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Fluoride supplements and fluorosis: a meta-analysis

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Abstract – This paper presents a systematic review of the dental literature that was carried out to investigate whether the regular use of fluoride supplements in non-fluoridated communities during the period of tooth development increases the risk of dental fluorosis. A MEDLINE search was organized for all documents published, in English, between January 1966 and September 1997 using the following key words: fluorosis, dental, fluoride, fluoride supplement or supplements, drop or drops, and tablet or tablets. Twenty-four studies that assessed the development of dental fluorosis in children who had used fluoride supplements earlier in their life were included in this review. Of the 24 studies, 10 were cross-sectional/case control studies and four were follow-up studies. These studies had data that allowed a quantitative estimation of the risk of developing dental fluorosis in users of fluoride supplements. The other 10 studies were excluded because they either did not present enough data or had other methodological problems. A qualitative review of the studies found a consistent and strong association between the use of fluoride supplements and dental fluorosis. The meta-analyses of the cross-sectional/case-control studies estimated that the odds ratio of dental fluorosis in users of fluoride supplements compared with non-users ranged between 2.4 and 2.6. The meta-analyses of the follow-up studies estimated that the relative risk in long-term users was between 5.5 and 12.2. This review confirmed that in non-fluoridated communities the use of fluoride supplements during the first 6 years of life is associated with a significant increase in the risk of developing dental fluorosis.

Key words: fluoride supplements; fluorosis; meta-analysis

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The objective of this paper is to present a systematic review of the dental literature to answer the following question: does the regular use of fluoride supplements in non-fluoridated communities during the period of tooth development increase the risk of dental fluorosis?

In the absence of direct evidence from randomized clinical trials, harm from interventions, such as fluoride products, should be determined following the criteria described by Lilienfeld & Stolley (1). Specifically, fluoride supplements are considered a risk factor of dental fluorosis if the association between the use of supplements and fluorosis is strong, consistent, and specific; has the correct temporal sequence of an exposure preceding the occurrence of disease; is dose-response dependent; and is biologically plausible.

To assess the strength of the association between the use of fluoride supplements and dental fluorosis, measures such as relative risk (RR) or odds ratios (OR) are used (1). The magnitude of these two measures determines the strength of an association between fluoride supplements and fluorosis. For instance, if the value of RR is at least 2.0 (the probability of disease in the exposed group is two times higher than the probability of disease in the unexposed group), then there is a possibility that the association may be causal if the other criteria are met as well. An OR estimates the odds of disease in the exposed group relative to the odds of disease in the unexposed group.

In addition to the strength of an association, consistency of an association refers to finding similar trends in several well-designed studies. Because recall error and confounding are associated with measuring the intake of fluoride during the first 6 years of life, replication is a necessary requirement for concluding that there is an association between the ingestion of fluoride supplements and dental fluorosis. One problem encountered in evaluating the consistency of an association is the diversity in the statistical significance of the findings because of small sample sizes and the different designs used in epidemiological studies. To resolve this problem, meta-analytical methods are used to aggregate data from different studies and provide a quantitative estimate of the OR or RR (2). In a meta-analysis, a systematic review of the literature is conducted and studies are included or excluded from the analysis depending on whether they meet the eligibility criteria for inclusion set by the reviewers. The data are combined statistically to provide a quantitative estimate of the size of effect of exposure and risk of disease (2).

The available evidence on dental fluorosis clearly indicates that there is a temporal sequence between exposure to fluoride during the period of tooth development (0–7 years of life) and the development of dental fluorosis (3–5). There is also some evidence that a dose-response relationship exists between the ingestion of fluoride and occurrence of dental fluorosis (6). Children who brushed their teeth and ingested fluoride supplements had a significantly higher risk of developing fluorosis (7) than children who only brushed their teeth with fluoridated dentifrices.

Regarding the biological plausibility of the association between fluoride supplements and dental fluorosis, there is evidence that the presence of fluoride in tissue fluids that surround the developing enamel organ causes several changes in the biochemistry of ameloblasts and their metabolism, and eventually the mineralization of enamel (8). Fluoride causes the retention of proteins such as amelogenins in the tooth structure leading to the formation of hypomineralized enamel (8) that has a different refraction index than sound non-fluorotic enamel. As a result, light reflection through enamel changes resulting in the appearance of white/chalky areas.

Methods

To answer the question posed at the beginning of this paper, a systematic analysis of the dental literature and a meta-analysis were conducted to determine the strength of the association between fluoride supplements and dental fluorosis. A MEDLINE search was organized for all studies published, in English, between January 1966 and September 1997. The following key words were used to search for all documents written in the English literature: fluorosis, dental, fluoride, fluoride supplement or supplements, drop or drops, and tablet or tablets. A search for unpublished studies was also carried out using contacts with researchers in the field. Two unpublished studies were located and one of them (which was subsequently published) was used in this review (permission was not obtained for the second paper).

The studies identified by the search were classified into two groups. The first group included cross-sectional/case-control studies where information on use of fluoride supplements was obtained from self-administered questionnaires or interviews with parents. The second group included follow-up studies where data on fluoride use were available for a group of children and the investigators conducted an examination for presence of fluorosis at a later date. Ten cross-sectional/case-control and four follow-up studies were located with enough data to allow for further quantitative analysis (Table 1 and Table 2).

A total of 10 studies were excluded. The reason for the exclusion of each study is summarized in Table 3. Most of the excluded studies did not present enough data to allow inclusion in the meta-analysis. Another reason for exclusion was the lack of external validity of some of the studies that either included a sample with very high prevalence of fluorosis or had too few users of fluoride supplements. In one clinical study of fluoride supplements the children resided in areas where the fluoride concentration in the water was higher than 0.6 mg/L (Table 3).

Evidence tables were prepared for each group of studies. The evidence tables summarized information on the authors, year of publication, method of data collection and age of exposure to fluoride supplements, groups of exposures included in the study, number of children by group, prevalence of fluorosis, odds ratios or relative risks, and 95% confidence intervals (CI) (except for study by Pendrys & Katz [3] where 99% CI were presented).

Table 1. Risk of fluorosis in users of fluoride supplements: cross-sectional/case-control studies

Authors	Year	Method/age of exposure	Groups	*n*	Prevalence	Odds ratio	95% CI
De Liefde & Herbison (10)	1985	Questionnaire 9 years of life	1. Non-F water	237	22.8%*		
			2. Up to 5–6 years of life	82	28.1%	1.3	0.8–2.3
			3. Continuous use up to 9 years of life	156	49.4%	3.3	2.1–5.1
			4. Fluoridated water	191	36.7%	2.0	1.3–3.0
Granath et al. (11)	1985	Questionnaire 0.25 mg F tablets between 6 months and 6 years	Tablet users	49	28.6%[1]	2.4	0.9–5.9
			Control group	69	14.5%		
Pendrys & Katz (3)	1989	Questionnaire 850 cases and controls	1. Not used	Total=850	NR[2]	1.0[1]	
			2. Year 1 of life			1.4	0.6–3.0
			3. Years 3–6			3.3	1.5–7.5
			4. Year 1 and years 3–6			3.9	1.6–9.2
Bagramian et al. (12)	1989	Questionnaire 206 children 9 to 13 years	Daily *vs* irregular users	Total=159	46.4%[3] 37.8%	1.4	0.7–2.8
Woolfolk et al. (13)	1989	Questionnaire 543 children aged 9 to 13 years	1. Never	119	13.4%[3]		
			2. <regular	90	21.1%	1.7	0.8–3.6
			3. Regular	170	32.4%	3.1	1.7–5.7
Riordan & Banks (14)	1991	Questionnaire Exposure to supplements between birth and 4 years	1. Little	NR	NR[4]	1.6	0.5–4.4
			2. Medium			0.9	0.3–2.5
			3. Optimal			4.6	2.0–10.9
Clark et al. (15)	1994	Questionnaire =6 years of life	1. None	93	1%[3]		
			2. <4 years	184	5%	4.8	0.6–38.4
			3. 4 or more years	96	10%	10.7	1.3–85.3
			4. Lifelong water fluoridation	109	11%	11.4	1.5–89.3
Lalumandier & Rozier (16)	1995	Questionnaire/ interview 113 patients exposed to non-fluoridated water	Daily fluoride supplement use *vs* < daily	113	NR[3]	6.5	2.2–19.4
Pendrys et al. (17)	1996	Questionnaire 460 cases and controls	1. Not used *vs* use during year 1 of life	111 280	NR[2] NR	1.3	0.8–2.2
			2. Not used *vs* use during years 2–8	58 333	NR NR	2.3	1.1–4.7
Wang et al. (18)	1997	Questionnaire 383 children 76% used fluoride supplements	1. Non-user	21	0%[4]		
			2. Seldom	20	2%		
			3. Periodically	85	18%	2.4[5]	0.5–11.4
			4. Regularly	257	45%	7.4[5]	1.7–32.6

* DDE (Developmental Defects of Enamel) (19): diffuse opacities.
[1] Dean's Fluorosis Index (20).
[2] Fluorosis Risk Index (21): Classification I.
[3] TSIF (Tooth Surface Index of Fluorosis) (22).
[4] Thylstrup-Fejerskov Fluorosis Index (23).
[5] Compared with those who "seldom" used fluoride supplements.

Meta-analysis

Any use of fluoride supplements

The first series of meta-analyses that was conducted included all potential users of fluoride supplements. The analysis included 10 cross-sectional/case-control studies and four follow-up studies. The summary odds ratios or relative risks (summary OR or RR) and 95% confidence intervals were obtained using the following three statistical methods:

1) Mantel-Haenszel method: uses 2×2 frequency tables to estimate the summary OR and its standard error (2).

2) Generalized variance method: uses the calculated OR (or RR) and the lower bound of the 95% confidence interval to obtain an estimate of the standard error (2).

3) DerSimonian-Laird method: uses 2×2 frequency tables to estimate the summary OR or RR and its standard error (9). No test of homogeneity is available for this method (2).

The Mantel-Haenszel and the DerSimonian and Laird methods require data from 2×2 frequency tables to estimate the summary measures (OR or RR) and their standard errors. Twelve 2×2 tables from the 10 cross-sectional/case-control studies and ten 2×2 tables from the four follow-up studies were created and used in the meta-analysis. The generalized variance method uses the calculated OR or RR and the lower bound of the 95% confidence interval (2). For this method, 19 separate odds ratios from the cross-sectional/case-control studies and 11 measures of relative risks were used. Tests of homogeneity of variances for the Mantel-Haenszel and the generalized variance method were performed as described by Petitti (2).

Appropriate use of fluoride supplements

The meta-analyses were repeated by including only the users of fluoride supplements who had regularly used fluoride supplementation during at least the first 6 years of life. This condition restricted the number of studies included to seven cross-sectional/case-control studies and four follow-up studies.

Results

Qualitative review

Cross-sectional/case-control studies: all users of fluoride supplements

These studies are listed in chronological order in Table 1. Children who used fluoride supplements during the first several years of life had a signi-

Table 2. Risk of fluorosis in users of fluoride supplements: follow-up studies

Authors	Year	Method/age of exposure	Groups	*n*	Cumulative incidence	Relative risk	95% CI
Aasenden & Peebles (24)	1974	Non-randomized Non-representative No control for confounding Non-fluoridated area	1. No fluoride	93	4.3%*		
			2. 0.5 NaF 0–3 years, 1.0 afterwards	100	67%	15.6	5.9–41.0
			3. Fluoridated water	92	32.6%	7.6	2.8–20.7
Holm & Andersson (25)	1982	Interviews Longitudinal study 6 months to 6 years Fluorosis was assessed at the age of 12 years	Age at start of use of NaF tablets (months):				
			1. 6	21	81%†	5.4	1.9–15.6
			2. 12	51	59%	3.9	1.4–11.4
			3. 24	8	38%	2.5	0.6–9.9
			4. 36	6	33%	2.2	0.5–10.4
			5. Sporadically	28	18%	1.2	0.3–4.4
			6. Not	20	15%	1.0	
Larsen et al. (26)	1985	70 children who received 0.5 mg F tablet/day between 2.5 and 9.4 years; 40 children with no tablets Blind examinations	Central incisors				
			1. 2.5–4.4 years	20	15%†	4.2	0.9–19.3
			2. 4.5–9.4; no tablets	84	3.6%		
			Lateral incisors				
			1. 2.5–4.4	19	15.8%	4.3	0.9–19.7
			2. 4.5–9.4; no tablets	82	3.7%		
Kalsbeek et al. (6)	1992	Dentists evaluated use of supplements between 1.5 anf 6 years; fluorosis was assessed at the age of 15 years	1. Not a user	55	7%†		
			2. Irregular user	125	10%	1.4	0.5–4.2
			3. Regular user	179	19%	2.6	1.0–7.0
			4. Frequent user	61	36%	5.0	1.8–13.5

* Dean's Fluorosis Index (20): very mild to moderate fluorosis.
† Thylstrup-Fejerskov Fluorosis Index (23).

ficant increase in the risk of developing dental fluorosis. Eight studies found statistically positive associations between the use of fluoride supplements and dental fluorosis (Table 1). The OR of developing fluorosis in users of fluoride supplements during the first 8 years of life ranged from a low of 1.3 to a high of 10.7.

Follow-up studies: all users of fluoride supplements

These studies are listed in chronological order in Table 2. The relative risk of developing fluorosis in children who used fluoride supplements during the first several years of life was highly significant (RR=15.6 with 95% CI=5.9–41.0 [24] or RR=5.0 with 95% CI=1.8–13.5 [6]). One study found that the earlier in life fluoride supplements were used the higher the risk of developing fluorosis (25). Children who started using fluoride supplements at the age of 6 months had 5.4 times higher incidence of dental fluorosis than children who did not use supplements at all (25). The use of fluoride supplements during the first year of life is associated with a statistically significant increase in risk of fluorosis (Table 2). Children who used supplements starting at the age of 24 months had an increased risk compared to non-users, but the RR was not statistically significant because of the small sample size (25). In another small study, children who used fluoride supplements between 2.5 and 4.4 years of their lives had a higher relative risk (4.2) than children who either did not use supplements or used them after the age of 4.4 years (26). This finding was not statistically significant because of the small sample size (95% CI: 0.9–19.3).

Table 3. List of excluded studies

Author	Year	Finding	Reason for exclusion
Hennon et al. (27)	1977	A randomized clinical trial with significant loss of subjects. Children who used 0.5 mg F supplements between 0–3 years and 1.0 mg F supplements between 3 and 6.5 years had significantly higher incidence of fluorosis compared with children who were on a placebo	The children in the study resided in area that had 0.6–0.8 mg/L fluoride in its drinking water
Thylstrup et al. (28)	1979	"A positive association between number of tablets prescribed and dental fluorosis was found in erupted permanent teeth"	Statistics included in the paper were not sufficient to estimate the risk of fluorosis
Allmark et al. (29)	1982	No differences in fluorosis between children who sucked 2.2 mg NaF tablets and those in the control group. Program started at the age of 6 years	Not applicable to 0–6-year-old age group
Wöltgens et al. (7)	1989	Daily fluoride intake before the age of 4 years may explain the high prevalence of "mottled" enamel	Inadequate data were presented
Kumar et al. (30)	1989	Daily use of fluoride tablets increased the risk of fluorosis	Inadequate data were presented
Ismail et al. (31)	1990	"The use of fluoride supplements was significantly associated with fluorosis". Odds ratio=1.8 (1.5–2.1)	Data were not presented separately for the fluoridated and non-fluoridated communities
Holt et al. (32)	1990	"There was a statistically insignificant, but consistent, trend for the prevalence of opacities to increase with increasing duration of use of fluoride supplements"	Only summary data were presented. The prevalence of fluorosis in the children who did not use fluoride supplements was >60%
Stephen et al. (33)	1991	No significant difference between children who used fluoride supplement at birth and those who had started at the age of 7 years	Inadequate data were presented on fluorosis and use of fluoride supplements
D'Hoore & Van Nieuwenhuysen (34)	1992	Children who used fluoride tablets exhibited mild fluorosis more frequently than non-users. Odds ratio=9.6	Inadequate data were presented on fluorosis and use of fluoride tablets
Riordan (35)	1993	Supplement use did not afftect caries or fluorosis prevalences	Fluoride supplements were used by only 4.6% of the children in the study

Table 4. Findings from the meta-analysis that included all users of fluoride supplements

Study type	Number of 2×2 tables	Methods	Summary OR or RR	95% CI	Test of homogeneity (χ^2 value, *P*-value)
Cross-sectional/	12	Mantel-Haenszel	2.3	(1.5, 3.4)	(12.1, 0.4)
case control	19	Generalized variance	2.2	(1.9, 2.6)	(34.2, 0.01)
	12	DerSimonian-Laird	2.1	(1.7, 2.5)	NA
Follow-up*	10	Mantel-Haenszel	6.6	(2.9, 15.2)	(15.2, 0.08)
	11	Generalized variance	1.3	(2.6, 5.3)	(16.6, 0.08)
	10	DerSimonian-Laird	3.5	(2.3, 5.5)	NA

NA=not applicable.
* Generalized variance estimate, confidence interval and test of homogeneity are based on the RR.

Meta-analysis

Cross-sectional/case-control studies: all users of fluoride supplements

Table 4 presents the findings of several meta-analyses using the previously described methods. The Mantel-Haenszel method estimated that the summary OR for the association between any use of fluoride supplements and dental fluorosis is about 2.3 (95% confidence interval: 1.5–3.4). The DerSimonian-Laird and generalized variance methods gave a summary OR of 2.1 (1.7–2.5) and 2.2 (1.9–2.6), respectively. Because of the lack of homogeneity of variances among the studies, the results of the Mantel-Haenszel method, which assumes equality of the variances of the odds ratios, may be invalid. The random-effect method that is the basis for the DerSimonian-Laird algorithm is preferred in this case. However, the DerSimonian-Laird method gives higher weight to small studies and hence, it may emphasize poor evidence at the expense of good evidence (2). Overall, the meta-analyses found that the summary OR on average is between 2.1 and 2.3, indicating that children who use fluoride supplements have two times higher odds of developing fluorosis than those who never used fluoride supplements.

Follow-up studies: all users of fluoride supplements

For the follow-up studies, the summary RR ranged between 1.3 (2.6–5.3) for the generalized variance method and 6.6 (2.9–15.2) for the Mantel-Haenszel method. The DerSimonian-Laird method estimated that the summary RR was 3.5 (2.3–5.5). The follow-up studies showed a stronger association between any use of fluoride supplements and dental fluorosis because the determination of exposure to fluoride supplements was based on records or detailed interviews rather than recall by parents or self-administered questionnaires.

Appropriate use of fluoride supplements

When the meta-analyses were restricted to children who had regularly used fluoride supplements during at least the first 6 years of life (Table 5), the summary OR were between 2.4 and 2.6 (Table 5). For the follow-up studies, the DerSimonian-Laird

Table 5. Findings from the meta-analysis that included appropriate users of fluoride supplements (during at least the first 6 years of life)

Study type	Number of 2×2 tables	Methods	Summary OR or RR	95% CI	Test of homogeneity (χ^2 value, *P*-value)
Cross-sectional/	7	Mantel-Haenszel	2.6	(1.7, 4.1)	(6.1, 0.4)
case control	12	Generalized variance	2.6	(2.1, 3.2)	(23.9, 0.01)
	7	DerSimonian-Laird	2.4	(1.9, 3.1)	NA
Follow-up*	5	Mantel-Haenszel	12.2	(4.9, 30.4)	(7.2, 0.13)
	5	Generalized variance	5.6	(3.4, 9.4)	(11.8, 0.02)
	5	DerSimonian-Laird	5.5	(2.7, 11.4)	NA

NA=not applicable.
* Generalized variance estimate, confidence interval and test of homogeneity are based on the RR.

method estimated a summary OR of 5.5 (2.7–11.4) (Table 5), which is higher than the 3.5 reported in the previous analysis (Table 4).

Discussion

This qualitative and quantitative review found that the use of fluoride supplements increases the risk of developing dental fluorosis by at least two times. Most of the fluorosis found in the studies included in this paper was of the very mild to mild type. The association between fluoride supplements and dental fluorosis is strong and consistent. There is a clear temporal sequence in that infants and toddlers who used fluoride supplements had a higher prevalence of fluorosis in their permanent teeth than those who did not use fluoride supplements. This finding was recently confirmed by an epidemiological study of a population that was exposed to about 3.0 mg/L naturally fluoridated water for a period of 7 years (5). Children who were not born or were less than 1 year old when the drinking water of the community was switched from a low- to a high-fluoride source experienced the highest levels of fluorosis compared with older children (5). The odds that a child who had used the high fluoride water during the first year of life developed dental fluorosis was 2.5 times higher than those of children who drank the same water after the age of 2 years (5).

The specificity of the association between dental fluorosis and the use of fluoride supplements is difficult to establish from epidemiological studies that rely on recall of past use of fluoride products. There is evidence that the combined use of fluoride supplements and toothbrushing with a fluoridated dentifrice during the first year of life significantly increases the odds of developing fluorosis (OR= 6.2) compared with toothbrushing alone (OR=1.5) (4). Hence, fluoride supplements have at least an additive effect on the risk of developing dental fluorosis in infants and toddlers who brush their teeth with fluoridated dentifrices.

In addition to the finding of this analysis there are other issues that need to be considered when prescribing supplements. The problem with getting professionals to comply with the current dosage schedules for use of fluoride supplements is an important factor to consider in assessing this vehicle for delivery of fluoride. There is now consistent evidence to support the observation that some health professionals prescribe fluoride supplements without taking into account the level of fluoride in the drinking water (36).

In addition, there are other sources of exposure to fluoride during infancy that have not yet been considered in the current guidelines for use of fluoride supplements. The use of soy-based milk formulae and tea raises the fluoride intake of some infants to "near optimal levels" (37). Infants' foods and drinks may also contain enough fluoride to provide the so called "optimal intake" (38). Considering these factors, it is imperative that new guidelines for fluoride supplements either take the total intake of fluoride of children into account or consider their caries risk status before recommending fluoride supplements.

While this paper did not address the question of the pre- and post-eruptive effects of fluoride on caries prevention, the other papers presented at this conference (39, 40) clearly show that fluoride works best when available in low concentrations in the oral environment for long periods during a day. The topical effect of fluoride on development of dental caries was documented over 50 years ago by Klein (41) who found a decline of 40%–60% between 1943 and 1945 in dental caries incidence among Japanese-American children who were forced to live in a detention camp, during World War II, that had a naturally fluoridated water (3.0 mg/L) compared with another group of Japanese-American children who were located to a low-fluoride camp. The effect of fluoride on protecting newly erupting teeth was higher than the effect on teeth that had erupted before the relocation to the detention camps (41). These findings closely parallel those reported in the water fluoridation studies and experiments conducted in the 1940s and 1950s (42).

Policy-makers should consider these factors when making a decision on new recommendations for fluoride supplements. It is important to weigh in the risks and benefits of using systemic fluoride supplements in infants and toddlers. Physicians and dentists need to consider that there are two well-established and accepted methods for caries prevention in our communities: water fluoridation and toothbrushing with fluoridated pastes or gels. An infant or toddler who brushes at least once a day receives a dose of systemic fluoride (43). Given the increased risk of dental fluorosis that could result from the combined use of fluoridated dentifrices and fluoride supplements, it is imperative and ethically necessary that health professionals consider the total exposure to fluoride in deciding whether to recommend fluoride supplements. Fluoride supplements should be targeted for infants and toddlers who, in the clinical opinion of a health professional, are at risk of developing dental caries. While the accuracy of the professional assessment of caries risk has not yet been studied, there is ample evidence that dental caries clusters in families with low socioeconomic and education status (44). Infants of mothers who are not concerned about the sugar intake levels of their infants should also be considered at high risk of developing dental caries (45). Mothers with a history of caries development are more likely to infect their children with cariogenic bacteria and put their infants and toddlers at increased risk of developing early childhood caries (46).

This analysis clearly shows that the use of fluoride supplements increases the risk of developing dental fluorosis. Though the severity of fluorosis in the large majority of children is very mild, dentists should inform the parents about the risks and benefits that are associated with the use of fluoride supplements. For many children, there may not be a need for an additional application of fluoride. For some children, the detrimental effect of a rampant caries attack outweighs the risk of developing dental fluorosis. For such children, an additional source of fluoride (in the form of drops and tablets that are chewed and swished in the mouth) may be beneficial.

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