Review

Review on fluoride-releasing restorative materials—Fluoride release and uptake characteristics, antibacterial activity and influence on caries formation

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Abstract

Objectives. The purpose of this article was to review the fluoride release and recharge capabilities, and antibacterial properties, of fluoride-releasing dental restoratives, and discuss the current status concerning the prevention or inhibition of caries development and progression.

Methods. Information from original scientific full papers or reviews listed in PubMed (search term: fluoride release AND (restorative OR glass-ionomer OR compomer OR polyacid-modified composite resin OR composite OR amalgam)), published from 1980 to 2004, was included in the review. Papers dealing with endodontic or orthodontic topics were not taken into consideration. Clinical studies concerning secondary caries development were only included when performed in split-mouth design with an observation period of at least three years.

Results. Fluoride-containing dental materials show clear differences in the fluoride release and uptake characteristics. Short- and long-term fluoride releases from restoratives are related to their matrices, setting mechanisms and fluoride content and depend on several environmental conditions. Fluoride-releasing materials may act as a fluoride reservoir and may increase the fluoride level in saliva, plaque and dental hard tissues. However, clinical studies exhibited conflicting data as to whether or not these materials significantly prevent or inhibit secondary caries and affect the growth of caries-associated bacteria compared to non-fluoridated restoratives.

Significance. Fluoride release and uptake characteristics depend on the matrices, fillers and fluoride content as well as on the setting mechanisms and environmental conditions of the restoratives. Fluoride-releasing materials, predominantly glass-ionomers and compomers, did show cariostatic properties and may affect bacterial metabolism under simulated cariogenic conditions in vitro. However, it is not proven by prospective clinical studies whether the incidence of secondary caries can be significantly reduced by the fluoride release of restorative materials.

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1. Introduction

Since the observation that secondary caries formation was rarely associated with fluoride-containing silicate cement restorations, increasing attention has been focused on the development of various fluoride-releasing products, to be used as restorative materials, lining cements, sealants and orthodontic cements.

Fluoride is well documented as an anticariogenic agent. A variety of mechanisms are involved in the anticariogenic effects of fluoride, including the reduction of demineralization, the enhancement of remineralization, the interference of pellicle and plaque formation and the inhibition of microbial growth and metabolism [1–4]. Fluoride released from dental restorative materials is assumed to affect caries formation through all these mechanisms and may therefore reduce or prevent demineralization and promote remineralization of dental hard tissues.

Today, there are several fluoride-containing dental restoratives available in the market including glass-ionomers, resin-modified glass-ionomer cements, polyacid-modified composites (compomers), composites and amalgams. Due to their different matrices and setting mechanisms the products vary in their ability to release fluoride. However, it is assumed that the antibacterial and cariostatic properties of restoratives are often associated with the amount of fluoride released.

This paper aimed to summarize the current status of fluoride-releasing dental restoratives, their ability to release and recharge fluoride, their antibacterial activity and cariostatic properties. Therefore, original scientific papers and reviews listed in PubMed or available from peer-reviewed German journals (published between 1980 and 2004) were included in the review. Clinical studies concerning the development of secondary caries at the margin of restorations were taken into consideration when performed in split-mouth design with an observation period of at least three years. Papers dealing with orthodontic or endodontic topics were not included in the review.

2. Fluoride release of restorative materials

2.1. Glass-ionomer cements

Glass-ionomer cements are composed of fluoride-containing silicate glass and polyalkenoic acids which are set by an acid–base reaction between the components. During the setting reaction a variety of ionic constituents is released from the glass, including fluoride. Two mechanisms have been proposed by which fluoride may be released from glass-ionomers into an aqueous environment. One mechanism is a short-term reaction, which involves rapid dissolution from outer surface into solution (process I), whereas the second is more gradual and resulted in the sustained diffusion of ions through the bulk cement (process II) [5–9]. These processes are presented by the right-hand first and second terms of the equation: 

\[ F_{t} = F_{0} = \sqrt{\frac{F_{t}}{t_{1/2}} + \beta \sqrt{t}} \]

The parameter \( t_{1/2} \) is the so-called ‘half-life’ of the process I to reach one-half of its maximum value which is given by \( F \). Parameter \( \beta \sqrt{t} \) is material depen-
dent and can be considered as a measure for the driving force of process II. For the most conventional and the resin-modified glass-ionomers and some high fluoride-releasing composites, the process follows a square root dependency on time suggesting that in some way a concentration gradient would be responsible for the driving force of the elution [5,10].

An initial high release from glass-ionomers over the first 24 h is likely due to the burst of fluoride released from the glass particles when reacting with the polyalkenoate acid during the setting reaction.

Karantakis et al. [11] evaluated that the highest fluoride dissolution occurred especially during the first 4 h after mixing amounting to 1.6–1.8 μg/mm². Bell et al. [12] showed that the concentration of fluoride released from glass-ionomer cement specimens (1.5 mm thick, 6 mm in diameter) into artificial saliva within 10 min after immersion amounted to 1 ppm and that the cumulative total fluoride in the first 24 h was nearly 15 ppm. In vitro, it is frequently confirmed that the maximum release occurred during the first 24–48 h [12–18] ranging from 5 to 155 ppm for different brands of glass-ionomer cements (1–1.5 mm thick, 6 mm in diameter) [12,14,16–19]. Metal-reinforced glass-ionomers seem to release less fluoride than conventional glass-ionomer cements [8,20–26]. This effect may be explained by the initial lower fluoride content of these materials due to the replacement by silver and the formation of silver fluoride which binds the fluoride ions into the cement preventing leaching of the fluoride [21]. In contrast, in glass-ionomers containing bioactive glass [27] or casein phosphopeptide–amorphous calcium phosphate [28] fluoride release seems to be increased compared to conventional glass-ionomers.

After the initial burst, fluoride release slows down and is followed by a prolonged long-term fluoride release, which occurs when the glass dissolves in the acidic water of the hydrogel matrix [22,29]. Studies have shown that the cumulative amount of fluoride ions released from glass-ionomer cements, after a short period of time, is diffusion controlled and follows a decreasing gradient, which is linear to the square root of time [10,30–32]. Thereby, the initial high amounts of fluoride rapidly decrease after 24–72 h [11,26,33] and plateaued to a nearly constant level within 10–20 days [8,15,26,29,34]. After 5–10 days the cumulative amount of leached fluoride is about 0.3–3 μg/mm² [11,29,35]. Creanor et al. [14] found that the concentration of leached fluoride in deionized water had slowed from 15–155 ppm at day 1 to about 0.9–4 ppm at day 60. After one year, the steady state fluoride release of four different glass-ionomers was approximately 0.5–7 ppm as shown by Perrin et al. [36]. In other in vitro studies, long-term fluoride release from glass-ionomers is reported to occur from several months to over three years [8,14,23,37,38].

In vivo, fluoride concentration of unstimulated saliva measured immediately after placement of one to six glass-ionomer restorations increased from approximately 0.04 to 0.8–1.2 ppm. However, after three weeks the fluoride release diminished by about 35% and after six weeks for an additional 30% [39]. Nevertheless, the fluoride level in saliva after one year amounted to 0.3 ppm and was therefore 10 times higher as baseline values [40].

2.2. Resin-modified glass-ionomer cements and polyacid-modified composites

Resin-modified glass-ionomer and polyacid-modified composite restoratives have been developed to overcome the problems of moisture sensitivity and low initial mechanical strengths typical for conventional glass-ionomers. Polyacid-modified resin composites (composers) claim to combine the mechanical and esthetic properties of composites with the fluoride-releasing advantages of conventional glass-ionomer cements.

Resin-modified glass-ionomers were basically formed by adding methacrylate components to the polyacrylic acid, which are polymerizable by light-curing supplementing the fundamental acid–base reaction. Polyacid-modified resin composites consist of conventional macromonomers also used in composites, such as Bisphenol-Glycidyl-dimethacrylate or urethane dimethacrylate, together with small amounts of acid-functional monomers. The filler glass is identical to the ion-leaseable glass fillers used in conventional glass-ionomer cements but in smaller sizes as known from composites. Initial setting is performed by light-activated polymerization which is followed by an acid–base reaction that arises from sorption of water. Recently, a new category of hybrid material (giomers) was introduced in the international market. Giomers include pre-reacted glass-ionomers to form a stable phase of glass-ionomer fillers in the restorative. Unlike composites, fluoro-alumino-silicate glass particles react with polyacrylic acid prior to inclusion into the resin matrix.

Resin-modified glass-ionomers were mostly found to have a potential for releasing fluoride in equivalent amounts as conventional cements [41], but may be affected not only by the formation of complex fluoride compounds and their interaction with polyacrylic acid, but also by the type and amount of resin used for the photochemical polymerization reaction [42–44]. The kinetics of the cumulative fluoride release of most resin-modified glass-ionomers are summarized by Verbreeck et al. [5] and Xu and Burgess [10] as described above: $F_c = F_I/\sqrt{t + t_{1/2}} + \beta \sqrt{t}$.

Fluoride release from different resin-modified glass-ionomer cements is also highest during the first 24 h and amounted to 5–35 μg/cm² depending on the storage media [11,15,16,35,45,46]. Mean concentration of fluoride release from resin-modified glass-ionomer specimens (1.5 mm thick, 6 mm in diameter) into deionized water over the first 24 h after setting amounted from 22–65 ppm for the first 6 h to 3–20 ppm for the 18–24 h period [14]. Daily release rates dropped from 8–15 ppm (1st day) to 1–2 ppm (7th day) within 1 week [16,17] and are stabilized from 10 days [14,33] to 3 weeks [47]. Resin-modified glass-ionomers continue to release fluoride in small amounts in vitro (about 1–2 ppm, depending on the specimens’ size) for 1–2.7 years [8,11,37,45,46,48,49].

In contrast to the conventional and resin-modified glass-ionomers, polyacid-modified composites are mostly shown to have no initial fluoride ‘burst’ effect [16,17,48,50], but levels of fluoride release remain relatively constant over time [17,51]. For the most polyacid-modified composite resins and microfilled composite resins, the zero-order kinetics are indicative of a matrix-controlled elution: $F_c = F_I/(t + t_{1/2}) + \alpha$. Thereby,
values of $\alpha$ are material dependent and can be considered as measure for the driving force of this process [5,10].

However, short-term fluoride release is slightly increased during the first few days [17,35,52], but is quite clearly lower compared to conventional or resin-modified glass-ionomers [18,33,48,51,53–56]. However, this finding was not corroborated by a study of Attin et al. [57] who found higher fluoride release for compomers than for glass-ionomer cements. The authors explained these differences by the composition of the compomer brands, which exhibited a higher fluoride content and contained smaller fillers, which might lead to a better reactivity due to the greater size of the specific surface.

However, the difference between glass-ionomers and polyacid-modified resin composites during the first phase of fluoride release could be due to the fact that after curing and before contact with water the fluoride in polyacid-modified composites is not free but bound in the filler particles which are enclosed in the polymerized matrix. It should be noted that in the first phase of setting, which is a light-activated polymerization, polyacid-modified composites completely behave like composites. Also, in the second process of fluoride release, diffusion of fluoride in a period of up to six months was reported to be smaller in polyacid-modified resin composites and composites than in glass-ionomers [11,29]. This mechanism is discussed to be the result from a more tightly bound and/or less hydrophilic matrix of the composite resin [29]. However, Asmussen and Peutzfeld [38] found that compomers might release relatively little fluoride during the first year after setting, but after this time the rate of fluoride release became equal to that of glass-ionomers.

The main filler fraction in compomers and composites does differ significantly. When in composites rather inert Baglasses or alike are typically used, the filler glass in a typical compomer is identical to that of glass-ionomers. Additionally strontium fluoride or ytterbium trifluoride is added for radio opacity and may increase fluoride release, too.

With regard to compomers, several authors found differences in fluoride release in products with different filler systems. Compomers containing glass fillers and ytterbium trifluoride are reported to release higher amounts of fluoride than SrF$_2$-containing products [18,57–63].

Daily fluoride release into an aqueous solution from compomers (1.5 mm thick, 6 mm in diameter) declines from 1–2.4 ppm for the 1st day to 0.17–0.23 ppm after 60 days [18]. With the initially light cured material takes up water, and the carboxylic groups of the acidic monomer promote an acid/base reaction with metal ions of the glass filler. The subsequent water sorption leads to ionization of the acid groups. This reaction takes place at a slow rate and reaches a saturation point after approximately four weeks [64]. Due to this kinetics, cumulative fluoride release of compomers during the first days is expected to be low as compared to conventional glass-ionomers [17].

Cumulative fluoride release from compomers into deionized water amounted to 0.08–0.12 $\mu$g/mm$^2$ after 7 days and to 0.39–0.41$\mu$g/mm$^2$ after 91 days [29]. After 253 days, weekly fluoride release into deionized water was reported to be 0.76 ppm or rather 1.92 $\mu$g/cm$^2$ [48]. Long-term release of fluoride from compomers was followed and measured up to three years [38,48]. Currently, less information is available about fluoride released from compomers [17,65]. Also, for glassomers, no initial ‘burst’ effect could be observed. Amounts of fluoride leached from glassomers seem to be slightly higher than from composites and compomers but lower compared to glass-ionomers [17,65]. After 24 h, mean fluoride release from specimens (1 mm thick, 6 mm in diameter) into deionized water amounted to 4.54 ppm and dropped to 0.06 ppm per day within one week [17].

2.3. Composite

Resin composites may contain fluoride in a variety of forms, such as inorganic salts, leachable glasses or organic fluoride. Thereby, not only the amount of fluoride but type and particle size of the fluoridated filler, the type of resin, silane treatment and porosity might be important factors contributing to fluoride release [10,66–69]. Moreover, the fluoride release increased with the hydrophilicity and the acid character of the polymer matrix [38].

Three different approaches for the development of fluoride-releasing composites have been reported including the addition of water-soluble salts such as NaF or SrF$_2$, fluoride-releasing filler systems or matrix bound fluoride (for review see [67]).

Incorporation of inorganic fluoride has resulted in increased fluoride release, but leads to voids in the matrix as the fluoride leaches out of the material. Dispersion of leachable glass or soluble fluoride salts into the polymer matrix allows for a water-soluble diffusion of fluoride from the composite resin in the local environment. Most of the fluoride is already released during the setting reaction, followed by a smaller amount of long-term fluoride release.

Mainly two filler types can be distinguished, sparingly soluble compounds, such as strontium fluoride (SrF$_2$) or ytterbium trifluoride (YbF$_3$) and leachable glass fillers [10,59,67]. The composites in which the radiopaque fluoridated filler YbF$_3$ was used most likely release fluoride by means of an exchange reaction. Water diffusion into the composite causes fluoride release from the particles followed by a diffusion gradient driven movement into the environmental solution (water and saliva). As mentioned before, fluoride silicate fillers in glass-ionomers and resin-modified glass-ionomers are more soluble and thus release more fluoride especially when reacting with the polyacrylic acid. Finally, organic fluoride components have been added to the matrix to increase the fluoride release. Matrix bound fluorides are available such as acrylic-amine-HF-salts, methacryloyl acid-fluoride and acrylic-amine-BF$_3$ [70].

Fluoride levels leached from composites are mostly much lower compared to levels released from conventional or resin-modified glass-ionomers and also somewhat lower as compared to polyacid-modified composites [11,18,29,37,38,71,72]. Initial fluoride release into deionized water within 24 h amounted to 0.04–2.7 ppm for different composite brands (1.5 mm thick, 6 mm in diameter), but decreased to 0.02–2 ppm within 30–60 days [16,18]. Weekly release from specimens (1 mm thick, 15 mm in diameter) is also reported to decrease from 3–4 to 1–2 ppm within a few weeks [73]. Cumulative fluoride-releasing rates in artificial saliva, lactic acid or deionized water amounted to less than 0.5 $\mu$g/mm$^2$ during 90–120
days [11,29]. Long-term release of different commercial and experimental resin composites is reported to last for up to five years [66,74–76].

It could be shown that experimental highly fluoridated composites and an ion-releasing composite (Ariston®) released higher amounts of fluoride than conventional fluoridated composites [16,66,77]. While most commercially available composites exhibited a fluoride release which is approximately proportional to the logarithm of time or to $t^{-1/2}$ [66,73], an experimental high-fluoridated composite showed a linear fluoride release, which is proportional to $t$ [66,78].

The high fluoride release of these experimental or high-fluoridated composites is discussed to be a result of a high fluoride content (F-Al-silicate and YbF$_3$) combined with high water solubility of the filler, high water uptake and a highly diffusible polymer matrix [10,16,66], the latter two reasons being the cause for clinical failures as shown by Braun et al. [79] and Merte et al. [80].

2.4. Amalgam

Several studies investigated fluoride levels released from amalgam [23,81–84]. Storage of conventional amalgam class V restorations in deionized water revealed fluoride values of less than 0.02 ppm within four weeks [84] and less than 0.08 ppm one year after insertion [83]. Cumulative fluoride content after placement of amalgam specimens (1.6 mm thick, 15.2 mm in diameter) in artificial saliva amounted to less than 0.1 µg/mm$^2$ within seven weeks [82]. These results are also confirmed for fluoride-containing amalgam samples (2 mm × 2 mm × 12 mm) [85]. The initial release of fluoride into hydroxyapatite decreased from 0.33 to 0.009 µg/mg within one week [85].

In summary, fluoride release from different fluoridated restorative materials may last for a long period. However, after a higher initial release, fluoride release from these materials may drop to very low levels.

3. Factors influencing the release of fluoride from restoratives

The elution of fluoride is a complex process. It can be affected by several intrinsic variables, such as formulation and fillers [27,28,31,42,86,87]. It is also influenced by experimental factors, i.e. storage media, frequency of change of the storage solution, composition and pH-value of saliva, plaque and pellicle formation [9,12,21,32,35,52,88–94]. It was shown that the powder–liquid ratio of two-phase-systems, mixing procedure, curing time and the amount of exposed area as well as the different storage media affected the fluoride release [21,29,32,36,92,95–98]. In vitro, fluoride release was dependent on exposed surface area and not on sample weight [32]. Radiant heat applied to glass-ionomers at different intensities and for different time intervals using a high-intensity fibreoptic quartz tungsten halogen light source had no effect of fluoride release [99].

Several laboratory studies investigated the quantity of fluoride released into water, artificial saliva or acidic solutions. Kinetic findings demonstrated that the patterns of fluoride release from conventional and resin-modified glass-ionomers as well as composites and composites in different storage media were similar. However, the amount of daily and accumulated fluoride release of these materials is different as mentioned above [11]. On long term, composites have mostly shown to release lower amounts of fluoride compared to glass-ionomer, resin modified glass-ionomer and compomer [11,23,29,38]. In general, the highest release is found in acidic and demineralizing–remineralizing regimes and the lowest in saliva [11,35,52,53,57,71,94,100–102]. Demineralizing–remineralizing regimes are chosen for simulating the pH-cycling that occurs during caries attack. The increasing amount of fluoride in acidic media could be explained by the fact that a decrease in pH increases the dissolution of the material leading to a higher fluoride level in the acidic immersion [11,52,63,94,102,103]. Thereby, the proportion of free (uncomplexed) fluoride to bound (complexed) fluoride was lower under acidic than under neutral conditions [94,103]. Artificial saliva tends to decrease the amount of leached fluoride to 17–25% of that found in water [12]. This observation might be explained by the fact that the diffusion gradient between the restorative material and ion-enriched saliva is lower as compared to the gradient between the restorative and distilled water. Moreover, it is suggested that components from saliva form a pellicle on the surface of the restorative material that impedes ion release [8,12,101,104]. Bell et al. [12] showed that salivary deposits on glass-ionomers formed within the first 10 min after immersion into saliva cause a retarding effect on fluoride release. Moreover, Arends et al. [67] found that the presence of a pellicle reduced the fluoride-releasing rate of a fluoridated composite by about 15–20%.

Nevertheless, in human saliva fluoride rates may be increased due to the activity of salivary enzymes. It was demonstrated that fluoride release from resin-modified glass-ionomers and composites may be increased in esterase-containing artificial saliva compared to artificial saliva free of enzymes [105–107]. It was also discussed that plaque-associated organic acids or salivary hydrolases may increase initial fluoride release in vivo [107]. The clinical relevance of fluoride released in human saliva or plaque will be discussed separately.

It should be noted that covering of the materials with adhesives or bonding agents may influence the short- and long-term release of components of dental filling materials. Immediate application of a surface coating agent might also be performed to protect glass-ionomers from moisture contamination and dehydration during initial setting. Even though fluoride-containing dental adhesives are able to release fluoride in a range from 4 to 30 µg/cm$^2$ during eight weeks [46,108,109], adhesive coating of the material surface significantly reduces the amount of fluoride leached from glass-ionomers and composites [15,62,90,100,110,111]. In vitro, fluoride leached from filling materials coated with an adhesive was reduced by a factor 1.5–4 [62,112,113].

Neither bleaching nor brushing of restorative materials increased the amount of fluoride release. Home-bleaching or in-office bleaching agents containing 10 or 35% carbamide peroxide have shown to be ineffective in increasing the
release of fluoride from conventional and resin-modified glass-ionomers as well as composites [114].

Removal of the outermost layer of compomers by air-polishing or finishing may lead to an increased fluoride release [90,115]. This pattern was explained by the fact that air-polishing removes the outer surface of a water-immersed specimen which leads to exposition of deeper zones of the material not depleted of fluoride. However, simulation of oral hygiene behavior by brushing of a polyacid-modified composite with a fluoride-free dentifrice did not maintain the initially high level of fluoride release for a longer period of time compared to unbrushed samples [60].

4. Fluoride recharge of restorative materials

The cariostatic action associated with fluoride-releasing materials is usually attributed to a sustained release of fluoride. Due to the fact that fluoride levels leached from fluoride-containing filling materials decreased over time (which is significant for glass-ionomers and resin modified glass-ionomers), the “recharging” of restoratives with fluoride has been suggested to maintain a continuously increased level of fluoride release. The ability of a restorative to act as a fluoride reservoir is mainly dependent on the type and permeability of fluoride release. The ability of a restorative to act as a fluoride reservoir than composite materials not depleted of fluoride. However, simulation of oral hygiene behavior by brushing of a polyacid-modified composite with a fluoride-free dentifrice did not maintain the initially high level of fluoride release for a longer period of time compared to unbrushed samples [60].

In vitro, comparison of fluoride leached from one-time refluoridated conventional and resin-modified glass-ionomers, ion-releasing composite as well as flowable and packable compomers and composites showed an increased fluoride release for 24 h followed by a rapid return to near pre-exposure levels already within several days [16,18,120,126–128]. Three months after single application of 1.23% APF to aged restorative materials, fluoride release of glass-ionomers and compomers was even lower than immediately before gel application [125].

Refluoridation of glass-ionomers, compomers and composites with a 500 ppm F− solution 13 times over a two-year period revealed different capacities among the materials with respect to absorption and release of fluoride. After 720 days, glass-ionomer-based materials displayed a far better potential to re-release fluoride (3–12 μg F/cm², 1 h post-recharge) than composites (0.2–0.3 μg F/cm², 1 h post-recharge) and performed somewhat better than composites (3.6–5 μg F/cm², 1 h post-recharge) [72].

In the oral environment, dental restorations are frequently exposed to exogenous sources of fluoride, such as fluoridated dentifrices, and mouth rinses or high-dose fluoride gels and varnishes. Regular fluoridation of restorative materials is mainly performed by toothbrushing with fluoridated dentifrices or fluoride gels.

Daily exposure of filling materials to fluoridated dentifrices has demonstrated a high rechargeability for glass-ionomers [52,119,122,129], while the replenishment of resin-based materials seems to be negligibly small [52,77,122]. Olsen et al. [129] evaluated fluoride release of an aged resin-modified glass-ionomer after daily exposure (30 min daily over 10 days) to different toothpaste slurries. Application of fluoridated (0.05%) and non-fluoridated dentifrices with pH 2.5, 5.7 and 8.3 increased the amount of fluoride release during the exposure period, but was highest for the acidic slurry regardless whether it was fluoridated or not. However, after the exposure period fluoride levels in all groups, except the fluoridated and non-fluoridated dentifrices with pH 2.5, decreased below baseline rates within 10 days [129]. Moreover, a constant decrease of fluoride release is also reported during the period of daily toothpaste exposure [52,118]. Attin et al. [52] found that 5 min toothpaste slurry (1250 ppm F− and 5 ml artificial saliva) application also increases the fluoride re-release from glass-ionomer specimens but not from compomers. Fluoride re-release of glass-ionomers might also be increased when application of the fluoridated dentifrice is performed by brushing of samples instead of storage of the samples in dentifrice slurrys only [130].

In general, refluoridation seems to be more effective with increasing concentration of the agent [117,131] and frequency of application [122,128] as well as under acidic conditions of the environment [52,118], e.g., in a simulated high caries challenge situation. This was also shown for fluoridation of restoratives with fluoride gels and solutions [19]. Daily immersion in 250, 1000 and 2500 ppm fluoride solution increased the amount of leached fluoride from glass-ionomers from 1 to 2–15 ppm per day over the experimental period [19]. Refluoridation of compomers and conventional and resin-modified glass-ionomers was also more effective after application of 0.2% NaF solution than after treatment with 0.02 or 0.04% NaF solution [33,132], but fluoride levels did not exceed 6.5 ppm [33]. With regard to the kind of fluoride, 1.23% APF gels seem to be more effective than neutral 1% NaF gel and 0.001% CaF2 or 4% SnF2 agents [47,133,134]. After refluoridation with
gels or solutions, initial peaks of fluoride leached from glass-ionomers and composites amounted to 10–65 ppm for 1.23% APF, 0.5–3 ppm for 1% NaF and 2–17 ppm for 4% SnF₂ [49]. However, due to the fact that APF gel may cause erosive damage of glass-ionomers and composites, it is not recommended to be applied frequently on these restoratives (especially on glass-ionomers), especially as the recharging effects are transitory [49,125,135,136].

In the oral environment the fluoride uptake and re-release may be influenced by saliva and plaque [123,137]. The higher viscosity of saliva may reduce the diffusion of ions in and out of the test material. Furthermore, the ionic composition may also have an influence on release from and recharge of the materials. In addition, the formation of a surface pellicle might act as barrier hampering the recharge process. A 2-h incubation of glass-ionomer samples in human saliva reduced the fluoride uptake by 50% and a 24-h incubation by 74% [137]. A salivary pellicle formed by one-week storage in human saliva reduced uptake by 49% and also caused some retardation of release in vitro [123]. However, fluoride release of intraorally aged and contaminated [138] specimens revealed no differences in fluoride release compared to extra-orally aged specimens [137].

5. Clinical relevance of fluoride released from restoratives in human saliva and plaque

In a number of studies reduced caries experience has been contributed to elevated salivary fluoride levels [138–140]. It has been stated that a constant supply of low levels of intraoral fluoride is of most benefit in preventing caries. An elevation of the fluoride level in saliva from 0.001 to 0.005–0.010 mmol/l, e.g. 5–10 times, for prolonged periods may be efficient for caries control [141].

After a single application of fluoride-containing dentifrices (1250 ppm) salivary fluoride concentration 10–15 min after application increases to approximately 1–3 ppm [142–144]. In comparison, subsequently after placement of glass-ionomer restorations salivary fluoride concentration increased from 0.04 to 0.8–1.2 ppm. After three and six weeks the fluoride concentration was decreased to 0.5–0.8 and 0.3–0.4 ppm, respectively. Even one year after placement of these glass-ionomer restorations fluoride concentration in unstimulated saliva amounted to 0.2–0.3 ppm, but it has to be noticed that the patients were allowed to use fluoridated dentifrices throughout the study period [39,40]. In another in vivo study, fluoride release from four glass-ionomer slabs (6 mm in diameter, 2.65 mm thick) led to net increase in salivary fluoride concentration ranging from 13 to 18 ng/ml during an eight-day period. The continued release of fluoride did not decrease during the course of the study [145]. Also, fluoridated amalgam specimens worn for 8 h daily led to an increase of mean salivary concentration of fluoride from 0.57–1.22 to 12.26–91.06 μmol/l within 24 h. After one week, the mean fluoride concentration decreased to 5.58–30.91 and 1.37–5.76 μmol/l after two weeks. Saliva fluoride concentration approached the basal level in most of the subjects after 20–25 days [81]. Insertion of amalgam restorations is mostly accompanied by the application of lining cements (such as glass-ionomer cements), which might increase the fluoride release from the restoration especially when marginal gaps lead to exposition of the liner [83,84]. Opening of gaps (which unfortunately still cannot be completely prevented by modern adhesive dentistry) may lead to moisture contact of previously non-exposed material at com- pomer fillings thereby triggering fluoride release from these surfaces into the gap.

However, salivary fluoride concentrations after insertion of different fluoride-releasing restoratives are less compared to fluoride concentration immediately after brushing with fluoridated dentifrices (approximately 100 μmol/l ≈ 1.9 mg fluoride/ml) [146]. Furthermore, regular use of fluoridated agents, such as fluoridated mouthrinses or dentifrices, may result in a long-term change in baseline salivary fluoride concentration [147].

Duckworth and Morgan [146] have shown that the kinetics of fluoride clearance after toothbrushing may be divided into two phases: an initial phase lasting 40–80 min, while fluoride concentration rapidly decreases due to a clearance of topical fluoride, and a second phase, while fluoride concentration is slowly declining likely due to fluoride release from oral fluoride reservoirs, such as tooth surfaces, mucosa and tongue. Therefore, it might be speculated that the main function of fluoride-releasing restoratives is not the short-time elevation of salivary fluoride, which is in the range of fluoride levels 15 min after topical fluoridation with fluoridated dentifrices, but the ability to act as a fluoride reservoir in the second phase of oral fluoride clearance. It was assumed that increased salivary fluoride levels due to release from restoratives might be short-time effective in patients who renounce to regular frequent topical fluoridation.

It was suggested that the caries-inhibiting effect of fluoride-releasing materials is most likely due to a localized fluoridation of the vicinity of a restoration rather than to an elevation of fluoride levels in saliva. Therefore, plaque fluoride content on or adjacent to fluoride-releasing materials was evaluated in clinical studies, but there was no agreement concerning the long lasting effect on fluoride concentration in dental plaque [148–150]. Elevation of plaque fluoride content adjacent to fluoride-releasing restoratives is reported to 7–21 μg F/g plaque [151,152], which is distinctly higher compared to plaque fluoride concentration following the use of fluoride-containing mouthwashes (approximately 1–5 μg F/g plaque) [147]. Therefore, further investigations are necessary to study caries progression in relation to the quantity of fluoride in plaque on or adjacent to dental restoratives.

6. Antimicrobial activity of fluoride-releasing materials

The effects of fluoride on oral bacteria and plaque are well documented by a considerably amount of literature (for review see [153–155]). The mechanisms by which fluoride may interfere with bacterial metabolism and dental plaque acidogenicity include the inhibition of the glycolytic enzyme enolase and the proton-extruding ATPase as well as the bacterial colonization and competition. Furthermore, intracellular or plaque-associated enzymes such as acid phosphatase, pyrophos-
phatase, peroxidase and catalase may be affected by fluoride ions [154]. Although even low fluoride levels may reduce bacterial growth, dental plaque composition and acid production in vitro [156–160], the clinical importance of the affection of plaque metabolism by fluorides is still unclear [161,162]. Fluoride concentrations needed for antimicrobial effects mostly surpass the concentration needed to reduce the solubility of apatite. In vitro, only small amounts of fluoride (approximately 0.03–0.08 ppm) in remineralizing solutions are necessary to shift the equilibrium from demineralization to remineralization. Therefore, it is often considered that the antimicrobial effect of fluoride is less important when the fluoride concentration required for inhibition of demineralization is exceeded.

However, several clinical studies found that the fluoride concentration of plaque on or adjacent to glass-ionomers is increased and the proportion of mutants streptococci in plaque is reduced [149,151,152,163–165]. Fluoride levels of 14-day-old plaque grown adjacent to glass-ionomers decreased from 19,985 ppm after 14 days to 5788 ppm after 28 days and 5019 ppm after 43 days, but was considerably higher than fluoride concentration of plaque grown on composite (about 200 ppm) [149]. Contradictory, Seppä et al. [148] found no increased fluoride concentration of approximal plaque of teeth close to glass-ionomer restorations either after two or four weeks. In patients using fluoridated toothpastes, fluoride levels detected in plaque adjacent to one-year-old resin-modified glass-ionomer (6 nmol/mg), compomer (3 nmol/mg) and resin composite (3.1 nmol/mg) restorations were only slightly increased compared to the fluoride content of enamel plaque (1.2 nmol/mg) [166].

Even refluoridation of three-year-old glass-ionomers with 1.2% fluoride gel did not increase plaque fluoride concentration significantly [149].

However, in a chemo-stat experiment it was shown that fluoride can inhibit the growth of oral streptococci in vitro at concentrations in the order of 0.16–0.31 mol/l [167]. This concentration is much higher as found in dental plaque adjacent to fluorid-containing restoratives. Due to this fact, the results of some in vivo investigations mostly showed that the fluoride concentrations released from one- to three-year-old restorative materials are not high enough to affect the metabolism of caries-associated bacteria, e.g. mutants streptococci and lactobacilli in dental plaque [150,166,168]. In contrast, studies investigating glass-ionomer restorations up to one month after insertion showed a correlation between fluoride release and reduced mutants streptococci counts in plaque [150,151,163–165] or saliva [39]. However, levels of mutants streptococci in plaque from composite or amalgam fillings were lower than in plaque formed on glass-ionomers [150,163–165].

The caries-preventive effect of resin-modified glass-ionomers has also been related to decrease in microbial colonization of carious dentin. In vivo, a resin-modified glass-ionomer restoration leads to a larger decrease in counts of mutants streptococci and lactobacilli in remaining carious dentin than amalgam [169,170]. In contrast, Weerheijm et al. [171] found no differences in numbers of oral streptococci and lactobacilli in dentin lesion two years after insertion of a glass-ionomer or a resin-based sealant.

It has already been discussed that other components simultaneously released from ionomeric-based (e.g. aluminium and zinc) or resin-based materials (monomers and catalysts) may be involved in the antibacterial activity of the materials [35,152,172].

In conclusion, fluoride is known to inhibit the biosynthetic metabolism of bacteria, but these antimicrobial effects in caries prevention are often regarded as little or of no importance as compared to the direct interactions of fluoride with the hard tissue during caries development and progression. There is still a lack in studies whether the antibacterial effects clinically contribute to the anticaries effect of fluoride and whether fluoride leached from restoratives into plaque or saliva may be relevant for these antibacterial effects.

7. Fluoride uptake of adjacent tooth structure

For many years the cariostatic effect of fluoride was attributed to the incorporation of structurally bound fluoride in the hydroxyapatite crystal lattice and the reduced solubility of the so-formed fluoridated hydroxyapatite. However, recent observations have found that fluoride in the aqueous phase surrounding the carbonated apatite crystals is much more effective in inhibiting demineralization than fluoride incorporated into the crystals [4]. Fluoride may precipitate onto tooth surfaces as calcium fluoride-like layer, which serves as a reservoir for fluoride when the pH drops [4]. This calcium fluoride-like material, so-called KOH-soluble fluoride, facilitates the precipitation of minerals by forming fluorapatite or fluorohydroxyapatite, thereby preventing further loss of mineral ions [4,173]. Nevertheless, enamel resistance to lesion formation also increased with increasing content of tooth-bound fluoride [174].

Glass-ionomers and other fluoride-releasing restorative materials are reported to increase both the structurally bound and KOH-soluble fluoride content of the adjacent dental hard tissues [151,175–182]. Fluoride uptake into dental hard tissues in the absence of an acidic medium mainly occurs by slow diffusion processes. Moreover, glass-ionomers containing bioactive glass are shown to induce precipitation of calcium fluoride-like compounds on dentin slabs, when immersed into simulated body fluid [27].

Kawai et al. [175] investigated the amount of structurally bound and KOH-soluble fluoride after fixation of fluoride-containing composite slabs onto enamel surfaces. Mean total fluoride uptake at 10 μm depth amounted to 300–600 ppm and decreased to approximately 200 ppm at 30 μm depth. However, amount of structurally bound and KOH-soluble fluoride at 10, 20 and 30 μm depths was not significantly different among the different fluoridated composites [175]. In vivo, fluoride uptake from fluoridated composite slabs fixed to enamel surfaces also decreased only slightly from 785 to 590 ppm at levels from 2.5 to 50 μm depth [183].

The mean penetration depth of fluoride released from fluoridated composites into the enamel and dentin side walls of class V restorations four weeks after insertion ranged from 19 to 47 μm [178]. Fluoride concentration at these cavity walls
ammounted to 4200–9400 ppm [178] which reflects the distinct fluoride uptake.

For conventional and resin-modified glass-ionomers, fluoride uptake was also found to be highly significant in both primary and permanent enamel [151,184]. Conventional glass-ionomer cemented seams seemed to be more effectively increasing the content of fluoride in enamel and root surfaces than metal-reinforced glass-ionomers due to a higher release of fluoride [24,185]. In vitro, one month after application of glass-ionomer-based restorations enamel fluoride uptake adjacent to the restoration amounted to 2400–4100 ppm [181] and was nearly the same after three and six months. In a distance of 1.5–7.5 mm to the margin of the restoration fluoride uptake by more than 2000 ppm was found [181].

Under in situ simulation of a high cariogenic challenge, enamel fluoride uptake around glass-ionomers was twice greater and mineral loss twice lower than in enamel restored with non-fluoridating composites [151].

Enamel fluoride uptake in the vicinity of 1 or 5% SnF₂ silver amalgam restoration was found to be approximately 100–200 ppm after one month [182].

Due to differences in microstructure and porosities of dental hard tissues, the amount of fluoride uptake from restoratives and the depth of fluoride penetration are higher for both dentin and cementum than for enamel [109,175,177,181,182].

Fluoride penetration from different restoratives into dentin was highest for conventional glass-ionomers (300 µm, one week after insertion) followed by resin-modified glass-ionomers and composites [180]. Fluoride concentration of dentin beneath a glass-ionomer cement filling might increase to approximately 2000 ppm compared to the fluoride concentration beneath a zinc phosphate cement filling [186]. Other investigations found higher amounts of fluoride uptake for fluoride-releasing resins (3000–12,000 ppm) [177,178] than for glass-ionomers (5000–6000 ppm) into side and axial walls of dentin cavities [177]. One month after insertion of a glass-ionomer restoration fluoride acquisition by cementum located 1.5–7.5 mm distant to the filling was about 14,000–16,000 ppm. Reevaluation of fluoride uptake after three and six months still revealed 6000–7000 and 5000–6000 ppm, respectively [181]. After insertion of various fluoride-containing composites, the concentration of total fluoride in cementum amounted to 200–3500 ppm at 10 µm depth and decreased to 100–2500 ppm at 30 µm. Thereby, levels of bound fluoride uptake were approximately 100–2000 ppm at 10 µm depth and 50–1000 ppm at 30 µm depth [175].

An increase of fluoride concentration in dental hard tissues is also reported for SnF₂ silver amalgam. Thereby, fluoride was taken up to a greater extent from 5% SnF₂ than from 1% SnF₂ and was generally higher in dentin than in enamel [182].

As mentioned above, fluoride uptake from fluoride-releasing restorations is higher in dentin and cementum than in enamel, but is influenced by the interface between restoration and tooth [180]. The presence of an intermediary micro-gap or material layer between the restoration and the dental hard tissues could restrict or promote the passage of fluoride. Gap formation between the filling material and the cavity wall will lead to a fluoride transport across the fluid-filled gap. Theoretically, a small gap with minimal fluid exchange will elevate fluoride concentration and create a greater diffusion potential. Some of the fluoride will adsorb onto apatite crystallites and become firmly bound. High concentrations of calcium, phosphate and fluoride at the interface may facilitate the precipitation of calcium fluoride-like compounds [187]. An infrared spectroscopic analysis concluded that the interface between glass-ionomers and dentin consisted of fluoridated carbonatoapatite. The presence of this sparingly soluble mineral at the interface between the tooth and the restoration may provide anticaries activity of modern restoratives is estimated.

By summarizing these data, fluoride uptake of the adjacent dental hard tissue is higher in dentin and cementum than in enamel, but is highly influenced by the interface between restoration and tooth. Thereby, an intermediary material layer, such as an adhesive hybrid layer, may hamper fluoride uptake. However, the amount of fluoride incorporated in dental hard tissues might be of minor importance compared to the fluoride concentration in a fluid-filled microgap between the restoration and the tooth structure. Thereby, several restorative materials might increase the fluoride concentration in the gap to the required range between 5 and 80 ppm, which is estimated to prevent caries.

8. Influence of fluoride-releasing restoratives on caries development and progression

8.1. Influence on demineralization of enamel adjacent to fluoride-releasing restoratives

8.1.1. In vitro studies

In vitro, several fluoride-releasing restoratives have shown to inhibit enamel and dentin demineralization produced by
acids or demineralizing buffer solutions. Thereby, inhibition of enamel demineralization is located up to a distance of 7 mm from the edge of the material (‘remote effect’). When compared with non-fluoride-releasing restorations, the placement of glass-ionomers reduces mineral loss by almost 80% at 0.22 mm distance from the restoration and by 37% 7 mm distant from the restoration margin [194]. Glasspoole et al. [195] examined the reduction in enamel demineralization provided by fluoride-releasing glass-ionomers and composites. Lesion areas were measured by polarized light microscopy at distances from 100 to 800 μm. At all distances, a significant inhibition of enamel demineralization was seen for all materials. Thereby, the degree of protection was highest in the closest vicinity of the material, but lesion areas increased with distance in an inverse relationship to the amount of fluoride release [195]. These results were confirmed by micro-radiographic assessment of artificial caries lesion depth and mineral density of enamel adjacent to a conventional and a resin-modified glass-ionomer. For both materials, lesion depth increased and mineral density decreased with increasing distance (1–3 mm) from the restoration margin [196].

As seen by polarized light microscopy, the placement of conventional glass-ionomers results in a reduction of wall lesion frequency and size of caries-like lesions in vitro. Reduction of enamel outer lesion size and depth ranged from 58 to 80% compared to the lesion size adjacent to non-fluoridated filling materials [180,197–199]. Wall lesion size and depth were also decreased and amounted to approximately 30% compared to the lesions adjacent to a non-fluoride-releasing restaurative [198]. For primary enamel samples it was shown that placement of an amalgam-bonding resin with fluoride-releasing capabilities provided a reduction of surface lesion depth by 30% and a decrease in cavity wall lesion frequency by 35% compared to a conventional amalgam restoration [200].

Six to 10 weeks after insertion of different fluoride-releasing materials, comparison of enamel surface and wall lesion development and progression adjacent to the restoration mostly revealed highest demineralization protection for glass-ionomers (reduction of lesion size compared to non-fluoridated control: 58–80%), followed by resin-modified glass-ionomers and composites (reduction of lesion size compared to non-fluoridated control: 35–75%) and composites (reduction of lesion size compared to non-fluoridated control: 9–40%) [180,197–199,201–204].

The amount of fluoride in the restorative material seems to influence the anticaries properties. In this sense, experimental fluoride-releasing composites showed that wall lesion development and penetration of enamel demineralization were more decreased adjacent to a resin containing 33% fluoride than for the composite containing 17% fluoride. However, both experimental materials exhibited significantly less demineralization of enamel surrounding the restoration than a non-fluoridated composite and less or equal demineralization than a fluoride-releasing silicate cement [205].

Other studies examined the remineralizing properties of fluoride-releasing restoratives. The mean size reduction of an artificial lesion adjacent to a fluoride-releasing composite restoration amounted to 12–27% after two weeks and 40–80% after three months compared to a non-fluoride-releasing restaurative [203].

8.1.2. In situ and in vivo studies

As shown in the above mentioned reports and investigations, several in vitro studies found fluoride-releasing materials effective in prevention of secondary caries. However, clinical relevance of these artificial caries experiments is debatable. Papagiannoulis et al. [190] evaluated the anticariogenic behavior of glass-ionomers and resin composite restorative materials and found no correlation between in vivo and in vitro data. In vitro, glass-ionomer and fluoride-free composite restorations applied in enamel cavities were stored in acidic gel for four weeks to produce artificial caries-like lesions. For the in vivo experiment, glass-ionomer and fluoride-free composite restorations were inserted into premolars in a split-mouth design. The premolars were extracted for orthodontic reasons after six months. At regions without gaps, glass-ionomers showed reduced lesion dimensions in vitro and no lesions in vivo. At regions with gaps, no differences were found in lesion depth between the tested materials in vitro, while in vivo lesion dimensions were significantly greater for glass-ionomers than for fluoride-free composites [190].

Currently, only few studies determined the demineralization behavior of enamel adjacent to fluoride-releasing restoratives in situ or in vivo [151,206–209].

Kielbassa et al. [206,207] evaluated the effects of a conventional and a resin-based glass-ionomer, different polyacid-modified composites, an ion-releasing material and a composite on enamel lesion formation in situ. Thereby, intraoral appliances were worn for four weeks without additional application of topical fluorides. Only the ion-releasing material ‘Ariston’ leads to significantly lower lesion depth and mineral loss in those areas of the developed caries lesions which were close to the restoration. All other materials exhibited no preventive effect on secondary caries formation [206,207].

As evaluated by microhardness measurement at various depths (10–110 μm) and distances (130 and 230 μm) from the edge of metallic restorations, fluoride-releasing resin-modified or resin-based luting materials were not effective in prevention of secondary caries of enamel and dentin in situ [152]. In contrast, a fluoride-releasing glass-ionomer luting cement was able to reduce secondary caries development in dentin but not in enamel [210]. The in situ simulation of a high cariogenic challenge provoked significantly higher microhardness values adjacent to a glass-ionomer cement than to a non-fluoridated composite [151].

In a further in situ investigation, the effect of different fluoride-containing composites (0–26 vol% fluoride) on enamel demineralization around an artificial gap of 200 μm width was quantified by micrographic measurements after one month. At the gap margins, all fluoridated composites reduced enamel demineralization (both lesion depth and mineral loss) significantly with respect to the non-fluoridated control. At the outer enamel surface next to the artificial gap, a beneficial effect of fluoridation was only observed near to the composite with the highest fluoride content [189]. It is noteworthy to mention that fluoride concentration of the highly fluoridated experimental composite was much higher than the content in commercially available composites.

In conclusion, several in vitro studies found evidence for an inhibition of enamel demineralization, while in situ and in vivo studies found contradictory results, which do not allow
for a final appraisal of the caries-inhibiting effects of fluoride-releasing restoratives.

8.2. Influence on demineralization of dentin adjacent to fluoride-releasing restoratives

8.2.1. In vitro studies
Several laboratory tests also investigated the ability of fluoridated materials to prevent or inhibit demineralization of adjacent dentin [180,211–219].

Both conventional and resin-modified glass-ionomers as well as composites increased dentin resistance to cariogenic or acidic challenges. Thereby, caries-like lesions in dentin and cementum root surfaces adjacent to class V restorations were reduced by 54–63% (glass-ionomers), 20–53% (resin-modified glass-ionomers) or 14–35% (composites and glicer), respectively, compared to non-fluoridated control materials [211,212,217,220,221]. Also, fluoridated composites and amalgams reduced the depth of caries-like lesions adjacent to restorations to 81 or 90.5%, respectively, compared to non-fluoridated amalgams [217]. However, after immersion of root dentin samples in a buffered demineralizing solution, an inhibition zone adjacent to both conventional and resin-modified glass-ionomer cements could be found which was less frequently observed around a fluoride-releasing composite [204].

Fluoride-releasing restoratives are also effective in prevention of artificially created dentin wall lesions [180,212]. Size of wall lesions adjacent to conventional or resin-modified glass-ionomers was inhibited by 30–40% compared to lesion size adjacent to a non-fluoridated composite [180]. When compared to unaltered materials, the incorporation of casein phosphopeptide–amorphous calcium phosphate or bioactive glass into a glass-ionomer cement was associated with an increase of fluoride release and an enhanced protection of the adjacent dentin when exposed to a demineralizing solution, an inhibition zone adjacent to both conventional and resin-modified glass-ionomer cements could be found which was less frequently observed around a fluoride-releasing composite [204].

Fluoride-releasing restoratives are also effective in prevention of artificially created dentin wall lesions [180,212]. Size of wall lesions adjacent to conventional or resin-modified glass-ionomers was inhibited by 30–40% compared to lesion size adjacent to a non-fluoridated composite [180]. When compared to unaltered materials, the incorporation of casein phosphopeptide–amorphous calcium phosphate or bioactive glass into a glass-ionomer cement was associated with an increase of fluoride release and an enhanced protection of the adjacent dentin during acid challenge [27,28]. Also, the extent of the cariostatic effect on root dentin provided by fluoride-containing restoratives was evaluated by Knoop microhardness measurement. While a fluoride-releasing composite and a compomer exhibited no cariostatic effect, the extent of the cariostatic effect was located up to 300 μm for the conventional glass-ionomer and 150 μm for the resin-modified glass-ionomer cement [222].

However, demineralization behavior at margins of fluoride-releasing restorations might be influenced by topical fluoride regimes. Glass-ionomers demonstrated significantly less dentin demineralization than amalgam restorations when no external fluoride was applied or when the restorations were either brushed with a fluoridated dentifrice twice daily or were exposed to a fluoride rinse. There was no significant difference in dentin demineralization adjacent to the materials when both a fluoride rinse and a fluoridated dentifrice were used on a daily basis over 30 days [223].

Determination of lesion depth by confocal laser scanning microscopy revealed differences in the caries-preventive properties of fluoridated materials when used in chemical or antimicrobial in vitro caries models [213]. Glass-ionomer cement demonstrated anticiaric properties for adjacent dentin when exposed to a demineralizing solution (chemical caries model). However, this was not true for glass-ionomer and resin-modified glass-ionomer nor compomer and composite restorations in a microbial caries model (inoculation of the specimens to a solution containing Streptococcus mutans and Lactobacillus casei) [213]. This finding was confirmed in situ when evaluating the remineralization of artificially demineralized dentin beneath glass-ionomers, when dentin was either contaminated with bacteria or not [224]. One year after insertion, nanohardness values of the bacteria-contaminated teeth were not different compared to the nanohardness values three days after insertion, but were significantly lower than in the non-bacteria-contaminated dentin [224].

8.2.2. In situ studies
Currently, there is only one study available evaluating the effects of fluoridated restoratives to dentin caries development in situ [225]. Superficial caries-like lesions (25 μm depth of demineralization) were submitted to severe plaque environment for three months in situ. Insertion of a glass-ionomer restoration adjacent to the artificial demineralization zone leads to a hypermineralization to an average depth of 125 μm. Also, for deeper lesions (100 μm) a hypermineralization of the dentin tissue up to a depth of 300 μm could be observed. However, non-fluoridated amalgam or composite controls exhibited either further demineralization or showed a large variety in the degree of remineralization or demineralization, respectively. From these results the authors also concluded that hypermineralization as promoted by the glass-ionomer cement may increase the acid resistance by limiting the number of diffusion pathways for acids formed in plaque [225]. Even though in vitro studies found evidence for the caries-inhibiting effect of fluoride-releasing restoratives on dentin, the small amount of in situ data do not suffice for final conclusions.

8.3. Clinical studies evaluating secondary caries adjacent to fluoride-releasing restoratives

Despite the cariostatic effects possibly achieved from fluoride-releasing materials, secondary caries is still one of the main reasons for clinical failure of restorations (for review see [226–228]).

Unfortunately, only few longitudinal studies with an observation period of three and more years exist which evaluate secondary caries adjacent to fluoride-releasing and non-fluoride-releasing materials. To estimate the impact of fluoride release on secondary caries development, split-mouth designed studies evaluating different materials in the same patients seem to be more appropriate than studies dealing with a single material in the respective patients. In split-mouth designed studies, test and control material are subjected to the same individual conditions and caries risk parameters. With regard to secondary caries development, however, these studies showed contradictory results.

Three-year success rate of class II restorations performed with either a compomer (Compoglass) and a non-fluoridated composite (TPH-Spectrum) [229] or a compomer (Dyract) and a non-fluoridated amalgam (Tytin) [230] found no differences between the materials in relation to caries development in primary molars. Also, a three-year clinical evaluation of either a compomer (Dyract), a composite (TPH-Spectrum) and a com-
pomer/composite (sandwich-technique, Dyract layered with TPH-Spectrum) [231] or a compomer/composite sandwich restoration and a composite restoration [232] of class II cavities found no differences in secondary caries development. These results are also confirmed for class I compomer/composite (sandwich) and composite restorations during an observation period of six years [233].

Van Dijken [234] found no differences in secondary caries development of class III cavities restored with a polyacid-modified glass-ionomer (Dyract), a conventional glass-ionomer (Fuji II LC) and a composite (Pekafill) in a three-year observation period. Also, an intra-individually comparison of ceramic inlays luted with either a resin-modified glass-ionomer cement (Fuji Plus) or a resin composite (Panavia) revealed no significant differences in secondary caries in a five-year clinical evaluation [235].

In contrast, clinical evaluation of paired compomer (Dyract) and glass-ionomer (Chemfil Superior) classes I and II restorations in primary molars revealed significantly better performance with regard to caries development for Dyract than for Chemfil Superior. Fifteen restorations failed during the follow-up period of 42 months. Thereby, six glass-ionomer restorations but none of the compomer restorations failed due to recurrent caries [236]. Also, comparison of conventional (Fuji II) and resin-modified glass-ionomer (Vitremer) class II restorations of primary molars exhibited less secondary caries at the margins of the resin-modified glass-ionomer (none of 53 restorations) than at the margins of the conventional glass-ionomer (4 out of 62 restorations) [237]. Three-year examination of resin-modified glass-ionomer and amalgam class II restorations of primary molars exhibited also better caries-preventive properties for the resin-modified glass-ionomer. While clinical evaluation found no differences between the materials, polarized light microscopy of the exfoliated teeth revealed significantly less enamel demineralization at restoration margins of the resin-modified glass-ionomer than at the margins of the amalgam restoration [238]. Six-year follow-up assessment of class I restorations in permanent molars exhibited significantly more secondary caries for amalgam (10%) compared to glass-ionomers (2%) [239]. In another five-year evaluation of glass-ionomer (Ketac-Fil) and amalgam (Amalcap) restorations in deciduous molars, the glass-ionomer had a lower survival time and showed greater loss of anatomic form and marginal integrity, but less recurrent caries compared to the amalgam [240]. However, fluoridated amalgam used in class I cavities of permanent molars exhibited less caries development within four years compared to non-fluoridated amalgam [241].

In vitro and in situ investigations found that glass-ionomer and resin-modified glass-ionomer restorations in direct contact to adjacent teeth prevent demineralization compared to non-fluoridated amalgam and composite [209,242]. However, additional application of topical fluoride (fluoridated dentifrice) significantly increased remineralization and decreased demineralization, respectively, in all groups independent from the material [209,242]. This was also confirmed in another in situ investigation, where glass-ionomers showed some slight caries-preventive effects compared to a fluoridated and a non-fluoridated composite when subjects performed oral hygiene without topical fluorides. The regular application of fluoridated toothpaste was, however, effective in prevention of secondary caries in all experimental groups [243]. In vitro, it could also be shown that placement of a resin-modified glass-ionomer exhibited nearly the same remineralization effects on adjacent caries as toothpaste application twice daily, but both fluoride regimes were less effective than the daily use of a fluoridated rinse [244]. A one-year evaluation of glass-ionomer, resin-modified glass-ionomer and resin composite class V restoration in xerostomic head and neck radiation patients found differences depending on the frequency of topical fluoridation. No recurrent caries was found in patients using fluoride gels at regular intervals. However, in patients using fluoride gels at irregular intervals, less enamel caries was evident for glass-ionomer and resin-modified glass-ionomer restorations than for composite fillings [245].

Therefore, it is assumed that topical fluoridation overwhelmingly increases the ability of the fluoridated restorative to inhibit demineralization and promote remineralization on the adjacent interproximal incipient caries lesion. On the other hand, it might be postulated that the use of fluoride-releasing restorative does provide additional protection for patients who might not strictly follow the recommended prophylactic measures.

The effect of a glass-ionomer, a resin-modified glass-ionomer, a compomer and a non-fluoridated composite on sound enamel of approximal teeth without additional topical fluoride treatment was also evaluated in situ. Specimens were worn for 70 days under cariogenic conditions. Enamel microhardness assessment was located at 0, 0.4, 0.8 and 1.2 mm distances from the contact point. Microhardness alteration was generally lowest for the resin-modified glass-ionomer, followed by the conventional glass-ionomer and the compomer. The resin-modified glass-ionomer exhibited none and glass-ionomers and compomers only slight alterations, while the non-fluoridated composite showed distinct formation of subsurface enamel lesions [208]. Also, remineralization of artificial caries-like lesions adjacent interproximally to teeth with class II restorations was higher in metal-reinforced glass-ionomers and amalgam than in glass-ionomer/resin composite restorations [246].

9. Influence on caries formation of teeth located in interproximal contact to fluoride-releasing restoratives

9.1. In vitro and in situ studies

It is also discussed whether fluoride-releasing restoratives might be effective in inhibition of incipient carious lesions of neighboring teeth located in interproximal contact to the restoration.

9.2. Clinical studies

Currently, only few clinical studies exist concerning the effects of fluoride-releasing restoratives at the caries development of proximal tooth surfaces.
In a three-year study in split-mouth design, caries development on tooth surfaces adjacent to class II amalgam (Dispersalloy) and glass-ionomer tunnel restorations was assessed. While the materials exhibited no differences with regard to secondary caries development at the restoration margins, primary caries was significantly reduced on tooth surfaces adjacent to the glass-ionomer restorations as compared to surfaces in contact to amalgam restorations [247]. A seven-year study on three resin-modified glass-ionomer cements (Fuji II LC, Photac-Fil and Vitremer) and a compomer (Dyract) showed that the restorative material and cavity conditioning influenced the survival of the restoration but not the progression of caries on adjacent surfaces [248].

In summary, clinical studies exhibited inconsistent results concerning the prevention of secondary caries by fluoride-releasing restoratives. Despite the high release of fluoride ions in some studies, secondary caries has been found to be the main reason for the clinical failure of glass-ionomer restorations [249,250]. Furthermore, glass-ionomer cements are not considered as having adequate mechanical strength for general use as definitive restorations in stress-bearing posterior teeth (for review see [251]). Thereby, the annual failure rate of glass-ionomers (7.2%) is distinctly higher as compared to direct composite (2.2%), compomer (1.1%) or amalgam (3.0%) restorations [251]. In contrast to glass-ionomers, compomer and composite restorations exhibit a good clinical performance over time concerning marginal integrity and discoloration, surface texture, anatomic form and occlusal wear. However, although composites and some composites are able to release fluoride in a range that might have cariostatic efficacy, it is still unproven whether their good clinical performance is attributed to their ability to release fluoride. Therefore, further investigations are necessary to determine the impact of fluoride-releasing compomer and composite materials on secondary caries formation. Furthermore, the development of restorative materials with excellent mechanical properties and a constant release of high amounts of fluoride seem recommendable.

10. Conclusion

There is a continuum of restorative materials that range from initially high fluoride release (conventional glass-ionomer and resin-modified glass-ionomer) to intermediate fluoride release (compomer) to low fluoride release (fluoride-releasing composite and fluoride-releasing amalgam) to no fluoride release (non-fluoridated composite resins and amalgam) [10,11,15,55,59,252,253]. However, the potential to release fluoride not only varies between different restorative materials, but also within different brands. Optimal fluoride release (short- and long-term release) from a restorative is related to their matrices, setting mechanisms and fluoride content and depends on several environmental conditions. Thereby, fluoride release is substantial only in the period immediately following placement of the fresh material. However, it is not evident whether initial burst or long-term release may be clinically more important to prevent caries as certain remineralizing mechanisms need rather low but constantly provided quantities of fluoride. Nevertheless, fluoride-releasing materials may act as a reservoir for fluorides from topical fluoridation and may lead to an elevation of the fluoride level in plaque or saliva in the immediate vicinity of the restorative. Despite the cariostatic effects achieved from an increase of fluoride content in saliva, plaque and dental hard tissues, clinical studies exhibited conflicting data as to whether or not these materials sufficiently prevent or inhibit secondary caries compared to non-fluoridated restoratives. Therefore, further clinical studies, preferably in split-mouth design, are needed to evaluate the impact of fluoride-releasing restoratives on secondary caries development and progression especially in patient groups that have limited access to or low compliance with prophylactic measures.

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