supernumerary teeth, and 10 due to tooth loss for any reason. Of the remaining 324 children's panoramic radiographs, 16 were excluded because they were Grade 2 or 3 quality. As a result, the radiographs of 308 children diagnosed with MIH were evaluated. The same number of sex- and age-matched children without MIH were selected as the control group.

Table 1 shows the agreement between dental age and chronological age according to the sex and different dental age estimation methods in children with and without MIH. The Cameriere-European formula was found to be more accurate for girls and the London Atlas for boys in the group with MIH. The London Atlas was found to be more accurate than the other two methods in both sexes in the children without MIH.

Table 2 shows that the comparison of dental age and chronological age for three different dental age estimation methods in both sexes and total sample for both groups. Willems method, Cameriere-European formula, and London Atlas caused underestimations of the age with MIH group (dental age – chronological age by 0.09, 0.09, and 0.23 years, respectively). On the other hand, without MIH group, the results of all three methods were observed as overestimated compared to chronological age (dental age – chronological age by 0.09, 0.07, and 0.31 years, respectively). The data obtained from the both groups were also evaluated separately in terms of sex and age groups. Table 3 shows the comparison of chronological age and dental age of different dental age estimation methods in both groups for different age groups for boys. In the group with MIH, overestimation was observed with the Camerie-re-European formula only in the age range of 6–6.99 years (dental age – chronological age by 0.44 years), and underestimation was observed in all methods in all other age ranges. Underestimation was observed in the group without MIH, in the 6 and 9 years of age with the London Atlas (dental age – chronological age by 0.26 and 0.06 years, respectively), and in the 8, 10, 11, and 12 years of age with the Cameriere-European formula (dental age – chronological age by 0.15, 0.03, 0.49, and 0.85 years, respectively). Overestimation was found in all age groups with the Willems method. Table 4 shows the comparison of chronological age and dental age of three methods in groups with and without MIH for different age groups for girls. In the group with MIH, in all three methods, overestimation was observed in 6 (dental age – chronological age by 0.10, 0.38, and 0.16, respectively) and 8 years of age (dental age – chronological age by 0.20, 0.10, and 0.11, respectively), while in the 7–7.99 years of age, underestimation was observed (dental age – chronological age by 0.15, 0.05, and 0.18, respectively). On the other hand, in all three methods, overestimation was observed in the 7 (dental age – chronological age by 0.07, 0.07, and 0.21, respectively), 8 (dental age – chronological age by 0.08, 0.01, and 0.26, respectively), and 9 years of age (dental age – chronological age by 0.25, 0.28, and 0.24, respectively) in the group without MIH.

When the chronological age and the ages determined by three different dental age estimation methods were compared between the group with and without MIH, there was a statistically significant difference only in the Willems method ($P = 0.001$). According to the London Atlas and Cameriere-European formula, which are more accurate in dental age estimation in both groups, no statistically significant difference was observed between the groups with and without MIH in terms of dental age ($P = 0.322$, $P = 0.290$, respectively) (Table 5). The relationship between the dental age – chronological age and the three dental age estimation methods in different age groups in boys with and without MIH is shown in Fig. 1, and Fig. 2 shows the same relationship in girls with and without MIH.

Spearman correlation coefficient test was used to analyze (dental age – chronological age) in groups with and without MIH for both sex and dental age estimation methods. The results showed that an intense linear correlation for three methods (ranging from 0.854 to 0.903 in the group with MIH, and ranging from 0.922 to 0.969 in the group without MIH) was statistically significant ($P < 0.001$).

4. Discussion

Ameloblasts, the cells responsible for enamel formation, are characterized by the expression of stage-specific genes such as *IRF6*, *MMP20,* and *KLK4* during the secretion and maturation stages of amelogenesis (Babajko, Jedeon, Houari, Loiodice, & Berdal, 2017; Chu et al., 2016; Hočevar et al., 2020; Zheng et al., 2014). Developmental enamel defects arise when a problem occurs in the secretion and/or maturation phases under the influence of different etiological factors (da Cunha Coelho et al., 2019). Although the etiology of MIH has not been fully elucidated yet, studies show that various diseases with prolonged periods of fever and/or various mediators formed by the immune response against these diseases may affect tooth development and cause MIH (Bussaneli et al., 2019; Fatturi et al., 2019; Sidaly et al., 2015). This indicates that various diseases and inflammatory conditions, especially those of genetic origin and/or pre-, peri- and/or post-natal periods, can cause MIH. Therefore, MIH, which is a developmental type of enamel defect, is likely to emerge as a finding in diseases that are affected by systemic and skeletal development, and tooth eruption.

Although developmental enamel defects may be caused by systemic and genetic factors that may affect the growth and development of the individual and therefore dental age, there are few studies evaluating the relationship between developmental enamel defects and tooth development. Tunc, Ulusoy, Bayrak, and Cankaya (2013) hypothesized that tooth development may be slower in hypomineralized enamel and root growth can also be affected by this situation. In their study to test this hypothesis, they evaluated tooth development in patients with severe MIH using the Demirjian method and reported that there was no statistically significant difference in terms of tooth development between groups with and without MIH. However, the most important limitation of their study is that they only evaluated severe MIH patients. In severe MIH patients, due to the rapid structural destruction and post-eruptive enamel breakdown observed in hypomineralized enamel, atypical caries reaching the pulp, which often affects root development, and tooth loss due to MIH are observed. For this reason, patients with pulpal and/or periodontal lesions that may affect the tooth and root development were not included in our study. In addition, patients who lost any of their permanent teeth for any reason were also excluded from the study, since the true cause of tooth loss was not known. There are studies on tooth development in children diagnosed with amelogenesis imperfecta, another developmental enamel defect with hypomineralized enamel findings of genetic origin. The results of Seow's study (Seow, 1995) show that tooth development is more accelerated in children with amelogenesis imperfecta. In the study of Kirzioglu et al. (2019), dental development in children with and without amelogenesis imperfecta was evaluated radiographically using three different dental age estimation methods. The results of their study indicate that amelogenesis imperfecta has no effect on tooth development and therefore on dental age. Finally, in the study of Gabardo et al. (2020), which investigated the effects of amelogenesis imperfecta on tooth and root development using the Demirjian method and Willems method, it was reported that dental maturation was similar in children with and without amelogenesis imperfecta. According to the results of our study, tooth development was found to be statistically slower in boys and the total sample with MIH in

the evaluation performed only with the Willems method ($P = 0.001$, $P = 0.001$, respectively). In the evaluations made with other methods, no statistically significant differences were observed between the groups with and without MIH in terms of tooth development. The first null hypothesis (there is no difference between children with and without MIH on tooth development and dental age estimation) was therefore partially rejected.

It is very important to correctly estimate the age of an individual in criminal and civil law (Koç et al., 2021). Since child labor and child marriages are problems that societies are sensitive to and need to overcome, the issue of age has gained more importance. Therefore, age estimation is a phenomenon used in legal, sociological, and forensic issues. In the dental age estimation methods used for this purpose, the closer the dental age – chronological age difference is to zero, the higher the success of the dental age estimation method gets. In addition, as the mean absolute error value decreases, the success of the method increases. Different methods have been used in dental age estimation studies with Turkish children living in different geographical regions of Turkey. In the study of Ercalikyalcinkaya, Dumlu, Bekiroglu, Kizilyel, and Kargul (2013), in which they evaluated the dental age estimation by Demirjian method in northwestern Turkish children, which was also the population evaluated in our study, it was reported that this method was not suitable for northwestern Turkish children. Koç et al. (2021) evaluated the panoramic radiographs of eastern Turkish children using the London Atlas, Willems method and Nolla method. They reported that the most appropriate dental age estimation method in these children was the Willems method, followed by the London Atlas. The result of the study of Çarıkçıoğlu and Değirmenci (2021), in which the radiographs of children living in the northwestern Anatolia region were evaluated using the Willems method, Cameriere formula, and Blenkin-Evans method, showed that the Willems and Blenkin-Evans methods are more suitable than the Cameriere formula. As a result of the study of Apaydin and Yasar (2018) which used the Demirjian method, Willems method, and Cameriere formula, it was reported that the most valid method for Turkish children was the Willems method. On the contrary, Ozveren, Serindere, Meric, and Cameriere (2019) compared the Cameriere formula and Willems method in their study and stated that the Cameriere formula provided a better percentage of accuracy in absolute difference values within one-year. In addition to these studies using the traditional formula introduced by Cameriere et al. (2006), Gulsahi et al. (2015) tested the Cameriere-European formula with the radiographs of Turkish children and concluded that it was accurate. In our study, dental age estimation was performed on panoramic radiographs using the Willems method, Cameriere-European formula, and London Atlas, and these methods' accuracies were compared in groups with and without MIH. The results of our study show that the Cameriere-European formula is accurate in both with and without MIH groups. In addition, the London Atlas was found to be highly accurate in the MIH group, especially for girls, and for boys in the group without MIH. On the other hand, the Willems method was found to be more inaccurate in predicting dental age than the other two methods. Therefore, the second hypothesis of the study, which tested that the three dental age estimation methods were at the same accuracy, was also rejected.

Our study is the first study in the literature in which the effects of MIH on tooth development are evaluated with different dental age estimation methods. It is also the first study in which the Willems method, Cameriere-European formula and London Atlas were used together. Therefore, the results should be evaluated carefully. On the other hand, as a limitation, all of the children included in the study were children living in a single geographic region. Nutritional, socio-economic, socio-cultural and environmental factors can be effective in the development of children living in different regions (Bunyarit et al., 2020). Moreover, factors such as environmental pollution, which is thought to be in the etiology of developmental enamel defects, also vary in different geographic conditions (Kuscu et al., 2009). Therefore, national and international studies in different populations and geographic regions will provide scientific development in this regard. Also, studies on MIH and other developmental enamel defects in larger populations using different methods will help increase the knowledge of tooth development in developmental enamel defects.

In conclusion, according to the evaluations made with accurate dental age estimation methods, molar-incisor hypomineralization does not affect dental age and tooth development. In addition, the estimation of dental age using the Cameriere-European formula and London Atlas in the groups with and without molar-incisor hypomineralization was found to be more accurate than the Willems method in this study.

More studies are needed on tooth development and dental age estimation in developmental enamel defects such as molar-incisor hypomineralization, whose incidence is gradually increasing. Studies to be conducted on this subject will bring along developments in the highly popular molar-incisor hypomineralization and dental age estimation methods.

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CRediT authorship contribution statement

Conceptualization: Berkant Sezer, Burak Çarıkçıoğlu; *Methodology:* Berkant Sezer, Burak Çarıkçıoğlu, Betül Kargül; *Formal analysis, Investigation:* Berkant Sezer, Burak Çarıkçıoğlu; *Writing – original draft:* Berkant Sezer; *Writing – review & editing:* Berkant Sezer, Burak Çarıkçıoğlu, Betül Kargül.

Conflict of Interests

The authors declare that they have no conflict of interest.

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