Stabilized stannous fluoride dentifrice in relation to dental caries, dental erosion and dentin hypersensitivity: A systematic review

Katarina Konradsson, RDH, PhD, **Peter Lingström**, DDS, PhD, **Claes-Göran Emilson**, DDS, PhD, **Gunnar Johannsen**, DDS, PhD, **Per Ramberg**, DDS, PhD & **Annsofi Johannsen**, RDH, PhD

Abstract: Purpose: To review the scientific evidence for the efficacy of stabilized stannous fluoride (SnF_2) dentifrice in relation to dental caries, dental erosion and dentin hypersensitivity. **Methods:** Medline OVID, Embase.com, and the Cochrane Library were searched until January 2018. Two researchers independently selected studies according to inclusion and exclusion criteria, data were extracted, the risk of bias in eligible studies was assessed and a meta-analysis was performed wherever feasible. **Results:** Three studies on dental caries, eight studies on dental erosion and 11 on dentin hypersensitivity were included. Risk of bias was judged as high for most of the caries and erosion studies and low or medium for the hypersensitivity studies. A similar or slightly higher anti-caries activity compared with non-stannous fluoride dentifrices was observed. Stannous fluoride showed a greater anti-erosive potential in seven of the eight studies. A mean difference score in favor of stannous fluoride dentifrices compared with controls was found in a meta-analysis including six 8-week hypersensitivity studies. (*Am J Dent* 2020;33:95-105).

Clinical significance: The use of stabilized stannous fluoride dentifrices to relieve dentin hypersensitivity and to prevent the initiation of dental erosion speaks in favor of this treatment strategy.

✉: Dr. Katarina A. Konradsson, Department of Odontology, Faculty of Medicine, Umeå University, SE-901 87 Umeå, Sweden. E-✉: katarina.a.konradsson@umu.se

Introduction

During the past few decades, dental health has improved steadily in western countries, but different conditions, such as dentin hypersensitivity, dental erosion and caries are still commonly found. These conditions affect oral health, which imposes a burden on both individuals and society.[1]

Globally, untreated caries in permanent teeth constitutes the most prevalent disease in humans, affecting 35% of the population, and it is further estimated to affect 60-90% of all schoolchildren.[2-4] The disease is caused by the metabolic activity of microorganisms in the dental biofilm, as a result of their formation of acidic end products from the fermentation of dietary carbohydrates, which may in the end, lead to demineralization of dental hard tissues.[5]

Dental erosion is the irreversible loss of dental hard tissue due to exposure to acids without the involvement of bacteria and a high occurrence is mostly present at younger ages.[6,7] The causal factors of erosion may be of either intrinsic or extrinsic origin, where intrinsic factors refer to bulimia or gastro-esophageal reflux disease, for example, while extrinsic factors refer to acidic drinks or food or extensive bleaching, for example.[8,9] In adults, aged from 18 to 88 years, studies have shown prevalence data that ranged between 4% and 100%.[10] The prevalence appears to be increasing and may vary extensively due to differences in assessment methods, types of population, age groups and type of dentition. Moreover, it can be difficult to differentiate dental erosion from other types of tooth wear.[11,12]

Both caries and erosion are the results of a complex interaction with other determinants such as socio-economics and individual susceptibility including saliva and lifestyle factors.[5,9]

Dentin hypersensitivity is relatively common and a prevalence of between 10-57% has been reported, mostly in patients in the age interval of 20-40 years.[13-15] It is defined as a short, sharp pain when eating, drinking or brushing the teeth and can occur in response to thermal, evaporative, tactile, osmotic or chemical stimuli. According to the hydrodynamic theory,[16] the different stimuli can produce a rapid fluid movement in open and exposed dentin tubules, outwards or inwards, which indirectly activates nerve fibers in the pulp nearest the dentin and within the pulp. The symptoms are more common in connection with gingival recession and exposed root surfaces.

Regarding dental caries, the treatment should focus on a reduction in the amount and frequency of sugar, while in the case of dental erosion, the focal point should be a reduction in the exposure to acidic substances. When it comes to dentin hypersensitivity, there are two ways to provide relief; either by using depolarizing agents to block the sensory nerve endpoints at the dentin-pulp border or by occluding the dentin tubules.

In the case of caries, erosion and hypersensitivity, the frequent use of fluorides has been strongly recommended during the past few decades. The main contributor to the decline in dental caries that is seen worldwide is the frequent use of fluoride dentifrices;[17] and in recent years it has been claimed that they provide protection from erosion.[18] In clinical trials, dentifrices containing different active ingredients and fluoride compounds have also been shown to occlude exposed dentin tubules and produce a desensitizing effect.[19-21]

Fluoridated toothpastes are found in a large number of both formulations and concentrations.[22] Stannous fluoride (SnF_2) was the first clinically proven fluoride agent used in a dentifrice in the 1950s for the prevention of dental caries.[23] Other fluoride formulations include sodium fluoride (NaF), sodium monofluorophosphate (SMFP) and amine fluoride. SnF_2 forms insoluble precipitates of stannous compounds, which attach to the dentin.[24,25]

Although SnF_2 has been on the market since the middle of the last century, it is only since the 1990s that the stabilized

Table 1. Inclusion and exclusion criteria.

Inclusion criteria
Randomized controlled trials (RCTs)
Controlled clinical trials (CCTs)
In the control group: no limitation
In the test group: stannous fluoride (SnF_2) or combinations:
0.454 % SnF_2
0.454 % SnF_2 + SHMP (sodium hexametaphosphate)
0.454 % SnF_2 + 5% sodium polyphosphate
0.454 % SnF_2 + calcium pyrophosphate
0.454 % SnF_2 + 350 ppm NaF (sodium fluoride)
Exclusion criteria
Articles published before 1990
Only abstract/Erratum
Reviews
Animal studies
In vitro studies
No control group
No relevant outcome variable
Mouthrinse or gel
Ionic toothbrush or laser in the treatment with SnF_2
SnF_2 + 5 % KNO_3 (potassium nitrate)
SnF_2 + AmF (amine fluoride)
$SnCl_2$ (stannous chloride)

form has been used. Stabilized SnF_2 refers to the addition of chelating agents (gluconate) in order to increase the bioavailability of SnF_2. This prevents the reaction of stannous fluoride with other compounds in the toothpaste and allows stannous fluoride to deliver a broader range of benefits.[26] One potential side effect connected with the use of the SnF_2 toothpaste is extrinsic discoloration, which was solved by the addition of calculus control agents, such as sodium hexametaphosphate (SHMP).[27]

The present systematic review examined the scientific evidence for the efficacy of stabilized stannous fluoride dentifrice in relation to dental caries, dental erosion and dentin hypersensitivity when compared with standard fluoride dentifrices in patients with, or at risk of these three dental conditions.

Materials and Methods

Eligibility - In the present review, a population/problem, intervention, comparison/control and outcome (PICO) process was used[29] to develop inclusion criteria: studies must be controlled trials, in vivo or in situ; the publication language English; publication year 1990 or later. Inclusion criteria were specified for each category:

Population/problem. Individuals with, or at risk of, dental caries, dental erosion or dentin hypersensitivity.

Intervention. Toothbrushing with stabilized SnF_2 dentifrice using a manual or electric toothbrush, or treatment with experimental slurries containing stabilized SnF_2.

Comparison. Toothbrushing with a non-stannous fluoridated dentifrice or non-fluoridated dentifrice/placebo, or no treatment.

Outcome. The primary outcome variable of dental caries was the caries increment measured in decayed, missing and filled permanent tooth surfaces (DMFS). The outcome of dental erosion was enamel dissolution measured as surface roughness and surface loss before and after acid challenges. The outcome of dental hypersensitivity was based on the Schiff air sensitivity scale 28 or the Yeaple probe.[29]

Exclusion criteria - Duplicates, reviews, in vitro studies, animal studies and non-controlled studies were omitted. Studies were

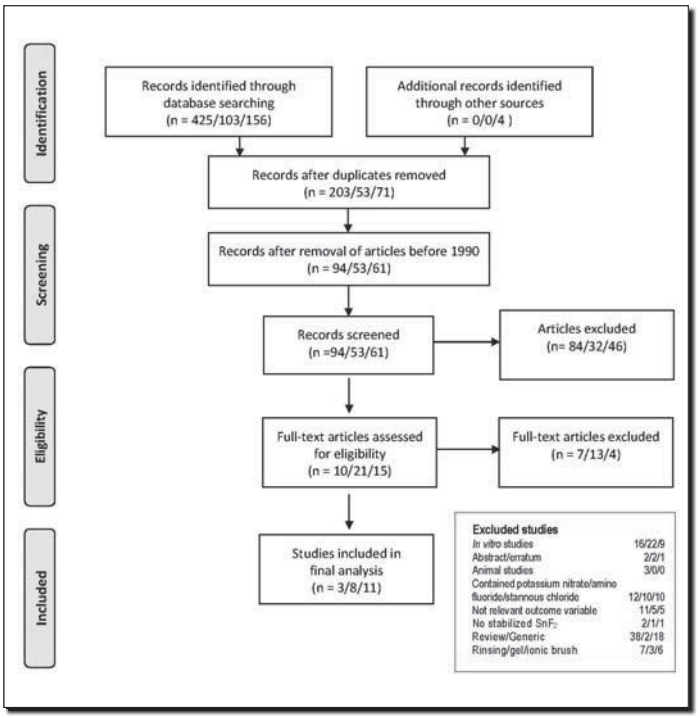

Fig. 1. Flow chart presenting the literature search for dentin hypersensitivity, dental erosion and caries (n = caries/dental erosion/dentin hypersensitivity).

excluded if the test dentifrices contained stannous chloride or stannous fluoride in combination with potassium nitrate, amino fluorides or chlorhexidine. In addition, studies including SnF_2 applied by gels, brushing with ionic or laser toothbrushes, or the use of mouthwashes were excluded (Table 1). Studies were also excluded if there were no clear outcome data regarding dental caries, dental erosion or dentin hypersensitivity.

Literature search strategy - The literature was retrieved from Medline OVID (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations), Embase.com, and the Cochrane Library.

The searches were based on medical subject headings (MeSH) associated with stannous fluoride dentifrice and each dental problem, e.g. dental caries, dental erosion and dentin hypersensitivity. The MeSH-terms identified in Medline were adapted to Embase and Cochrane. In addition, free-text terms were utilized. If appropriate, the search terms were truncated and/or combined with proximity operators.

The following search terms were utilized: dental caries, caries, carious, macula curiosa alba, tooth erosion, acid, dental, tooth, teeth, gastric, dentin, enamel, erosive, anti-erosive, dentin sensitivity, dentin desensitizing agents, dentin, tooth, sensitivity, hypersensitivity, desensitivity, tin fluorides, stannous, stannic, fluoride, difluoride, tetrafluoride, stannofluoride, snf, dentifrices, paste, toothpaste, as well as the free-text terms; crest pro health, crest gum care and crest plus gum care. No restrictions were applied in the search strategy.

The databases were searched from database inception until June 2017 (dental erosion) and until January 2018 (dental caries, dentin hypersensitivity) by information specialists at the university library at the Karolinska Institute in Stockholm, according to the PRISMA flow chart.[30] Manual searches were also conducted by the authors. The reference lists of retrieved full-text articles were read in order to identify additional articles.

Study selection - The reviewers formed pairs. Each pair reviewed

Table 2. Characteristics of included studies of dental caries.

Authors Year	Study design Study type Eval. method duration	Study population N (gender) Age (range) Country	Intervention toothpaste	Intervention (I) Positive/ Negative	Treatment	Outcome	Comments	Risk of bias
Papas et al. 2007	In vivo 279 lesions random-ized double-blind parallel group single center lesion hardness soft/leathery lesions 24 months	n=440 subjects SnF_2 +SHMP USA	I: 0.454% (1,000 ppm F) +	C: 0.22% NaF triclosan/copolymer positive control	Unsupervised brushing at home 1 minute twice/day	Lesion size/ Remineralization: I: 22% (29/134) C: 26% (38/145) P= 0.40	Xerostomic patients Received fillings/ lost lesions during the 2-year study: study: I: 10.4% (14/134) C: 9.0% (13/145) Sponsored by Procter & Gamble	High
Stookey et al. 2004	In vivo randomized double-blind 4 treatment groups 2 examiners Visual-tactile caries ± Rx exams 24 months	n=955 (472 males/ 483 females) I1: n=238 (123 males/ 115 females) 10.6 ±1.1 yrs I2: n=242 (120 males/ 122 females) I3: n=235 (113 males/ 122 females) 10.6±1.1 yrs Puerto Rico	I1: 0.454% SnF_2+SHMP (1100 ppm F) I2: 0.11% NaF (500 ppm F) I3: 0.616% NaF (2800 ppm F)	C: 0.243% NaF (1100 ppm F) positive control	Brushing 1 minute twice/day, supervised brushing in classroom during school hours. Brushing performed *ad libitum* outside school hours	Caries increment (% DMFS) reduction I1: Examiner A: 11.9% P=0.065 I2: Examiner A: 0.4% P= 0.521 Examiner B: 24.8% P= 0.002 I3: Examiner A: 13.0% P= 0.045 Examiner B: 23.2% P= 0.003	Drop-out: 28.5% Sponsored by Procter&Gamble	High

NaF (sodium fluoride), SnF_2 (stannous fluoride), SHMP (sodium hexametaphosphate), NS= not significant.

one of the problem categories: dental caries, dental erosion, or dentin hypersensitivity. To identify potentially eligible studies, each of the reviewers in a pair independently screened all titles and abstracts for a category according to the inclusion and exclusion criteria (Table 1). The reasons for excluding a study were noted. Full-text articles were then obtained and assessed for eligibility. Any disagreement between the two reviewers was resolved by discussion. Neither authors nor journals were blinded to reviewers. Figure 1 summarizes the literature search and article selection in a flow chart.

Data extraction - Data were extracted and tabulated from all studies meeting the inclusion and exclusion criteria (Table 1). Only baseline and final evaluations were reported in the present review. Mean values and standard deviations (SDs) or standard errors (SEs) were extracted from the provided studies.

Risk of bias assessment - The two reviewers in each pair independently scored the possible risk of bias for each included study using a tool for risk bias assessment developed by the Swedish Agency for Health Technology Assessment and Assessment of Social Services.[31] The SBU tool is similar to the Cochrane tool.[32] In short, selection bias, performance bias, detection bias, attrition bias and reporting bias were rated. Based on this information, risk of bias was judged as low, medium or high. Disagreement was resolved by discussion with the other authors.

Data analysis - The outcome of the intervention compared with placebo was of interest in order to estimate the treatment efficacy. For 8-week studies of dentin hypersensitivity, a meta-analysis was feasible and random effects meta-analyses were performed due to expected variability. Reported means and standard deviations (SD) of Schiff's air blast score[29] were used to estimate the standardized mean difference (SMD) and 95% confidence interval (95% CI). The heterogeneity among studies was examined using the I^2 statistic and tested using Cochran's Q statistic. A probability level of $P< 0.05$ was considered significant. Descriptive analyses were applied for studies of dental caries and dental erosion since few studies were available to form the same pairwise comparisons, and for data provided by studies that could not be analyzed by meta-analyses.

Results

The literature search identified 425 articles referring to dental caries, 103 to dental erosion, and 160 to dentin hypersensitivity (Fig. 1). After duplicates and articles published before 1990 were excluded, 208 abstracts were screened. No article published in the 1990s met all inclusion and exclusion criteria. Finally, 10 articles were reviewed in full text with regard to dental caries, 21 to dental erosion, and 15 to hypersensitivity. Hand searching yielded no additional articles.

Dental caries

Three full-text articles,[33-35] published between 2002 and 2007, met the inclusion criteria (Table 1) and were included in the final descriptive analysis. The study design, characteristics, outcome variables, results and risk of bias in the included studies are presented in detail (Table 2). A randomized 24-month study,[33] performed in Puerto Rico, evaluated %DMFS reduction after using three different sodium fluoride toothpastes in comparison to a stannous fluoride toothpaste. All individuals were evaluated independently by two examiners. A significant difference in caries reduction was found between the two examiners, but the 0.454% SnF-SHMP and the 2,800 ppm F

(NaF) resulted in a significantly higher caries reduction compared with the toothpaste containing 1,100 ppm F (NaF).

In an in situ crossover study, Wefel et al[34] tested a 0.454% SnF_2/13% SHMP toothpaste in comparison with four other fluoride toothpaste formulations. Sound root sections and sections with root surface lesions and with enamel surface lesions were placed in the oral cavity temporarily. After one month's use of a toothpaste product, the changes in the lesion size were evaluated by polarized light microscopy. The use of the experimental 0.454% SnF_2/13% SHMP and NaF dentifrice formulations suggested similar anti-caries activity in comparison to their controls.

In a randomized clinical study,[35] root caries remineralization was evaluated after 24-months' use of a dentifrice

Table 3. Characteristics of included studies of dental erosion.

Authors Year	Study design Study type Eval. method duration	Study population N (gender) Age (range) Country	Intervention (I)	Control Positive/ Negative	Treatment	Outcome	Comments	Risk of bias
Barlow et al. 2009	In situ randomized single-blind placebo-controlled crossover design erosion resistance	n= 56 32±12.1 yrs UK	I: 1100 ppm F as SnF_2	C1: 1150 ppm NaF positive control C2: 1100 ppm NaF positive control C3: Placebo (0 ppm F) negative control	Treated bovine enamel 25 min in grapefruit juice water rinsing swishing for 1 min water rinsing	Treatment difference: I vs C1: -7.5, P<0.01 I vs C2: - 6.3, P<0.05 I vs C3: 22.5, P<0.0001	Sponsored by GlaxoSmithKline Advantage C1, C2	High
Bellamy et al 2014	In situ randomized parallel group contact profilometry	n=12 Germany	I: 1100 ppm SnF_2 + 350 ppm NaF	C1: 1450 ppm NaF Positive C2: Tap water` negative control	Treated human enamel swishing with TP slurry twice/day water rinsing between citric acid 5 min 4 times/day Total 300 mins	Enamel loss in µm (mean ±SE): I: 2.03 (±0.57) C1: 15.53 (±3.53) C2: 18.94 (±3.53) I vs C1: P= 0.0044 I vs C2: P= 0.0011 C1 vs C2: NS	Sponsored by Procter&Gamble	High
Hooper et al. 2007	In situ single-blind single-center profilometry 15 days	n=15 18-35 yrs UK	I: SnF_2+ SHMP (test formulation)	C1: NaF positive control C2: "Volvic" mineral water negative control	Treated human enamel rinsing with TP slurry twice/day for 1 min orange juice 4 times/day	Enamel loss in µm (mean ±SE): I: − 0.946 ±1.413 C1: −2.258 ±3.628 C2: −3.233 ±4.424 I vs C1: P=0.009 I vs C2: P= 0.001	Sponsored by Procter&Gamble	High
Hove et al 2014	In situ randomized single-blind white light interferometry 9 days	n=8 22-30 yrs Norway	I1: 1450 ppm F (1100 ppm SnF_2 + 350 ppm NaF) I2: 1000 ppm SnF_2	C1: Fluoride-free TP negative control C2: Fluoride-free TP + SnF_2 solution positive control	Brushed human enamel water rinsing 2 min in hydrochloric acid (0.01 M)	Enamel wear in µm (mean ±SE): I1: -33.3±7.4 I2: -14.5±9.3 C1: - 29.2±10.5 C2: +0.4±1.3	Sponsored by Lilleborg AS SnF_2 solution (C2) gave full protection Advantage I2	High
Huysmans et al. 2011	In situ randomized double-blind single-center between the combined split- mouth and crossover light profilometry 5 days	n=12 (11 females/ 1 male) 20-50 yrs Netherlands	I1: 1400 ppm F (1050 ppm SnF_2 +350 ppm AmF) I2: 1450 ppm F (1100 ppm SnF_2 + 350 ppm NaF)	C1: 1450 ppm NaF Positive C2: water negative control	Brushed (brushing machine) human teeth citric acid 5 min water rinse	Enamel wear in µm (% ±SD): I1: 34% (39%) P<0.01 I2: 26% (25%) P<0.01 C1: 7% (20%) (NS) Reduction compared to water-brushed control (C2)	Not funded by manufacturer No differences between SnF_2 TP Advantage SnF_2 (I1 and I2)	Low
West et al. 2017a	In situ randomized double-blind controlled crossover contact profilometry 10 days	n=33 44.6 yrs UK	I: 1450 ppm F (1100 ppm SnF_2 + 350 ppm NaF)	C: 1450 ppm SMFP + arginine positive control	Treated human enamel swishing twice/day With dentifrice slurry sipping and swishing orange juice 10 times during 10 min 4 times/day	Enamel loss in µm (mean ±SE): I: 0.0747± 0.008 C: 1.2255± 0.138 P < 0.0001	Drop-out: n=1 Sponsored by Procter&Gamble Advantage I	High
West et al. 2017b	In situ randomized double-blind single center crossover contact profilometry 15 days	n=33 44.8±12.15 (23-65) yrs USA/UK	I: 1450 ppm F (1100 ppm SnF_2 + 350 ppm NaF)	C: 1450 ppm NaF positive control	Treated 4 study periods swishing twice/day water rinsing orange juice application	Enamel loss in µm Median, 95% CI: I: 1.60 (1.40-1.82) C: 5.03 (4.42-5.72) P< 0.0001	Drop-out: n=3 Sponsored by Procter&Gamble	High

AmF (amine fluoride), NaF (sodium fluoride), SnF_2 (stannous fluoride), SHMP (sodium hexametaphosphate), SMFP (sodium monofluorophosphate), TP= toothpaste, NS= not significant.

Table 3. Characteristics of included studies of dental erosion. (Continued).

Authors Year	Study design Study type Eval. method duration	Study population N (gender) Age (range) Country	Intervention (I)	Control Positive/ Negative	Treatment	Outcome	Comments	Risk of bias
Young et al. 2006	In vivo blinded calcium (Ca)-analysis, model 3300 atomic absorption spectrometry	n=20 31 (19-50) yrs Norway	I: SnF_2 (0.4 % SnF_2 + 1 % stannous pyrophosphate + 0.1 % NaF)	C: 0,15 % NaF positive control	Treated anterior teeth citric acid application, water rinsing, fluoride TP application	Ca content (10 nmol ±SE): I: 0.649 ± 0.126 C: 1.502 ± 0.188 P< 0.001 Ca content (100 nmol ±SE): I: 3.43 ± 0.355 C: 6.42 ± 0.468 P< 0.001	Not funded by manufcaturer SnF_2 provided significant protection compared to NaF with the weak acid, while no protection with the strong acid	Low

AmF (amine fluoride), NaF (sodium fluoride), SnF_2 (stannous fluoride), SHMP (sodium hexametaphosphate), SMFP (sodium monofluorophosphate), TP= toothpaste, NS= not significant.

containing 0.454% SnF_2/SHMP in comparison to a NaF/ triclosan/copolymer dentifrice in xerostomic subjects. The two treatments resulted in similar remineralization.

Dental erosion

Eight full-text articles,[18,36-42] published between 2006 and 2017, met the inclusion criteria, and were included in the final descriptive analysis and presented in Table 3. The two most used endpoints were enamel dissolution and surface roughness. In the in vivo study,[36] the dissolution of enamel following citric acid exposure was measured. Treatment with either SnF_2 or NaF toothpaste was evaluated and the SnF_2 toothpaste resulted in lower dissolution values.

In the other seven in situ studies, six used human enamel[37-42] and only one[18] used bovine enamel. Pieces of enamel were applied in different kinds of appliances and were worn in the mouth for different periods of time. In most of the studies they were swished in a toothpaste water slurry, outside the mouth two to four times a day. In two studies, the specimens were brushed.[37,38] The surface roughness and surface loss following different acidic challenges were evaluated by contact profilometry,[39-42] by light profilometry and scanning electron microscopy (SEM),[37] by white light interferometry[38] and by a relative erosion-resistance technique.[18] Different erosive products, such as orange juice, grapefruit juice, citric acid and hydrochloric acid (HCL), with various types of erosion cycle, were used. In seven of the eight eligible studies the SnF_2 containing toothpaste showed significantly lower dissolution and surface roughness values compared with controls. One study[18] showed lower values for the use of the control toothpaste containing NaF.

Dentin hypersensitivity

The 11 included articles (Table 4) were published between 2005 and 2016.[43-53] They were all controlled, randomized, examiner-blind and parallel-group trials and represented 1,361patients with 618 patients in the test group and 617 in the control group. The age of the participants ranged between 18 and 70 years (mean 39 years), with 66% female subjects. A total of 1.1% of the subjects were lost to follow-up at the end of the test periods. Most of the studies were performed in the United States, but two were performed in China[43,44] and one in Ireland.[45] All the included studies were supported by the manufacturers or had authors employed by the companies. The study period was 3 days in one study,[43] 2 weeks in four studies,[44-47] and 8 weeks in six studies.[48-53] The test dentifrice contained stabilized 0.454% SnF_2 in four studies[44- 47] and combined with SHMP in three studies,[48-50] combined with sodium-polyphosphate in three studies,[45,52,53] and combined with NaF in two studies.[43,51] Of the control dentifrices, eight were negative controls and three were positive controls. The negative control dentifrices contained 0.24% NaF in three studies,48-50 and 0.76% SMFP in five studies.[45-47,52,53] Two positive control dentifrices contained SMFP and 8% arginine,[43,44] and one positive control dentifrice contained NaF and 0.3% triclosan.[51]

To assess dentin hypersensitivity, the Schiff air blast test was used in all the studies,[43-53] the Yeaple probe for tactile assessment in nine of the studies[43-53] and the VAS scale in five studies.[43-46,53] The Schiff air blast test showed that the SnF_2 toothpastes significantly reduced the dentin hypersensitivity compared with the controls in all studies (P< 0.001) except in one of the three sub-studies by Parkinson et al.[45] At the end of each test period, the change from baseline in the mean sensitivity score was 1.42 in the SnF_2 groups and 0.55 in the control groups. The mean difference between the test and control groups in the Schiff air blast score for all studies was 0.84, which yielded a mean percentage reduction of 40.9% (range 9.0-74.2%). In the studies in which both the Yeaple probe and Schiff air blast test were used, the results of both test methods showed the same significant P-values (Table 4).

A random-effects meta-analysis (Fig. 2), based on six 8-week studies reporting the Schiff air blast scores,[48-53] showed a mean difference score in favor of the SnF_2 toothpaste compared with positive controls (P> 0.0001).

The assessment of risk of bias was judged as high in one study and low and medium in four and six studies respectively. The risk of conflict of interest was judged as high in all studies due to the fact that either the authors were employed by a company or the study was funded by a company.

Discussion

In the present study, toothpaste-containing stabilized stannous fluoride, both with and without sodium hexameta-phosphate (SHMP), has been shown to have preventive and therapeutic effects on dentin hypersensitivity and dental ero-

Table 4. Characteristics of included studies of dentin hypersensitivity.

Authors Year	Study design Study type Eval. method duration	Study population N (gender) Age (range) Country	Intervention (I)	Control Positive/ Negative	Treatment	Outcome	Comments	Risk of bias
Chaknis et al. 2011	Randomized parallel group double-blind single-center airblast (Schiff score) tactile stimulus (Yeaple probe) 8 weeks	n=118 (14 males/ 104 females) I1: n=40; I2:n=39; C: n=39 I1: 52.1 yrs (18-70) I2: 47.1 yrs (21-63) C: 53.4 yrs (41-70) USA	I1: 0.3% triclosan + 0.24% NaF (1100 ppm F) I2: 0.454% SnF_2 I2: 0.454% SnF_2 + SHMP + zinc lactate	C: 0.24% NaF (1100 ppm F) negative control	Tooth brushing 1 min twice/day	Schiff air score: BL: I1: 2.50, I2: 2.50, C: 2.40 8 w: I1: 0.99, I2: 1.36, C: 1.50 I1 vs I2: P< 0.05, 27.2% I2 vs C: NS, RD:9.3% Yeaple probe score: BL: I1: 13.63, I2: 14.10, C:13.08 8 w: I1: 33.05, I2: 23.97, C:20.51 I1 vs I2: P< 0.05, RD:37.9% I2 vs C: NS, RD:16.9%	Sponsored by Colgate-Palmolive Significant differences between I1 and I2 (SnF_2) No difference between I2 (SnF_2) and negative	Medium
He et al. 2011a	Randomized parallel group examiner-blind single-center airblast (Schiff air score) visual analogue scale (VAS) 3 days	n=81 (6 males/ 75 females) I: n=40, C: n=41 43 yrs (20-62) China	I: 0.454% SnF_2 + 0.077% NaF (1450 ppm F)	C: SMFP (1450 ppm F) + 8.0% arginine and calcium carbonate positive control	Tooth brushing 2 min twice/day	Schiff air score: BL: I: 2.26, C: 2.38 3 d: I: 1.01, C:2.20 I vs C:P<0.001, 54.1% VAS: BL: I: 6.98, C: 7.13 3 d: I:1.66, C: 6.42 I vs C: P<0.001, RD:74.1% BL vs 3d: P<0.0001 for both	Sponsored by Procter & Gamble Both dentifrices showed a desensitizing effect, SnF_2 dentifrice significantly better than control	Medium
He et al. 2011b	Randomized parallel group examiner-blind airblast (Schiff air score) tactile stimulus (Yeaple probe) visual analogue scale (VAS) 2 weeks	n=111 (35 males/) 76 females I: n=56, C: n=55 44 yrs (19-64) USA	I: 0.454% SnF_2	C: 0.76% SMFP (1000 ppm F) negative control	Tooth brushing 2 min twice/day	Schiff air score: BL: I: 2.79, C: 2.86 2 w: I: 1.07, C: 2.75 I vs C: P<0.0001, RD: 61.3% Yeaple probe score: BL: I:10, C:10 2 w: I:42.86, C:12.64 I vs C: P<0.0001, RD:239% VAS: BL: I:76.9, C:78.7 2 w: I:23.6, C:70.7 I vs C: P<0.0001	Sponsored by Procter & Gamble Significant desensitizing effect of SnF_2 dentifrice	Medium
He et al. 2011c	Randomized parallel group examiner-blind stratified single-center airblast (Schiff air score) visual analogue scale (VAS) 2 weeks	n=80 I: n=40, C: n=40 43 yrs (18-56) China	I: 0.454% SnF_2	C: SMFP (1450 ppm F) + 8.0% arginine and calcium carbonate positive control	Tooth brushing 2 min twice/day	Schiff air score: BL: I:2.38, C:2.53 2 w: I:1.60, C:2.00 I vs C: p<0.001, RD: 20% VAS: BL: I: 6.88, C: 7.19 2 w: I: 3.98, C: 5.54 I vs C: P<0.0001 BL vs 2w: P<0.01 for both	Sponsored by Procter & Gamble Both dentifrices showed a desensitizing effect, SnF_2 dentifrice significantly better than control	High
He et al. 2014a	Randomized parallel group stratified double-blind single center airblast (Schiff air score) tactile stimulus (Yeaple probe) 2 weeks	n=116 (26 males/ 90 females) I: n=58, C: n=58 45.7 yrs (24-65) USA	I: 0.454% SnF_2	C: 0.76% SMFP (1000 ppm F) negative control	Tooth brushing 2 min twice/day	Schiff air score: BL: I: 2.45, C: 2.46 2 w: I: 0.51, C: 1.98 I vs C: P<0.0001, RD:74.2% Yeaple probe score: BL: I: 10, C: 10 2 w: I: 44.5, C: 13.8 I vs C: P<0.0001, RD:125%	Sponsored by Procter & Gamble Both dentifrices showed a desensitizing effect, SnF_2 dentifrice significantly better than control	Low
He et al. 2014b	Randomized parallel group double blind single center airblast (Schiff air score) tactile stimulus (Yeaple probe) 8 weeks	n=100 (20 males/ 77 females) I: n=49, C: n=48 45.5 yrs (21-65) USA	I: 0.454% SnF_2 + 0.077% NaF (1450 ppm F)	C: 0.32% NaF (1450 ppm F) + 0.3% triclosan positive control	Tooth brushing 1 min twice/day	Schiff air score: BL: I: 2.63, C: 2.65 2 w: I: 0.61, C: 1.90 I vs C: P<0.0001, RD:68% Yeaple probe score: BL: I: 10, C: 10 2 w: I: 37.3, C: 13.1 I vs C: P<0.0001, RD:184%	Drop-out: n=3 Sponsored by Procter & Gamble SnF_2 dentifrice significantly better than control	Low
Parkinson et al. 2013	Randomized parallel group stratified examiner-blind single center airblast (Schiff air score) tactile stimulus (Yeaple probe) 8 weeks	n=118 (35 males/ 83 females) I: n=60, C: n=58 36 yrs (21-65) USA	I: 0.454% SnF_2 + 5% STP experimental	C: 0.76% SMFP (1000 ppm F) negative control	Tooth brushing 1 min twice/day	Schiff air score: BL: I: 2.7, C: 2.7 8 w: I:1.8, C: 2.2 I vs C: P<0.0001, RD:20.2% Yeaple probe score: BL: I: 10, C: 10 8 w: I: 31.2, C: 14.3 I vs C: P<0.0001, RD:119.9%	Sponsored by GlaxoSmithKline Both dentifrices showed a desensitizing effect, SnF_2 dentifrice significantly better than control	Medium

NaF (sodium fluoride), SnF_2 (stannous fluoride), SHMP (sodium hexametaphosphate), SMFP (sodium monofluorophosphate), STP (sodium tripolyphosphate), BL=baseline, NS= not significant, RD= relative difference.

Table 4. Characteristics of included studies of dentin hypersensitivity. (Continued).

Authors Year	Study design Study type Eval. method duration	Study population N (gender) Age (range) Country	Intervention (I)	Control Positive/ Negative	Treatment	Outcome	Comments	Risk of bias
Parkinson et al. 2015	Randomized parallel group stratified examiner-blind single center airblast (Schiff air score) tactile stimulus (Yeaple probe) visual analogue scale (VAS) 8 weeks	n=119 (27 males/ 92 female) subjects who completed: I: n=59, C: n=60 42.7 yrs (19-65) USA	I: 0.454% SnF_2 + 5% STP experimental	C: 0.76% SMFP (1000 ppm F) negative control	Tooth brushing 1 min twice/day	Schiff air score: BL: I:2.25, C: 2.26 8 w: I: 0.79, C: 2.09 I vs C: P<0.0001, RD:62.8% Yeaple probe score: BL: I: 10.4, C: 10.1 8 w: I: 41.9, C: 14.3 I vs C: P<0.0001, RD:186% VAS: BL: I=58.2, C=58.4 8 w: I=21.8, C=43.8 I vs C: P<0.0001, RD: 49.5%	Drop-out: n=5 Sponsored by GlaxoSmithKline Both dentifrices showed a desensitizing effect, SnF_2 dentifrice significantly better than control	Low
Parkinson et al. 2016	Randomized parallel group examiner-blind airblast (Schiff air score) tactile stimulus (Yeaple probe) visual analogue scale (VAS) 2 weeks	Study 1: n=118 (44 males/ 74 females) I: n=59, C: n=59 36 yrs (18-65) USA, Ireland	I: 0.454% SnF_2	C: 0.76% SMFP (1000 ppm F) negative control	Tooth brushing 1 min twice/day	Study 1: Schiff air score: BL: I:2.81, C 2.78 2 w: I:1.57, C:2.06 I vs C: P<0.0001, RD:24% Yeaple probe score: BL: I: 10, C: 10 2 w: I: 15.85, C: 8.69 I vs C: P=0.0004, RD:82% VAS: I: 60.2, C: 60.4 2 w: I: 29.9, C: 37.1 I vs C: P=0.0400	Drop-out, total: n=3 Sponsored by GlaxoSmithKline Study 1 showed significant improvements for the SnF_2 dentifrice compared with control	Low
		Study 2: n=113 (34 males/ 79 females) I: n-56; C: n=57 36 yrs (19-64) USA, Ireland	I: 0.454% SnF_2 + 5% STP experimental	C: 0.76% SMFP (1000 ppm F) negative control	Tooth brushing 1 min twice/day	Study 2: Schiff air score: BL: I: 2.69, C: 2.69 2 w: I :1.49, C: 2.32 I vs C: P<0.0001, RD:36% Yeaple probe score: BL: I: 10, C: 10 2 w: I: 32.94, C: 13.52 I vs C: P<0.0001, RD: 144%	Study 2 showed significant improvements for the SnF_2 dentifrice compared to the control	
		Study3: n=120 (45 males/ 75 females) I: n=60, C: n=60 29 yrs (18-63) USA, Ireland	I: 0.454% SnF_2 + 5% STP experimental	C: 0.76% SMFP (1000 ppm F) negative control	Tooth brushing 1 min twice/day	Study 3: Schiff air score: BL: I: 2.51, C: 2.51 2 w: I: 1.16, C: 1.35 I vs C:P=0.177 Yeaple probe score: BL: I: 10.8, C: 11.5 2 w: I: 25.69, C: 23.48 I vs C: P=0.487 VAS: I: 53.6, C: 61.1 2 w: I: 29.9, C: 41.3 I vs C: P=0.153	In study 3, no difference between SnF_2 dentifrice and I vs C: P=0.153	
Schiff et al. 2005	Randomized parallel group stratified double-blind airblast (Schiff air score) tactile stimulus Yeaple probe 8 weeks	n=77 (33 males/ 44 females) I: n=38, C: n=39 31.4 yrs (18-65) USA	I: 0.454% SnF_2 + SHMP	C: 0.24% NaF (1100 ppm F) negative control	Tooth brushing 1 min twice/day	Schiff air score: BL: I=2.55, C=2.71 8 w: I=0.92, C=1.63 I vs C: P<0.0001, RD 44% Yeaple probe score: BL: I=10, C=10 8 w: I=29.1, C=14.4 I vs C: P<0.0001, RD:102%	Sponsored by Procter & Gamble Both dentifrices showed a desensitizing effect, SnF_2 dentifrice significantly better than control	Medium
Schiff et al. 2006	Randomized parallel group stratified double-blind airblast (Schiff Sens score) tactile stimulus (Yeaple probe) 8 weeks	n=90 (42 males/ 48 females) I: n=45, C: n=45 32.2 yrs (20-64) USA	I: 0.454% SnF_2 + SHMP	C: 0.24% NaF (1100 ppm F) negative control	Tooth brushing 1 min twice/day	Schiff air score: BL: I=2.69, C=2.64 8 w: I=1.10, C=1.95 I vs C: (P<0.0001), RD:44% Yeaple probe score: BL: I=10, C=10 8 w: I=25.3, C=14.8 I vs C: P<0.0001, RD:71%	Sponsored by Procter & Gamble Both dentifrices showed a desensitizing effect, SnF_2 dentifrice significantly better than control	Medium

NaF (sodium fluoride), SnF_2 (stannous fluoride), SHMP (sodium hexametaphosphate), SMFP (Sodium monofluorophosphate), STP (sodium tripolyphosphate), BL= baseline, NS= not significant, RD= relative difference.

sion. Although there is some support for the stannous fluoride-containing formulations compared with the control products in terms of dental caries, the small number of longitudinal clinical studies within this area limits the opportunity to draw any clear conclusions about the caries prevention effect, regarding both the development of new lesions and the progression of existing lesions. Moreover, regarding erosion, there is a lack of in vivo studies, which can be explained by the fact that both dental caries and erosion develop during a long period, often over several years, and longitudinal studies are both costly and difficult to perform for ethical reasons.

Dental caries

In the present study, the in vitro studies were excluded, leaving only two in vivo studies,[33,35] and one in situ study.[34] A significant reduction in caries prevalence after use of stabilized

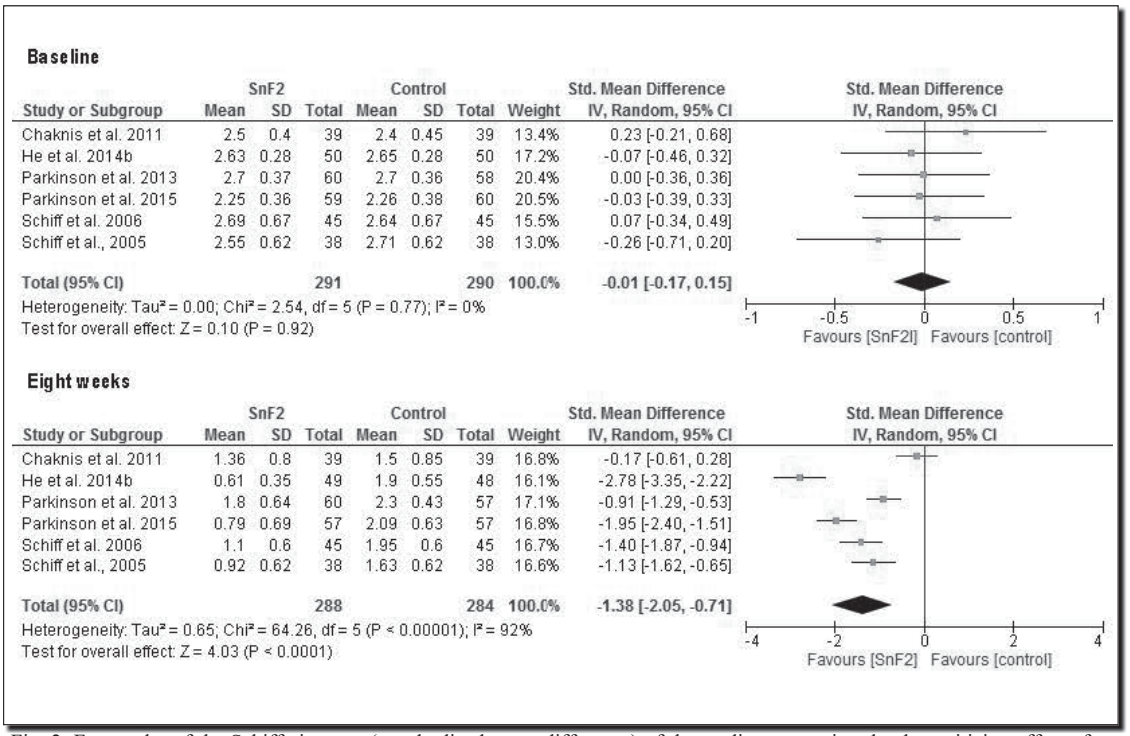

Fig. 2. Forest plot of the Schiff air score (standardized mean difference) of the studies comparing the desensitizing effect of a stabilized stannous fluoride (SnF_2) dentifrice with that in the control group at baseline and after 8 weeks of daily toothbrushing.

stannous fluoride (SnF_2) in comparison to a sodium fluoride toothpaste, both with a concentration of 1,100 ppm F, was found after supervised toothbrushing in schoolchildren for two years.[33] However, limitations in the study were the relatively high dropout, a large difference in the registration of lesions between the two examiners and the fact that the study was both sponsored and had co-authors employed by the manufacturer. The other study reported on the demineralization of root surface lesions in dry-mouth individuals by lesion hardness.[35] The in situ study[34] evaluated the effect of unsupervised brushing with a SnF_2/SMFP toothpaste and analyzed the demineralization of enamel and dentin surface lesions using polarized light microscopy. In the studies by Papas et al[35] and Wefel et al,[34] the SnF_2/SMFP dentifrice resulted in a slight improvement or similar effect in comparison to their respective controls.

The fact that few clinical studies of SnF_2 in relation to dental caries have been performed may seem surprising. It would have been desirable to have more studies evaluating and verifying the positive effect of SnF_2 compared with other fluoride compounds against dental caries. However, the stabilized form of stannous fluoride was introduced during a period in which a clear decline in caries prevalence had been observed in most countries. The basic recommendation to brush twice daily with fluoridated toothpaste had already been shown to be successful for caries prevention and limited attention has since been paid to factors such as fluoride compounds. It is therefore possible to question whether different surrogate measures, e.g. effects on cariogenic bacteria and the dental biofilm, should have been taken into consideration.

Dental erosion

The results showed that most studies were in favor of stabilized stannous fluoride, in terms of providing a protection from dental erosion. These results are in line with the consensus report from the European Federation of Conservative Dentistry,[54] which stated that one possible option for slowing down the progression of erosive tooth wear is to use a mouth rinse or toothpaste containing stannous fluoride or stannous chloride.

However, when analyzing the results and the methods applied in the studies included in the present review, there are limitations that need to be discussed and commented on. First, there is a lack of in vivo studies. In the present review, the in vitro studies were excluded, leaving only in situ studies and one in vivo study. The variety of methods used make it difficult to compare the results, as both the evaluation and experimental methods differ. In most in situ studies, human or bovine tooth enamel or dentin specimens were worn in special appliances in the mouth for different periods of time. However, in almost all the studies, they were not brushed inside or outside the mouth, instead they were "treated" outside the mouth in a toothpaste slurry for a period of time, which does not reflect the true use of toothpaste.

In two of the eight studies.[37,38] the teeth were brushed. In these two studies, which furthermore were not funded by a company, the advantage of an SnF_2-containing dentifrice was demonstrated. In the other six studies, the specimens were swished in a dentifrice-water slurry and no brushing performed. Furthermore, different types of erosion cycle and also different erosive materials were used in the different studies, also making comparisons difficult. It is therefore difficult to translate these results into a clinical reality where actual toothbrushing is recommended. This was highlighted in the article by Young et al,[36] who claimed that the combination of toothpaste and the physical movements of a toothbrush may result in a higher mineral loss.

The favorable erosion protection benefit of stannous fluoride was recognized both in studies that received financial

support from manufacturers and in studies in which no funding or employee connection could be detected.[36-38] Another concern, which has been highlighted by a few authors,[55-57] is the importance of other ingredients in a toothpaste, e.g. the abrasive particles, which might influence the results. A toothpaste contains between 8-20% abrasive particles of which the most common today are different kinds of silica composition.[58]

From a clinical perspective, it is important to point out that a surface that has been severely eroded does not have much enamel left and the abrasiveness of a toothpaste might therefore be of concern. In the case of severely eroded teeth, sometimes almost all the enamel has been eroded, thereby leaving just the dentin or softened enamel and an increase in the significance of the abrasiveness of the toothpaste. Furthermore, toothbrushing with conventional fluoridated dentifrices, which might be more abrasive than the experimental ones, might have completely removed this thin softened layer rather than allowing the remineralization of CaF_2 precipitates, as suggested by Moron et al.[59] Taking this in consideration, the use of mouth rinses with SnF_2 or other treatment options in severely eroded patient cases might be preferable.

As toothpaste formulations also differ in terms of other components, it is obvious that it is difficult to claim that the anti-erosion effect is due to a single compound. It would be interesting to compare toothpastes where the only difference was the claimed erosion protection ingredient.

Dentin hypersensitivity

In the present review, stabilized stannous fluoride-containing dentifrices showed significant improvements in dentin hypersensitivity when used twice daily for 1 minute in comparison with both negative and positive control toothpastes. The efficacy was noted after just 3 days and was maintained for up to 8 weeks. The average sensitivity-inhibiting effect in the 11 SnF_2 treatment studies included here was 41% for the Schiff sensitivity score using the endpoint data of the study period. According to the criteria of the American Dental Association (ADA),[60] a treatment is thought to be effective if it leads to a 33% reduction in dentin hypersensitivity in at least two published studies. The present study demonstrated that all 11 included studies showed statistically significant improvements in dentin hypersensitivity, resulting in an average reduction well above the ADA criteria for clinical relevance. In addition, the forest plot of the meta-analysis, based only on six 8-week studies, demonstrated that toothbrushing with stabilized SnF_2 reduced dentin hypersensitivity to a higher degree than standard fluoride toothpastes.

Two well-accepted efficacy measurements were used for the assessment of dentin hypersensitivity, the Yeaple Probe for tactile measurement and the Schiff air blast test for thermal measurements. In nine of the 10 studies in which both were used, they followed each other in revealing statistically significant differences between the SnF_2 dentifrices and their controls. However, in order to minimize the heterogeneity of the studies, this review has focused on the results of the air blast test as the stimulus, as this test has been suggested to be a more accurate method of evaluating dentin hypersensitivity.[20] Furthermore, it involves more exposed tooth surfaces and was used in all 11 studies.

All dentifrices, whether test or control, were associated with statistically significant improvements in terms of dentin hypersensitivity. The magnitude for the stannous fluoride toothpaste was significantly higher compared with control products. The reduced sensitivity from baseline in the negative control groups may also be due to a placebo effect, as shown in earlier studies of dentin hypersensitivity.[61-63] In one of the sub-studies by Parkinson et al,[45] the reduction in dentin hypersensitivity for the negative control resulted in a non-significant difference from the SnF_2 test toothpaste. It is possible that the different control products are able to explain the variability and heterogeneity between the published studies.

From an age perspective, the included subjects were relevant for the study objective. A previous systematic review of dentin hypersensitivity[21] concluded that the most problematic aspect was the large-scale heterogeneity in the study designs. The present review comprised studies with different combinations of test and control group, where other active ingredients were also evaluated. Moreover, in the test groups, the stannous fluoride was combined with different compounds which alone, or in combination, can have an effect on dentin hypersensitivity. Only in two studies[46,47] was SnF_2 tested alone. The SnF_2 groups were also tested against positive control groups containing arginine or triclosan. In the two short-term studies directly comparing arginine with SnF_2, the latter substance demonstrated a significantly better effect in terms of reducing the pain of dentin hypersensitivity.[43,44] Chaknis et al[48] evaluated a dentifrice containing 0.3% triclosan and reported a significant reduction in dentin hypersensitivity after 8 weeks. In this study, the triclosan-containing dentifrice produced significant improvements in dentin hypersensitivity compared with a commercially available stannous fluoride dentifrice with SMFP and zinc lactate. In the study by He et al[51] the stannous-containing toothpaste without zinc lactate had a significantly better desensitizing effect than the triclosan-containing dentifrice. The lengths of the test periods varied from 3 days to 2 and 8 weeks, which implied that the test substances showed both short- and long-lasting efficacy. All the studies were randomized and had parallel groups, thereby overcoming the problem with a carry-over effect if a split-mouth design had been tested.

Bias

In analyzing the included articles, the SBU´s recommendations for quality assessment were used. Many of the included studies were sponsored by the manufacturers or had authors employed by a toothpaste manufacturer. Although the studies were carefully executed with good quality in terms of body of evidence, it was regarded as a factor influencing bias. Additional studies that are less dependent on commercial interests and performed by independent researchers are needed. Studies with more similar designs, including comparable test and control products, are essential.

Clinical significance

The choice of dentifrice may have an impact on dental health. The use of stabilized stannous fluoride dentifrices to

relieve dentin hypersensitivity and to prevent the initiation of dental erosion speaks in favor of this treatment strategy.

Conclusion

The present review found that stabilized SnF_2 dentifrice had a positive effect on the reduction of dentin hypersensitivity. An improved anti-erosive effect, especially in terms of preventing the initiation of dental erosion, and also a certain anti-caries effect compared to toothpastes not containing SnF_2 has been observed but the there is a great need of a new generation of well-conducted studies for further support of these findings.

Acknowledgements: To Magdalena Svanberg and Klas Moberg, librarians at Karolinska Institute, Huddinge, Sweden, for their assistance with the literature search. We also thank Helena Domeij, DDS, PhD, and the Swedish Agency for Health Technology Assessment and Assessment for Social Service for assistance with the meta-analyses.

Disclosure statement: The authors declared no conflict of interest.

Dr. Konradsson is Associate Professor, Department of Odontology, Faculty of Medicine, Umeå University, Umeå, Sweden. Dr. Lingström and Dr. Emilson are Professors, Department of Cariology and Dr. Ramberg is Associate Professor, Institute of Odontology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. Dr. G. Johannsen is Professor and Dr. A. Johannsen is Associate Professor, Department of Dental Medicine, Division of Oral Diseases, Karolinska Institute, Huddinge, Sweden.

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