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Incidence of Dental Discoloration After Tetracycline Exposure in Korean Children: A Nationwide Population-Based Study

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ABSTRACT

Purpose: Tetracycline is not recommended for children under 12 by guideline due to the risk of tooth discoloration. We aimed to assess the incidence of dental discoloration in Korean children prescribed tetracyclines and investigate whether its risk was greater in tetracycline-exposed children than in the general population.

Methods: This population-based cohort study using the Health Insurance Review and Assessment service database included children aged 0–12 years exposed to tetracyclines for at least 1 day between January 2008 and December 2020. The primary outcome was the incidence rate of dental discoloration ≥6 months after prescription, and the standardized incidence ratio (SIR) was evaluated as secondary outcome.

Results: 56,990 children were included—1,735 and 55,255 aged <8 and 8–12 years, respectively. 61% children were prescribed tetracycline for <14 days with mostly second-generation tetracyclines, doxycycline (61%) and minocycline (35%). The 5- and 10-year cumulative incidence rates of dental discoloration were 4.1% (95% confidence interval [CI], 3.0–5.7%) and 5.7% (95% CI, 4.1% to 7.8%), respectively, in the 0–7 years age group and 0.8% (95% CI, 0.7% to 0.9%) and 1.3 (95% CI, 1.1% to 1.4%), respectively, in the 8–12 years age group. Tetracycline exposure did not increase such risk compared to that in the general population (SIR, 1.08; 95% CI, 0.69 to 1.60).

Conclusions: The incidence of dental discoloration was lower than previously suggested. Relieving the age restriction for prescribing tetracyclines may be considered.

Keywords: Tetracycline; Tooth discoloration; Doxycycline; Minocycline; Korea

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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INTRODUCTION

Tetracyclines, including doxycycline, minocycline, and tigecycline, are widely used broad-spectrum antibiotics that inhibit protein synthesis by targeting the 30S ribosomal subunit.[1] These effective but underappreciated antibiotics are the drugs of choice in children with diseases including Rocky Mountain spotted fever (RMSF), malaria, Q fever, and Lyme disease. Furthermore, tetracyclines are an important therapeutic option for macrolide resistant-*Mycoplasma pneumoniae* (MRMP), which is emerging in the Asia-Pacific region.[2-7] However, despite their clinical usefulness, their prescription has been limited due to the risk of permanent dental discoloration in newborns and children aged ≤8 years in the US, Canada, and Taiwan and those aged <12 years in the UK.[8] In Korea, the Food and Drug Administration contraindicates tetracycline prescription <12 years while the Korean Center for Disease Control and Prevention (CDC) restricts the age limit ≤12 years. Nevertheless, a recent study showed that short-term use of doxycycline use did not increase dental discoloration.[9] In line with this, the World Health Organization and US CDC suggested to use tetracyclines for a short course when benefits clearly outweigh risks.[6] However, due to the rarity of this adverse effect, the real-world incidence of dental discoloration has not been evaluated. Thus, there is insufficient evidence to assess whether its risk is increased in children aged 8–12 years, the grey zone of the age restriction in many countries, including Korea.

This study investigated the incidence of dental discoloration in children aged 0–12 years exposed to tetracyclines using a Korean population-based database. In particular, this study aimed to evaluate whether the risk of dental discoloration was greater among children aged 8–12 years than that among those aged 0–7 years. Additionally, we explored whether children exposed to tetracyclines had a higher incidence of dental discoloration than that in the age-matched general population.

MATERIALS AND METHODS

1. Data source

The Health Insurance Review and Assessment (HIRA) service database was used (subject No. M20210129975). The National Health Insurance Service (NHIS) is the universal single payer in Korea, which covers approximately 98% of the Korean population, and the HIRA reviews all NHIS claims. This database includes not only diagnostic code data based on the International Classification of Diseases and Related Health Problems, 10th revision (ICD-10), but also data on prescription codes, healthcare institutions, and demographics (including sex and age).

2. Study design

This nationwide, population-based cohort study included children aged 0–12 years exposed to tetracyclines between January 2008 and December 2020. We included 12 years old children in our study group by adhering to Korean CDC recommendation, which prohibits its prescription ≤12 years. Children who were prescribed tetracyclines in 2008 were excluded as the washout period in order to define those who were prescribed for the first time. The primary outcome was the incidence of dental discoloration ≥6 months after tetracycline exposure. Additionally, standardized incidence rates (SIRs) were calculated to compare the risk of dental discoloration in tetracycline-exposed children to that in the general population. Cases in which the first input date of the dental discoloration diagnosis code was earlier than the first tetracycline prescription date, those in which a dental discoloration diagnosis code was registered within 6 months of the first tetracycline prescription date, and those reporting

death or those lost to follow-up within 6 months of the first tetracycline prescription date were excluded from the tetracycline-exposed group.

3. Cases definition

Tetracycline exposure was defined as having the Anatomical Therapeutic Chemical Classification System (ATC) code corresponding to a tetracycline prescribed for at least 1 day. Cases with diagnosis codes for dental discoloration (K03.6 and K03.7, K00.8 and K00.83) were considered to have dental discoloration. The detailed ICD-10 codes and ATC codes for tetracyclines are listed in **Supplementary Tables 1** and **2**, respectively. Cases with diagnosis codes for comorbidities (**Supplementary Table 3**) within 6 months before the first tetracycline prescription date were considered to have comorbidities. The duration of tetracycline exposure was defined as the total number of tetracycline prescription days from the first tetracycline prescription date to 6 months after the initial prescription.

4. Statistical analysis

Demographic characteristics are presented as percentages and median (interquartile range) for non-normally distributed continuous variables. Cumulative incidence rates of dental discoloration per year were calculated using the Kaplan–Meier estimation with the log-rank test with 95% confidence intervals (CIs). The observation period for dental discoloration was from the tetracycline claim date to <13 years of age. However, for the 8–12 years age group, follow-up was continued until under 24 years of age. We investigated the incidence of dental discoloration after tetracycline prescription and compared the incidence by age group (0–7 vs. 8–12 years or 0–3 vs. 4–7 years vs. 8–12 years age group) since the age restriction includes 12 years old in Korea[8] and duration of tetracycline exposure (≤7 vs. 8–14 vs. ≥15 days). The incidence rate was presented per 100,000 person-years. A Cox proportional hazard regression model with Firth's bias correction was used to analyse the relative risk of dental discoloration. SIRs were used to compare the incidence among patients prescribed tetracyclines to that in the age-matched general population. Poisson distribution was used to calculate 95% CIs of SIRs. To calculate SIRs, data from all children aged 0–12 years with the prescription codes for dental discoloration between July 2009 and December 2020 were also collected. For comparison, the population structure of Koreans in 2014 by Statistics Korea was used. Joinpoint Regression Analysis software, version 4.9.0.0 (National Cancer Institute, Bethesda, MD, USA), was used to calculate the annual percentage change (APC) from 2009 to 2020 with 95% CIs to quantify the changes in trends of the incidence of dental discoloration in tetracycline-exposed patients. Because there was no statistically significant change in the trend, "0 joinpoint" model without an inflection point was used in the analysis. All statistical tests were 2 sided, and *P*-values <0.05 were considered statistically significant. SAS Enterprise Guide 7.1 (SAS Institute, Cary, NC, USA) was used for statistical analysis.

5. Ethics statement

This study was approved by the Institutional Review Board of Yonsei Medical University (IRB No. 4-2020-0316) and exempted from the requirement for informed consent due to the nature of the de-identified population-based data.

RESULTS

From 2009 to 2020, 63,923 children were prescribed tetracyclines at least once. Among them, 6,933 children diagnosed with dental discoloration prior to tetracycline

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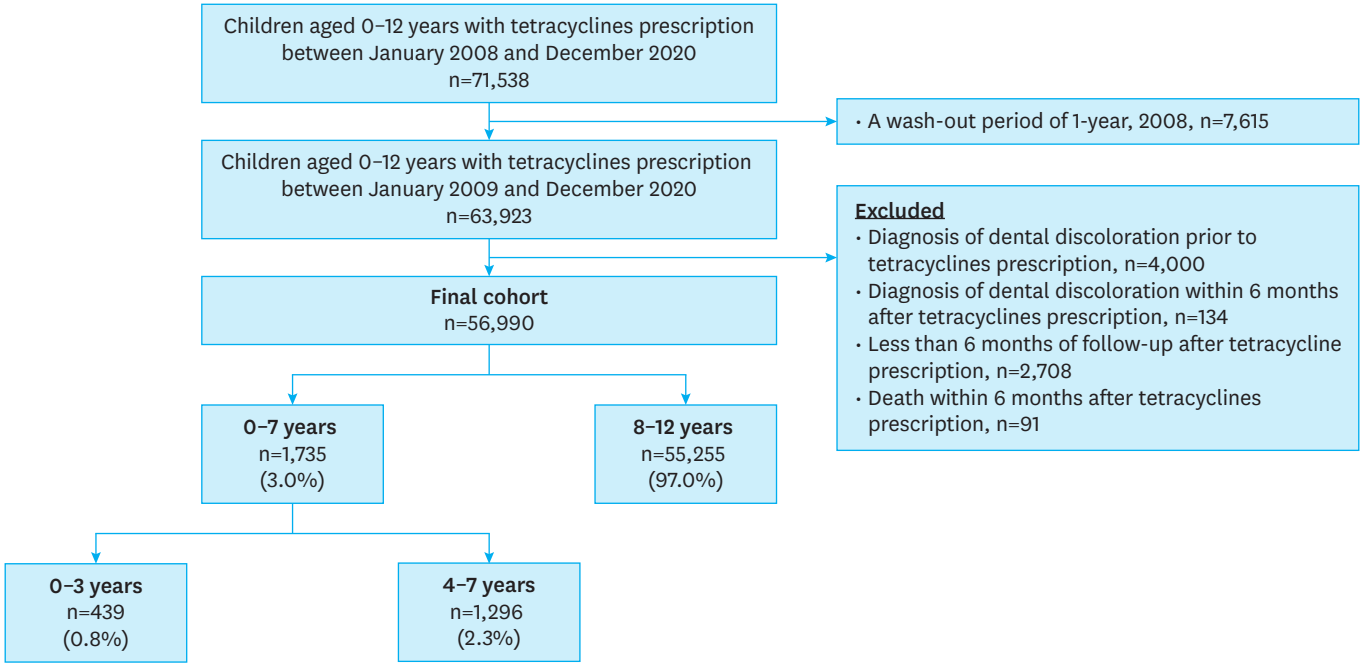

Fig. 1. Flowchart of included and excluded cohort.

prescription (n=4,000), those with follow-up duration less than 6 months after tetracycline prescription (n=2,708), those with diagnosis of dental discoloration within 6 months after tetracycline prescription (n=134), and those who died within 6 months after tetracycline prescription (n=91) were excluded (**Fig. 1**). Consequently, 56,990 patients were included in this retrospective cohort. A slight decrease was observed in the number of children prescribed tetracyclines yearly since April 2007 when the drug utilization review (DUR) was implemented on tetracyclines to limit and monitor the prescription of contraindicated drugs (APC, −2.7%; 95% CI, −5.2% to 0.0%, P=0.048; **Supplementary Fig. 1**).[10] Children aged <8 and 8–12 years accounted for 3% (n=1,735) and 97% (n=55,255), respectively, of the cohort. The second-generation tetracyclines, doxycycline (60.8%) and minocycline (35.1%), accounted for 96% of total tetracyclines prescribed, while first-generation tetracyclines such as oxytetracycline (0.001%) and tetracycline (4.0%) consisted a minority (**Supplementary Table 2**). The detailed characteristics of the children are described in **Table 1**.

1. Incidence and risk factors for dental discoloration

In total, 545 dental discolorations were identified, and only 46 (8%) cases were reported in children aged <8 years. The incidence rate in the 0–7 years age group (734 cases per 100,000 person-years) was significantly (approximately 5 times) higher than that in the 8–12 years group (143 cases per 100,000 person-years, P<0.001; **Table 2**). Subgroup analysis of the 0–7 years age group showed no significant difference in the incidence rates between the 2 subgroups, with 679 and 756 cases per 100,000 person-years in the 0–3 and 4–7 years age groups, respectively (P=0.74). The age-related hazard ratios (HRs) showed similar results in multivariable Cox regression analysis and adjusted for sex and comorbidities (**Table 3**). The 0–7 years age group had an approximately 5 times greater risk of dental discoloration than the 8–12 years age group (HR, 5.1; 95% CI, 3.8 to 6.9; P<0.001). A comparable tendency was observed in 0–3 and 4–7 years age groups (HR, 5.1; 95% CI, 2.9 to 8.9; P<0.001 and HR, 5.2; 95% CI, 3.6 to 7.3; P<0.001, respectively).

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Table 1. Clinical characteristics stratified by age group

Characteristics	0–7 years age group		8–12 years age group	
	Patient without dental discoloration (n=1,689)	Patient with dental discolorations (n=46)	Patient without dental discoloration (n=54,756)	Patient with dental discoloration (n=499)
Age (yr)	5 (3–7)	5 (3–6)	12 (12–12)	12 (12–12)
Sex				
Male	876 (51.9)	20 (43.5)	24,329 (44.4)	198 (39.7)
Female	813 (48.1)	26 (56.5)	30,427 (55.6)	301 (60.3)
Follow-up years from index date	1.4 (1.1–5.4)	1.9 (0.9–3.6)	6.6 (3.4–9.3)	2.6 (1.3–4.9)
Comorbidities	117 (6.9)	6 (13.0)	1,482 (2.7)	17 (3.4)
Neurological and neuromuscular	23 (1.4)	1 (2.2)	153 (0.3)	2 (0.4)
Cardiovascular	18 (1.1)	0 (0.0)	79 (0.1)	1 (0.2)
Respiratory	10 (0.6)	1 (2.2)	17 (0.03)	0 (0.0)
Renal and urological	8 (0.5)	2 (4.4)	73 (0.1)	0 (0.0)
Gastrointestinal	18 (1.1)	0 (0.0)	95 (0.2)	1 (0.2)
Haematological or immunological	19 (1.1)	0 (0.0)	65 (0.1)	1 (0.2)
Metabolic	27 (1.6)	1 (2.2)	554 (1.0)	8 (1.6)
Congenital/genetic defect	8 (0.5)	1 (2.2.)	494 (0.9)	6 (1.2)
Malignancy	28 (1.7)	1 (2.2)	110 (0.2)	1 (0.2)
Premature and neonatal	12 (0.7)	0 (0.0)	14 (0.03)	0 (0.0)
Exposure to tetracyclines				
Prescription days	7 (3–10)	5.5 (3–9)	7 (5–14)	7 (4–12)
≤7 days	915 (54.2)	30 (65.2)	33,644 (61.4)	325 (65.1)
8–14 days	673 (39.9)	14 (30.4)	10,516 (19.2)	88 (17.6)
15–28 days	76 (4.5)	1 (2.2)	6,091 (11.1)	41 (8.2)
≥29 days	25 (1.5)	1 (2.2)	4,505 (8.2)	45 (9.0)
Outcome index				
Dental discoloration	N/A	35 (76.1)	N/A	425 (85.2)

Values are presented as number (%) or median (interquartile range).
Abbreviation: N/A, not applicable.

Table 2. Incidence rate of dental discoloration in children with tetracycline exposure

Age at dental discoloration diagnosis	0–3 years	4–7 years	8–12 years	13–17 years	18–23 years	Total	Person-years	Incidence rate* (95% CI)
Age at the time of tetracycline prescription								
0–7 years	5	24	17	N/A	N/A	46	6,268.2	733.9 (537.3–978.9)
0–3 years	5	6	1	N/A	N/A	12	1,768.3	678.6 (350.7–1,185.4)
4–7 years	N/A	18	16	N/A	N/A	34	4,500.0	755.6 (523.3–1,055.8)
8–12 years	N/A	N/A	26	376	97	499	349,886.8	142.6 (130.4–155.7)
Total	5	24	43	376	97	545	356,155.0	153.0 (140.44–166.43)

Abbreviations: CI, confidence interval; N/A, not applicable.
*Per 100,000 person-years.

The 5- and 10-year cumulative incidence rates of dental discoloration after tetracycline exposure were 4.1% (95% CI, 3.0% to 5.7%) and 5.7% (95% CI, 4.1% to 7.8%), respectively, in the 0–7 years age group and 0.8% (95% CI, 0.7% to 0.9%) and 1.3 (95% CI, 1.1% to 1.4%), respectively, in the 8–12 years age group (P<0.001; **Fig. 2A**). There was no significant difference in the 5-year cumulative incidence rates of dental discoloration between the 0–3 (3.1%; 95% CI, 1.5% to 6.3%) and 4–7 (4.5%; 95% CI, 3.1% to 6.5%) years age groups (P<0.001; **Fig. 2B**). Furthermore, there was no significant difference in the cumulative incidence according to the duration of tetracycline exposure (P=0.43; **Fig. 2C**). Additionally, there was no significant difference in the incidence of dental discoloration according to the duration of tetracycline exposure between the 0–7 and 8–12 years age groups (**Figs. 2D and E**, **Supplementary Table 4**).

There was an increased risk of dental discoloration in children aged <8 years, girls, and children with respiratory and metabolic comorbidities. The risk was significantly higher

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Table 3. Cox regression risk factor analysis for dental discoloration and enamel dysplasia

Variables	Crude HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Sex						
Male	1 (ref)		1 (ref)		1 (ref)	
Female	1.2 (0.998–1.4)	0.05	1.2 (1.0–1.4)	0.03	1.2 (1.0–1.4)	0.03
Comorbidities						
Neurological and neuromuscular	2.1 (0.7–6.6)	0.19	1.8 (0.6–5.2)	0.28	1.8 (0.6–5.1)	0.28
Cardiovascular	1.1 (0.2–7.7)	0.94	1.0 (0.2–4.9)	0.99	1.0 (0.2–4.8)	0.99
Respiratory	6.7 (0.9–47.6)	0.06	7.8 (1.5–40.6)	0.01	7.9 (1.5–40.8)	0.01
Renal and urological	2.9 (0.7–11.6)	0.13	2.8 (0.8–9.4)	0.10	2.8 (0.8–9.4)	0.10
Gastrointestinal	1.0 (0.1–7.1)	>0.99	0.6 (0.1–2.9)	0.49	0.6 (0.1–2.9)	0.49
Haematological or immunological	1.7 (0.2–12.3)	0.58	1.5 (0.3–7.2)	0.61	1.5 (0.3–7.2)	0.61
Metabolic	2.1 (1.1–4.0)	0.03	2.2 (1.1–4.1)	0.02	2.2 (1.1–4.1)	0.02*
Other congenital or genetic defect	1.6 (0.7–3.3)	0.25	1.6 (0.8–3.4)	0.18	1.6 (0.8–3.4)	0.18
Malignancy	2.0 (0.5–7.8)	0.34	1.2 (0.4–4.0)	0.77	1.2 (0.4–4.0)	0.77
Premature and neonatal	3.7 (0.2–60.0)	0.35	0.3 (0.02–7.2)	0.48	0.3 (0.02–7.1)	0.48
Age at the time of tetracycline prescription (1)						
0–3 years	4.6 (2.6–8.2)	<0.001	5.1 (2.9–8.9)	<0.001		
4–7 years	5.1 (3.6–7.2)	<0.001	5.2 (3.6–7.3)	<0.001		
8–12 years	1 (ref)		1 (ref)			
Age at the time of tetracycline prescription (2)						
0–7 years	4.9 (3.7–6.7)	<0.001			5.1 (3.8–6.9)	<0.001
8–12 years	1 (ref)				1 (ref)	

Abbreviations: HR, hazard ratio; CI, confidence interval.
*Firth's correction was used.

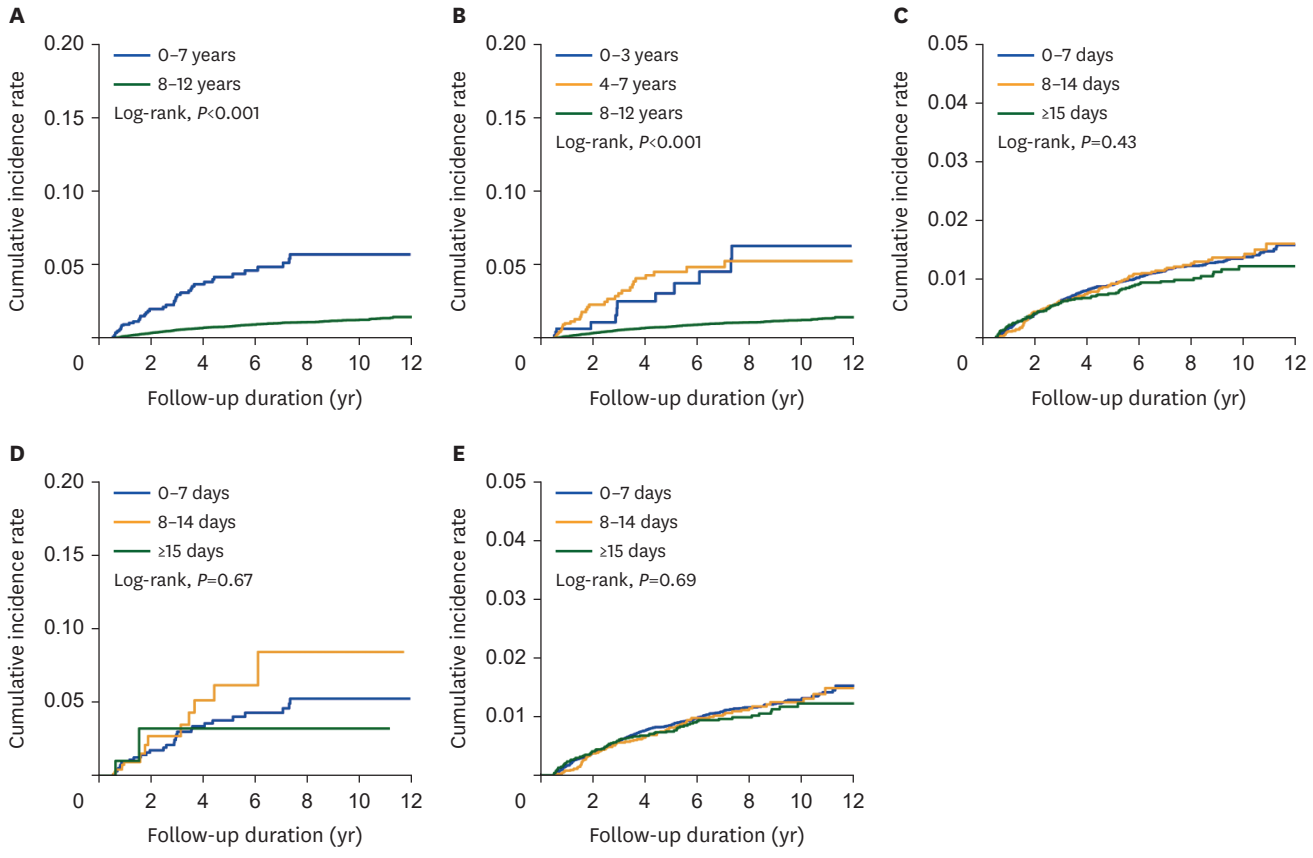

Fig. 2. The cumulative incidence rate of dental discoloration 5 and 10 years after tetracycline prescription according to age group and duration of tetracycline exposure. (A) Comparison of the cumulative incidence rate between the 0–7 (blue) and 8–12 years age groups (green) (B) Subgroup analysis of the cumulative incidence rate by age group: 0–3 (blue), 4–7 (orange), and 8–12 years (green). (C) Comparison of the cumulative incidence rate according to duration of tetracycline exposure (0–7 days, blue; 8–14 days, orange; and ≥15 days, green). (D) The cumulative incidence rate in the 0–7 years age group according to the duration of tetracycline exposure. (E) The cumulative incidence rate in 8–12 years age group according to the duration of tetracycline exposure.

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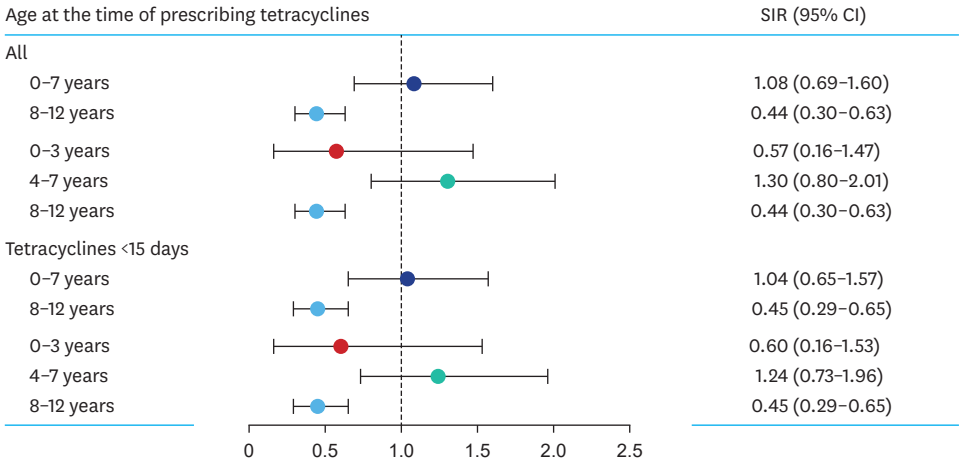

Fig. 3. SIR of dental discoloration according to age at the time of tetracycline exposure and treatment duration.
Abbreviations: SIR, standardized incidence ratio; CI, confidence interval.

in children with underlying diseases, including respiratory (HR, 7.9; 95% CI, 1.5 to 40.6; *P*=0.01) and metabolic diseases (HR, 2.2; 95% CI, 1.1 to 4.1; *P*=0.02), than that in female children (HR, 1.2; 95% CI, 1.0 to 1.4; *P*=0.03; **Table 3**). However, only 1 case of dental discoloration in each high-risk comorbidity group was included in the 0–7 years age group, which limits further interpretation.

2. Risk of dental discoloration in the tetracycline-exposed group versus the general population

In the 0–7 years age group, tetracycline exposure did not significantly increase the risk of dental discoloration compared to that in the general population (SIR, 1.2; 95% CI, 0.7 to 1.6; **Fig. 3**). Similarly, there was no significant difference in the incidence between the tetracycline-exposed group and the general population in the 0–3 (SIR, 0.6; 95% CI, 0.2 to 1.5) and 4–7 (SIR, 1.3; 95% CI, 0.8 to 2.0) years age groups. When the duration of tetracycline exposure was limited to ≤14 days, the SIR was 1.0 (95% CI, 0.7 to 1.6) in the 0–7 years age group, and no significant increase in the risk of dental discoloration was observed according to tetracycline exposure. Unexpectedly, the incidence of dental discoloration was significantly lower in the tetracycline-exposed group than in the general population (SIR, 0.5; 95% CI, 0.3 to 0.7) in the 8–12 years age group.

DISCUSSION

In this population-based study, the incidence rate of dental discoloration after tetracycline exposure was 153 per 100,000 person-years in Korean children aged 0–12 years. The incidence of dental discoloration in the 8–12 years age group was approximately 80% lower than that in the 0–7 years group. Moreover, no increased risk of dental discoloration was observed in tetracycline-exposed children compared to that in the general population in the 0–7 years age group. To our knowledge, this is the largest investigation to determine the incidence and risk factors in tetracycline-exposed children. Our findings suggest that some countries, including Korea, need to reconsider the 8–12 years age restriction for tetracyclines such as doxycycline.

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Even in children aged ≤8 years, the incidence of dental discoloration after tetracycline exposure was relatively low. The 5- and 10-year cumulative incidence rates were 4.1% and 5.7%, respectively, in the 0–7 years group. These were comparatively lower than that reported in previous studies in the 1960s.[11,16] Since 1958, when dental discoloration was first observed in neonates,[16] a high but variable incidence (38–92%) was reported.[11,15] There are feasible explanations for this variability. First, the use of first-generation tetracyclines, which have a higher affinity for calcium ions in dentin than second-generation tetracyclines, such as doxycycline, during the critical period of odontogenesis known to be around 7–8 years of age, may have caused a higher risk of dental discoloration. This possibility has been suggested since 1969 in a study that highlighted that only 1 of 25 premature infants who received doxycycline had discoloration 1 year after treatment.[16] Second, a longer duration and higher cumulative tetracycline dose were used in past practice, which might have contributed to a greater frequency of dental discoloration.[11] However, recently, the likelihood is low, especially in children older than neonates, with short-course doxycycline. In 2007, Volovitz et al.[17] found no dental discoloration in children with average age of 10 years with atypical pneumonia treated with short-term doxycycline in a randomized controlled study. Furthermore, a retrospective cohort in 2015 found no tooth staining in Indian American children aged <8 years with RMSF treated with short-course doxycycline at routine dose (95% CI, 0% to 3%).[9] These findings support the US CDC guidelines recommending the use of doxycycline as first-line treatment for RMSF and other tick-borne rickettsia diseases in adults and children, including those aged <8 years. Moreover, the American Academy of Pediatrics permits short-course doxycycline (up to 21 days) in children, regardless of age for aforementioned indications.[18] Therefore, our results provide additional evidence that the risk of dental discoloration attributable to tetracyclines, especially doxycycline, is minimal.

Regarding the tetracycline prescription pattern in Korea, our study reflects the gradual yearly decline in tetracycline prescription in children due to the effect of the DUR program implemented in April 2007 in Korea. The DUR is the world's only drug safety inspection system that checks a patient's medication history in real time to prevent overuse or restrict the prescription of contraindicated drugs.[19] Consequently, in our study, the number of children aged ≤12 years with tetracycline prescriptions decreased sharply from 5,215 in 2008 to 3,216 in 2020, and the APC showed a significant decrease of -2.7 when the DUR was implemented (**Supplementary Fig. 1**). However, if the health authorities relax the age restriction, clinicians will prescribe tetracyclines with more confidence when indicated. Thus, our finding serves as an important stepping stone toward lowering the standards for prescribing tetracyclines to children for treating life-threatening but treatable diseases, such as RMSF, Lyme disease, malaria, and MRMP.[19,20]

Lowering the age restriction for tetracyclines from 12 to 8 years in Korea could be recommended because the 8–12 years age group demonstrated a significantly lower incidence of dental discoloration than the 0–7 age group. In many countries, including Korea and the UK, tetracycline use is limited to individuals aged ≤12 years compared to ≤8 years in the US. This variable age restriction is due to different views on the completion of odontogenesis and maturation in children.[21] However, our results indicate that the 10-year cumulative incidence in the 8–12 years group is approximately 20% of that in the 0–7 years group. Since the prevalence of MRMP is higher among older children and adolescents, especially in East Asia,[2,3] having doxycycline and minocycline (with well-established efficacy) as additional treatment options is reassuring. Minocycline and doxycycline were approved in Japan for children aged >8 years with *M. pneumoniae* infection treatment failure in 2004. A 2012 study

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showed that tetracyclines were used in >50% patients with MRMP (n=125/202) in Japan, and this group achieved better clinical outcomes, including achieving defervescence within 24 hours and less DNA copies after 3 days of treatment.[2] Furthermore, a retrospective study conducted in Korea emphasized that using doxycycline for treating MRMP in children (median age, 5 years) did not result in any dental discoloration.[22]

Our study additionally described the risk factors, other than age, for dental discoloration in tetracycline-exposed children—female sex and respiratory and metabolic comorbidities. There is a paucity of reports on risk factors for dental discoloration; instead, positive correlations have been proposed between first-generation tetracycline exposure and several patient and treatment factors, such as birth weight, gestational age, long treatment duration, and high cumulative dosage.[14] In our study, female sex and respiratory and metabolic comorbidities were associated with a higher risk of dental discoloration with tetracycline exposure. Thus, these children may have an underlying predisposition, developing dental discoloration with an additional contribution of tetracyclines. For instance, cystic fibrosis is a multi-organ genetic disease, and because saliva production affects tooth color, patients with cystic fibrosis may be at a higher risk of tooth staining due to the different saliva composition.[23] Moreover, children with metabolic disorders, such as vitamin D-resistant rickets, Alstrom syndrome, and familial steroid dehydrogenase deficiency, have a higher incidence of dental manifestations.[23] Therefore, we suggest an additional contribution of tetracyclines in children who are already susceptible to dental discoloration. Nonetheless, due to variable results regarding the risk factors for tooth staining, further studies using match-controlled and randomization methods are warranted to better evaluate whether patients' demographic features can increase the risk of dental discoloration.

This study has several limitations. First, the retrospective design may limit further implications regarding a causal relationship between tetracycline exposure and dental discoloration. Second, unexpectedly, the risk of dental discoloration was lower in the 8–12 years age group than in the 0–7 years age group. It is possible that unexpected biases might have been involved in the comparisons with the tetracycline-naive general population (control group). For example, "staining of teeth" and "colour changes during tooth formation" in healthy children, even with a mild observation of tooth discoloration, are commonly diagnosed with these codes in real-world practice. The "intrinsic staining for teeth NOS" code was the most common code in paediatric outpatient cases aged 5–9 in 2021.[19] This over-diagnosis might have been corrected by filtering those who were treated for staining; however, information regarding treatment was not gathered in our study partially due to inadequate data from dental clinics. This could have excluded the mild cases of tooth staining in the general population. In addition, since the database is mainly for NHIS medical billing, information on treatment and medical records describing the severity of the patient symptoms were not included. This might have minimized over-diagnosis and under-diagnosis. Also, the lack of knowledge on the onset time of dental discoloration after tetracycline exposure resulted in setting the washout period as 6 months, because most population-based studies frequently use washout period of 6 months to 2 years.[24] If further investigation on the natural course of tetracycline's dental effects is done, a more accurate washout period may have been set. Lastly, the operational definition of dental discoloration might not have accurately reflected actual tooth staining. However, because the definition was applied to both the study cohort and general population, this bias might have been compensated for when calculating the SIR. In the future, more well-designed, population-based studies, such as propensity score matching case-controlled studies, might be required for clarification.

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Despite these limitations, to our knowledge, this is the first nationwide population-based investigation on dental discoloration after tetracycline exposure in children and the first study to analyse its risk factors in Korea. Further, the real-world data are meaningful as they reflect the current practice of tetracycline prescription in Korea.

In conclusion, the incidence of dental discoloration was significantly lower in tetracycline-exposed 8–12-year-old children than in tetracycline-exposed 0–7-year-old children. Further studies using match-controlled methods should be conducted to substantiate our finding that the potential risk of tetracyclines in children is lower than expected to relieve the age restriction.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

ICD-10 codes for dental discoloration

Supplementary Table 2

ATC codes for tetracyclines

Supplementary Table 3

Categories of comorbidities and the corresponding ICD-10 codes

Supplementary Table 4

Cumulative incidence of dental abnormalities 5 and 10 years after TCs prescription

Supplementary Fig. 1

The number of tetracycline prescriptions by year for those under 13 years old.

REFERENCES

1. Weisblum B, Davies J. Antibiotic inhibitors of the bacterial ribosome. Bacteriol Rev 1968;32:493-528. PUBMED | CROSSREF
2. Okada T, Morozumi M, Tajima T, Hasegawa M, Sakata H, Ohnari S, et al. Rapid effectiveness of minocycline or doxycycline against macrolide-resistant *Mycoplasma pneumoniae* infection in a 2011 outbreak among Japanese children. Clin Infect Dis 2012;55:1642-9. PUBMED | CROSSREF
3. Tanaka T, Oishi T, Miyata I, Wakabayashi S, Kono M, Ono S, et al. Macrolide-resistant *Mycoplasma pneumoniae* infection, Japan, 2008-2015. Emerg Infect Dis 2017;23:1703-6. PUBMED | CROSSREF
4. D'Alessandro M, Loy A, Castagnola E. Management of lyme disease in european children: a review for practical purpose. Curr Infect Dis Rep 2017;19:27. PUBMED | CROSSREF
5. Anderson A, Bijlmer H, Fournier P, Graves S, Hartzell J, Kersh G, et al. Diagnosis and management of Q fever — United States, 2013: recommendations from CDC and the Q Fever Working Group. Atlanta: Center for Disease Control and Prevention, 2013.
6. Center for Disease Control and Prevention (CDC). Research on doxycycline and tooth staining [Internet]. Atlanta: CDC; 2019 [cited 2022 Apr 1]. Available from: https://www.cdc.gov/rmsf/doxycycline/index.html.

7. Pereyre S, Goret J, Bébéar C. *Mycoplasma pneumoniae*: current knowledge on macrolide resistance and treatment. Front Microbiol 2016;7:974. PUBMED | CROSSREF
8. 2019 Acute respiratory infection Control Guideline. Cheongju: Korea Disease Control and Prevention Agency, 2019:127-31.
9. Todd SR, Dahlgren FS, Traeger MS, Beltrán-Aguilar ED, Marianos DW, Hamilton C, et al. No visible dental staining in children treated with doxycycline for suspected Rocky Mountain Spotted Fever. J Pediatr 2015;166:1246-51. PUBMED | CROSSREF
10. Ministry of Food and Drug Safety (MFDS). Announcement on contraindications for combination and contraindications for certain ages [Internet]. Cheongju: MFDS; 2007 [cited 2022 May 9]. Available from: https://www.mfds.go.kr/docviewer/skin/doc.html?fn=d8253ddac3dd4204f9a36d5527077d90&rs=/docviewer/result/ntc0004/9574/1/202205.
11. Wallman IS, Hilton HB. Teeth pigmented by tetracycline. Lancet 1962;1:827-9. PUBMED | CROSSREF
12. Swallow JN, De Haller J, Young WF. Side-effects to antibiotics in cystic fibrosis: dental changes in relation to antibiotic administration. Arch Dis Child 1967;42:311-8. PUBMED | CROSSREF
13. Shwachman H, Fekete E, Kulczycki LL, Foley GE. The effect of long-term antibiotic therapy in patients with cystic fibrosis of the pancreas. Antibiot Annu 1958-1959;6:692-9. PUBMED
14. Conchie JM, Munroe JD, Anderson DO. The incidence of staining of permanent teeth by the tetracyclines. Can Med Assoc J 1970;103:351-6. PUBMED
15. Porter PJ, Sweeney EA, Golan H, Kass EH. Controlled study of the effect of prenatal tetracycline on primary dentition. Antimicrob Agents Chemother 1965;5:668-71. PUBMED
16. Forti G, Benincori C. Doxycycline and the teeth. Lancet 1969;1:782. PUBMED | CROSSREF
17. Volovitz B, Shkap R, Amir J, Calderon S, Varsano I, Nussinovitch M. Absence of tooth staining with doxycycline treatment in young children. Clin Pediatr (Phila) 2007;46:121-6. PUBMED | CROSSREF
18. Kimberlin DW, Lynfield R, Sawyer MH. Red book: 2021 report of the Committee on Infectious Diseases. 32th ed. Itasca: American Academy of Pediatrics, 2021.
19. Health Insurance Review and Assessment (HIRA). Drug utilization review (DUR) [Internet]. Wonju: HIRA; c2023 [cited 2022 Apr 20]. Available from: https://www.hira.or.kr/dummy.do?pgmid=HIRAA990001000330.
20. Gaillard T, Briolant S, Madamet M, Pradines B. The end of a dogma: the safety of doxycycline use in young children for malaria treatment. Malar J 2017;16:148. PUBMED | CROSSREF
21. Reid DJ, Dean MC. Variation in modern human enamel formation times. J Hum Evol 2006;50:329-46. PUBMED | CROSSREF
22. Ha SG, Oh KJ, Ko KP, Sun YH, Ryoo E, Tchah H, et al. Therapeutic Efficacy and safety of prolonged macrolide, corticosteroid, doxycycline, and levofloxacin against macrolide-unresponsive *Mycoplasma pneumoniae* pneumonia in children. J Korean Med Sci 2018;33:e268. PUBMED | CROSSREF
23. Atar M, Körperich EJ. Systemic disorders and their influence on the development of dental hard tissues: a literature review. J Dent 2010;38:296-306. PUBMED | CROSSREF
24. Son M, Jo S, Lee JS, Lee DH. Association between oral health and incidence of pneumonia: a population-based cohort study from Korea. Sci Rep 2020;10:9576. PUBMED | CROSSREF

요약

목적: 테트라사이클린 (tetracycline, TC)은 소아청소년을 대상으로 복용하였을 시 영구적 치아 변색의 위험이 증가된다는 보고에 따라 미국에서는 8세 이하, 국내에서는 12세 미만으로 처방이 가이드라인상 추천되지 않고 있는 실정이다. 이에 본 연구에서는 TC에 노출된 소아청소년을 대상으로 치아 변색의 발생률을 분석하고, TC에 노출되지 않은 일반 인구 집단과의 발생률 차이를 비교하고자 하였다.

방법: 본 코호트 연구는 2008년 1월부터 2020년 12월 사이 최소 1일 이상 TC에 노출된 소아청소년(0-12세)에 대한 건강보험심사평가원 데이터베이스 정보를 기반으로 분석하였다. TC 노출 6개월 이후 치아 변색 관련 진단코드의 입력여부를 기준으로 치아 변색 발생률을 도출하였고, 추가적으로 연령 보정이 된 TC에 노출되지 않은 일반 인구집단을 추출하여 이를 변수로 한 표준화한 치아 변색 발병률(standardized incidence ratio, SIR)을 구하였다.

결과: 총 56,990명이 포함되었으며, 이 중 8세 미만은 1,735명, 그리고 8-12세는 55,255명이었다. 이 중 61%가 14일 미만 동안 TC를 처방받았으며, 독시사이클린(61%)과 미노사이클린(35%)을 포함한 2세대 TC가 가장 많은 비중을 차지하였다. 0-7세 연령군에서의 5년 및 10년 누적발생률은 4.1% (95% confidence interval [CI], 3.0% to 5.7%) 및 5.7% (95% CI, 4.1% to 7.8%)으로 확인되었고, 이에 비해 8-12세 연령군에서는 0.8% (95% CI, 0.7 to 0.9%) 및1.3 (95% CI, 1.1% to 1.4%)으로 상대적으로 낮았다. TC노출 후 치아 변색의 발생률은 연령 보정된 일반 인구 집단과 비교하였을 때 통계학적으로 유의미한 차이는 없었다 (SIR, 1.08; 95% CI, 0.69 to 1.60).

결론: TC 노출은 일반 인구에 비해 치아 변색 위험을 유의하게 증가시키지 않았으며, 특히 8-12세 사이의 TC 노출군은 그 이하 연령군에 비해 유의미하게 낮은 발생률을 보였다. 따라서, 국내에서 TC 처방에 대한 연령 제한 완화를 고려할 필요가 있다.

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