A Review on Dental Whitening

Abstract

Objectives: To provide a narrative review on vital dental whitening chemistry, toxicity and safety, vital dental whitening techniques, whitening systems, potential side effects of whitening and cyclic whitening using products with a range of concentrations and pH values. In addition, new developments and recommendations in the field of vital dental whitening will be presented to help clinicians understand the whitening process, its advantages, limitations, and the impact of whitening concentration and pH on enamel providing guidance in tailoring whitening treatments.

Data: Data were gathered using the following keywords: dental whitening, roughness, hardness, sensitivity, hydrogen peroxide, whitening pH, whitening concentration, whitening chemistry, colour, and toxicity.

Sources: An electronic search was performed using PubMed and Scopus databases. Bibliographic material from papers reviewed was then used to find other relevant publications.

Conclusions The effectiveness of vital dental whitening depends on many factors, such as the concentration/pH of the whitening agent, application duration, chemical additives, and re-mineralising agents used. Developing new whitening products and technologies such as nano-additives and alternative carrier systems is showing promising results, and might prove efficient in maximising whitening benefits by accelerating the whitening reaction and/or minimising expected reversible/irreversible enamel structural damage.

Keywords: dental whitening, hydrogen peroxide, whitening pH, whitening concentration, whitening chemistry.

Introduction

Aesthetic dentistry has evolved in relation to the high public demand in the 21st century. Public concern regarding smile aesthetics redirected clinicians and scientists towards formulating minimally invasive treatments such as tooth whitening, as an alternative to potentially destructive and harmful veneer or crown placements purely for cosmetic gain [1, 2].

In the late 1980's, whitening products (in-office and over the counter) were introduced to the U.S market, to accommodate for the high public demand in obtaining perfect white teeth [3]. The effects of carbamide peroxide (CP) on dentition were discovered during World War I, when it was used as an antiseptic agent to treat acute necrotizing ulcerative gingivitis (ANUG) [4]. In 1962, Klusmier introduced the concept of using CP-containing gel to treat inflamed periodontium after orthodontic treatment, which lead to the incidental discovery of the lightening effect of peroxide on enamel, and therefore, the possibility of using peroxides as tooth whitening agents. The personal communication sent by Kusmier to the Arkansas Dental Society was, however, left unnoticed until Haywood and Heymann described the technique in 1989 [5, 6].

This narrative literature review discusses vital dental whitening chemistry, toxicity and safety, vital dental whitening techniques, whitening systems, potential side effects of whitening and cyclic whitening using products with a range of concentrations and pH values. In addition, new developments and recommendations in the field of vital dental whitening will be presented to help clinicians understand the whitening process, its advantages, limitations, and the impact of whitening concentration and pH on enamel providing guidance in tailoring whitening treatments.

Chemistry of Dental Whitening

Carbamide peroxide is a stable structural complex that ultimately reacts with water and breaks down to its active components (Figure 1) [7]. Its structural stability leads to its slow degradation, which allows for a prolonged active whitening process when compared to HP. Hydrogen peroxide is an unstable compound that decomposes into water and reactive oxygen radicals. It is highly soluble, giving an acidic solution with a pH that differs according to the concentration, for example a 1% HP solution was reported to have a pH of 5-6 [8].

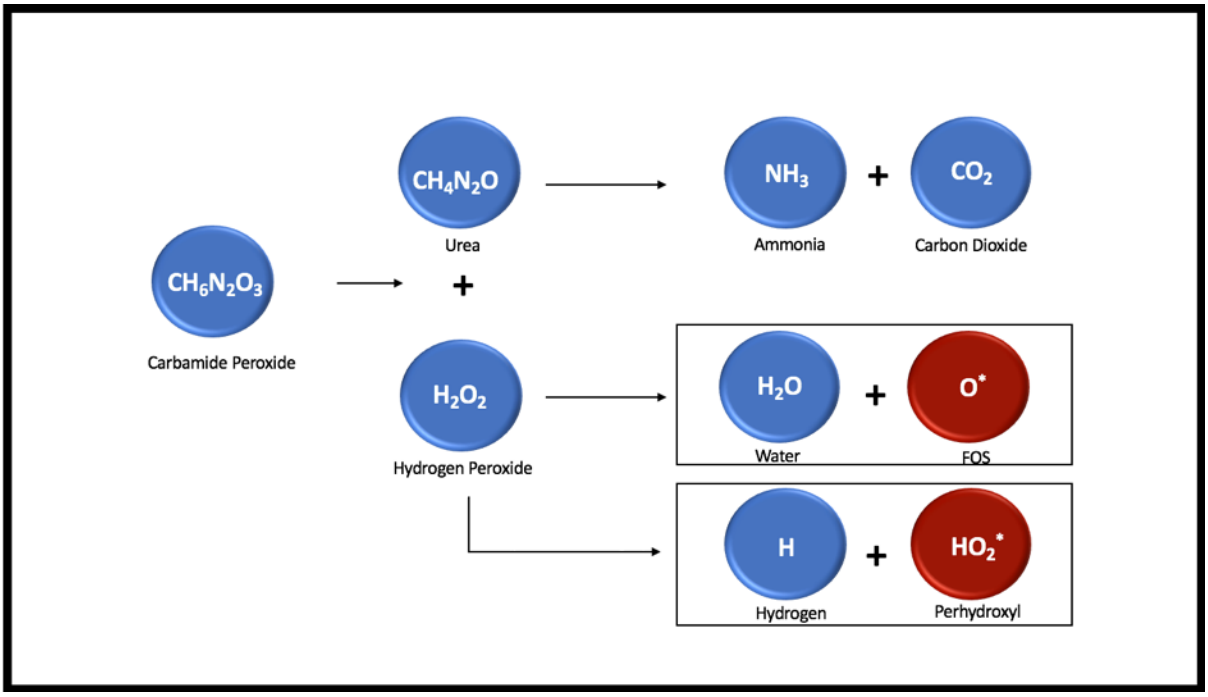

Figure 1 Shows the breakdown of CP to hydrogen peroxide and urea. Hydrogen peroxide will then breakdown into water and free oxygen species (FOS) which actively degrades chromogens. At higher pH levels >7 there is a greater chance that HP will breakdown forming hydrogen and perhydroxyl which leads to better whitening results as compared to FOS.

Tooth whitening products may contain hydrogen peroxide as an active agent, glycerine as a carrier, carbopol as a thickening agent, and finally, a number of flavouring agents [9, 10]. Whitening occurs through the process of chemical degradation of chromogens. Chromogens are the cause of dental discolouration, and are either present as large organic compounds with double bonds, or as metallic containing compounds, the latter being less likely to be whitened using hydrogen peroxide. In contrast, oxygen radicals released by HP react with organic chromogens more effectively through an oxidising process which breaks the strong double bonds, destabilising the chromogenic compound, and ultimately reducing tooth discolouration [11].

Whitening agents can be either products that can be applied with no activation step, such as HP on its own, or that require activation by either light, chemical mixing or a combination of both. Controversy over the most efficient and least harmful activation system is evident in the literature [12]. Chemical activators such as manganese gluconate, manganese chloride, and ferrous sulphate have been reported to improve the performance of whitening gels through accelerating the chemical reaction of HP on the enamel surface, therefore reducing exposure time and post whitening sensitivity [13, 14]. Ziemba *et al*, on the other hand, claim that the addition of a photo Fenton activator to the whitening gel and using an ultraviolet light activation system (UV) for 45 minutes significantly improves the Vita® shade score as compared to a

chemically activated system [15]. Other studies disagree with this, claiming no spectrophotometric shade difference after using a light activation source such as ultraviolet light or plasma arc light [12, 16]. It is important to note that in the study by Polydorou *et al*., whitening was conducted for short time intervals averaging 18 minutes, which might not be enough to produce any significant findings.

Some argue that short in-office light activation treatment leads to the absorption of energy which transforms into heat, causing pulpal damage and enamel dehydration, the latter giving the illusion of whiteness [16, 17]. The exact whitening process as explained in the literature is vague and many whitening studies do not allow for the full remineralisation cycle by saliva to take place where many side effects subside. There seems to be a consensus, however, on the oxidation process of chromogens by active whitening ingredients, but opinions diverge in regards to the ideal whitening activation process [18].

Toxicity of whitening agents

According to the Agency for Toxic Substances and Disease Registry (ATSDR) in the U.S., HP is a powerful oxidizing agent that has the potential to causes irritation to the skin, eyes, and mucous membranes upon exposure to high concentrations (>10%) [19]. Public Health England's Centre for Radiation, Chemicals, and Environmental Hazards, reports that HP generates hydroxyl radicals, which cause lipid peroxidation, DNA damage, and cellular death [20]. The maximum reported concentration of HP without causing mucosal irritation was 5% with damaging effects seen at 8%. Much higher concentrations can be formulated and HP is considered a corrosive substance at 50%. Toxicity of whitening agents are dependent on the concentration of HP, composition of the whitening agent, and duration of treatment [11]. Upon application, its low molecular weight enables it to penetrate to the dental pulp chamber and periodontal ligament, causing an inflammatory reaction that might be sufficient to initiate cervical root resorption, and damage to pulp, fibroblasts, or DNA [21, 22]. Reactive oxygen radicals may cause genotoxicity and cytotoxicity, but unless administered in very high concentrations (30% HP), these radicals are reported to be unable to cross cell membranes and inflict damage [23].

Subsequently, guidelines were developed and policies put in place to regulate the use of HP, and ensure public safety and wellbeing. The Cosmetic Products Enforcement Regulations in the UK set the maximum allowed concentration of HP to be used for dental whitening to 6% [24, 25], and according to the national guidelines from WorkSafe in Australia, HP is considered a hazardous substance in concentrations above 5% [8]. The American Dental Association

(ADA) awards the seal of acceptance to products having the maximum concentration of 10% CP (3.5% HP) [9]. Reported concentrations of commercially available products, however, ranged up to 40% according to previously published studies [26, 27]. To date, long term adverse effects caused by whitening agents used in accordance with guidelines and regulations have not been reported [9, 11, 28, 29]. Longitudinal evaluation of the long term adverse effects of whitening agents is required, including potential impact on the overall structural and mechanical integrity of tooth structure.

Vital tooth whitening

In-office

In accordance with UK regulations [24], in-office whitening may only be performed by a registered dental professional under the direct supervision and direction of a dentist, and cannot be carried out for example by beauty therapists. Historically, a whitening gel with high concentrations of chemically or light activated HP is applied for a short duration (45min-1hr). The high concentration of HP usually used for in- office products (30-38%) requires less time to release high levels of free oxygen radicals, thus, immediate results are observed following the whitening procedure [4, 30]. According to the literature, it is possible to get the tooth colour 5-8 shades lighter following multiple whitening cycles, with stability in results for up to 9 to 24 months [31, 32]. Although, in-office whitening products attracted attention for their ability to immediately whiten teeth, a high association with post-whitening tooth sensitivity and soft tissue ulcerations was noted [33, 34].

In an effort to minimise sensitivity while maintaining whitening efficacy, the incorporation of a titanium dioxide photo-catalyst into lower concentrations of HP (3.5-6%) was proposed. Researchers reported that exposure to light of a wave length ranging from 380-450nm accelerates the HP reaction and release of radicals, improving enamel colour [34, 35]. Research shows that this novel approach is as effective in whitening with less post-whitening sensitivity when compared to a 35% HP whitening agent [35, 36]. Skocaj *et al*, however, argue that titanium dioxide has the disadvantage of inducing oxidative stresses which ultimately cause cell damage, inflammation, and genotoxic side effects [37]. While the results published to date on titanium dioxide containing whitening agents are promising, long term effects and outcome stability are yet to be investigated and therefore, results must be viewed with some caution.

Dentist Supervised At-Home

Night-guard vital whitening is considered the gold standard in tooth whitening and commonly prescribed by dentists. It is self-administered by patients, with fewer reported side effects, and is a more cost effective whitening solution [38]. This whitening process includes the application of 10% CP to a custom tray and worn overnight for 2-6 weeks [39].

Evidence suggest that At-Home whitening using 10% CP applied for 8-10 hours, nightly, for 14 days has more than double the overall whitening effect (ΔE) (ΔE= 12.3) of a 35% HP gel applied in-office for 30 minutes once a week for two weeks (ΔE=5.3) [40]. These findings were confirmed by another clinical study [41]. A subsequent clinical study did not find this [42], a 10% CP gel applied for 2 hours, nightly, for 3 weeks showed no significant difference in its whitening effect in comparison to a 35% HP gel applied for three 8 minute cycles, once a week, for a total of three weeks. Both techniques showed a median shade change from baseline of 4-7 Vita®-shade guide units. The subjective evaluation of colour change in this study may have led to a greater margin of error in comparison to the objective readings obtained in the studies using a colorimeter [40, 43, 44]. Considering differences in shade measurement techniques, results indicate that At-Home night guard dental whitening using 10% CP produces similar or a greater whitening effect in comparison to in-office whitening.

At-Home day whitening techniques range from 2-4 hours daily for an average duration of 2 weeks. The reported ΔE after treatment using a 15% CP gel applied for 2 hours, daily, for 2 weeks range from 4.6-5.3 [45], lower than that reported for the night guard dental whitening using a lower CP concentration. This is probably attributed to the difference in the whitening duration; 2-4 hours during the day and 8-10 hours during the night. The limited exposure time of CP is important to consider, as only 50% of CP breaks down to its active components after 2 hours of treatment [46, 47].

Over the Counter

Over the counter (OTC) dental whitening products are purchased and applied without professional supervision. The whitening gel is usually carried in disposable plastic trays, on plastic strips designed to fit labial and buccal surfaces of teeth, carried in containers to be applied using a brush, or incorporated in tooth pastes and mouth rinses. Active whitening agents commonly present in OTC products are CP or HP, however, legal restrictions on HP and CP based products enforced by the EU Council Directive 2011/84/EU, have led to the rescission and discontinuation of their production in many markets across Europe. The

directive states that '*Tooth whitening or bleaching products containing concentrations greater than 0.1 % or less than 6 % of H_2O_2 (hydrogen peroxide), present or released are to be only sold to dental practitioners*.' [48]; making the use of products containing less than 0.1% HP insufficient to achieve the desired whitening results. In an attempt to overcome this issue, new OTC whitening products were introduced into the market with new active ingredients such as sodium chlorite, sodium carbonate peroxide, and Phthalimidoperoxycaproic acid (PAP).

According to an *In-vitro* study on human enamel, commonly purchased OTC whitening products containing sodium chlorite or PAP showed the greatest enamel structural alteration according to scanning electron microscopy; visible as etching patterns [49]. In addition, there was a significant reduction in enamel hardness (Vickers) compared to other products. Results also showed that sodium carbonate peroxide and PAP based products, surprisingly, produced less colour change than saline which was used as a negative control. Sodium chlorite, on the other hand, produced a greater whitening effect than CP which was used as a positive control. Sodium chlorite was additionally reported to cause a greater reduction in enamel micro-hardness in comparison to HP and CP [50]. This could be attributed to the presence of citric acid in combination with sodium chlorite and many other OTC products which could result in the structural alterations and reduction in hardness due to their low pH value.

Whitening toothpastes are popular products; with high public demand. According to Monteiro, the efficacy of removing extrinsic stains is determined by the physical characteristics of minerals within whitening toothpaste [51]. Whitening toothpastes act by chemically whitening and/or abrasively removing extrinsic stains [52]. Aside from the standard constituents of toothpastes such as fluoride, the active whitening agents include HP, CP, or sodium citrate, which chemically whiten enamel, and silica, calcium carbonate, or alumina to abrasively remove extrinsic stains [53].

Other factors to consider in addition to the composition of whitening toothpastes, include particle size of minerals incorporated and the type of tooth brush used. Measurements obtained by a surface profilometer, reveal that larger particles cause more enamel damage than smaller ones, and a medium textured tooth brush proved to be 1.4 times more abrasive than a soft tooth brush [54].

Although some authors report significant improvement in tooth colour following the use of HP containing toothpastes [55] or a combination of HP and hydrated silica whitening toothpastes [56], the effectiveness of one or both modes of action (chemical and mechanical) have been called into question [57, 58]. According to results gathered using the radioactive Relative Dentine Abrasion procedure (RDA), used to quantify the amount of abraded surface, it has

been concluded that whitening toothpastes were more abrasive than non-whitening toothpastes [57]. In addition, according to Soares *et al*, chemicals added to whitening toothpastes such as HP have no significant whitening effect [58]. Researchers attributed the lack of efficacy to deeply seated stains and/or to the short contact time, making the very low HP percentage commonly used in toothpastes (1%) inefficient.

Impact of whitening pH

As more whitening products are introduced, focus in research has been mostly on the overall impact of whitening agents on enamel surface morphology and mechanical behaviour, and not on the level of contribution peroxide pH has on the initiation of a destructive chain reaction during the whitening process. According to laboratory studies, enamel exposed to whitening products with different pH levels showed an increased risk of enamel demineralisation and root resorption upon prolonged exposures to highly acidic products with pH values falling below 5.2 or highly basic products >7 [7, 59].

The pH values of 26 commercially available tooth whitening products in Canada, ranged from 3.67 indicating a highly acidic product, up to a highly basic product with a pH value of 11.13 [7]. Twenty-one commercially available tooth whitening products in the South African market had similar pH values, reporting a minimum pH of 3.76 and a maximum pH value of 9.68 [60]. Products in Brazil and Iran had reported pH values as low as 2.39 and 2.97 respectively [61, 62]. Whilst the erosive effects acids inflict on enamel have been widely studied, exposing enamel to alkaline agents proved to be equally destructive. Alkaline products breakdown organic matter (protein), which is the main constituent of the protective pellicle surrounding enamel surfaces. Such products also target proteins present in the enamel microstructure, mainly amelogenin, which encapsulates enamel prisms, connects prisms to each other, and links mineral crystals within each prism [63]. The loss of organic matter in enamel by alkaline products makes it vulnerable to acidic attacks that were intended to cross numerous organic barriers before attacking apatite crystals.

The pursuit for an optimal whitening pH have lead scientists to formulate a neutral HP by either adding sodium hydroxide or hydroxyapatite. It proved to be significantly less destructive to enamel when compared to acidic HP. This was attributed to the alkaline salt evenly adhering to enamel surface lessening the direct contact between HP and enamel, thus, forming a protective layer [64]. Superiority of alkaline and neutral whitening agents was confirmed by a laboratory study which subjected human enamel to acidic, neutral, and alkaline 30% HP solutions. Colour values revealed a greater whitening effect with least structural change in

enamel whitened using neutral or alkaline HP compared to the erosive damage caused by the acidic whitening agent [65]. The lack of any structural changes in enamel whitened with alkaline or neutral HP was attributed to the oxidation reaction occurring in the dentine instead of enamel, therefore resulting in superior whitening with little or no harm to enamel. The erosive damage of the acidic HP on the other hand, was confined to the external surface of enamel, not penetrating deep into enamel and dentine which could explain the reported limited whitening effect. Consensus on the superiority of Alkaline HP, however, did not exist in the literature. Research revealed that alkaline HP alters enamel morphology through accelerating the oxidation reduction reaction [66, 67]. This could be attributed to the greater HP: caustic soda ratio required for the creation of an alkaline solution, causing an auto-accelerating reaction that generates oxygen and heat; leading to irreversible damage to enamel [68].

The fluctuating and inconsistent findings when studying the effects of HP pH is probably attributed to the varying components of the whitening gel used as opposed to being purely caused by their pH value. Research suggests that at a constant pH value of 7, whitening efficiency of HP is influenced by the type of conditioner added [69]. The pH values of pH conditioners such as sodium hydroxide (NaOH), sodium bicarbonate ($NaHCO_3$), sodium carbonate (Na_2CO_3), and potassium bicarbonate ($KHCO_3$) were not mentioned in the study, however, adding them to HP revealed that in the cations, the potassium ion had a greater whitening effect than the sodium ion, and the bicarbonate ion had a greater whitening effect than the hydroxide and carbonate ions in the anions. Therefore, the greatest whitening effect of HP with controlled concentration and pH was recorded when $KHCO_3$ was added. The least whitening effect under the same circumstances was recorded in the K_2CO_3 and Na_2CO_3 groups [70, 71].

Potential side effects

Enamel Hardness

Tooth whitening agents cause a number of adverse effects on the hardness of human enamel, making it more susceptible to deformation and fracture [72, 73]. Enamel specimens exposed to 7.5% HP exhibit a significant reduction in enamel hardness (Knoop hardness reduced by more than two thirds, from 294 to 78 MPa) [74]. This is explained by the oxidation process that the organic and inorganic components of enamel undergo when exposed to whitening agents. This leads to changes in enamel morphology by the development of porosities and micro-cracks, ultimately causing a reduction in hardness [75, 76].

Furthermore, the pH of whitening products plays an important role in determining the degree of impact whitening agents have on the hardness of whitened enamel. Whitening agents with acidic pH cause greater reductions in hardness when compared to products with neutral or slightly alkaline pH [77]. It has been reported that whitening using a 25% HP with a pH of 3.2 caused a significantly greater decrease in enamel hardness in comparison to a 38% HP whitening product with a pH of 6.7 [75]. In contrast, research has also revealed that whitening using two 10% CP products with pHs 6.79 and 6.23 for 8hrs/day for a duration of 14 days have resulted in no significant changes in enamel hardness [78, 79]. All studies reported had artificial saliva as a storage medium for whitened enamel to provide samples with an opportunity to undergo remineralisation between whitening cycles.

According to the literature, enamel hardness changes occurring post whitening are irrespective of the type of light activation source used. Araujo *et al.*, claimed that enamel hardness reduction recorded post whitening was 5.81% regardless of the type of light used (LED, Halogen, or Argon Laser) [80]. This indicates that enamel mechanical changes post-whitening appear to be dependent on the chemical reaction and oxidation process, which, in turn, is directly proportional to the concentration and pH of whitening agents used, and is independent of the type of activation source used to initiate the reaction [38].

Additionally, the duration of application has a greater impact on enamel micro-hardness values post whitening than HP pH and concentration [67]. Limited exposure time could possibly contribute to the absence of any significant side effects in whitened enamel, and this could mean that the impact of pH and concentration become significant when the exposure time exceeds a certain limit.

Other whitening gel components have been reported to cause a significant reduction in micro-hardness values. According to McCracken and Haywood, enamel treated using a product containing carbopol caused a significant micro-hardness reduction in the outer 25 μm of enamel specimens tested [81]. Knoop hardness values of bovine enamel whitened using a neutral 10% CP product containing carbopol for 21 days were recorded to drop by approximately 77% [82]. Carbopol is used as a thickening agent and is an acidic polymer that could potentially demineralise enamel surface, inhibit the formation of hydroxyapatite through its high calcium binding capacity, and ultimately contribute to the reduction in enamel micro-hardness [70].

Enamel Roughness

Constituents released by the breakdown of CP or HP (Figure 1) following a whitening procedure create porosities, grooves, and cracks in enamel, making it rough and more susceptible to extrinsic staining when measured *in vitro* [23, 74, 75, 83]. However, replicating this *in vivo* has not provided consistent results. For instance, while post-whitened enamel was up to one-third rougher after canine enamel was treated using 10% and 20% CP, and 25% HP concentrations [84] a randomised clinical trial in humans revealed no significant difference in enamel roughness following the application of 38% HP and 35% CP [85]. One potential explanation for this disparity is that in the latter study, [85], roughness was measured indirectly using a two stage polyvinyl siloxane impression of the whitened enamel surface, which was then analysed using non-contact profilometry. This could possibly increase the risk of error and affect the accuracy and repeatability of results as a consequence [86].

Enamel roughness is affected by the concentration and pH of the applied whitening gel. A number of studies comparing between whitening products with a variety of pHs used, ranging between 3.2 and 10.8 [64], [75], [87], [88] revealed an increase in roughness in whitened enamel as whitening agent concentration increases and pH decreases. The thickening agent, carbopol, is acidic and ionic in nature and is derived from carboxylic acid. It has been reported that carbopol in whitening products causes an increase in enamel roughness in comparison to products containing natrosol, a cellulose-based non-ionic polymer, thickening agent [89]. Others, however, report a greater impact of the application time in comparison to the concentration of the whitening agent applied [90, 91]. In essence, research suggests that prescribing non-acidic whitening agents with low concentrations, for a relatively short duration would minimise harmful side effects of whitening agents.

Enamel surface loss

Dental enamel is highly permeable to peroxides (CP and HP), and the penetration depth of whitening agents across enamel, dentine, reaching to the pulp chamber is directly proportional to the duration of application and concentration [92]. Many whitening agents have an acidic pH, creating an erosive environment, and contributing to the loss of enamel inorganic matter [93]. Friction tests using a tribometer, showed that tooth surface loss and reduction in hardness in bovine enamel exposed to acidic HP whitening agents (pH 2.7 to 3.9) were 2-3 times the level of loss caused by neutral HP (pH 7.1) [94]. According to laser induced fluorescence, the depth of destruction of inorganic matter in enamel following whitening with 30% HP was

directly proportional to the pH and application time (up to >1000μm after 60 seconds), and was confined to the external surface of enamel in direct contact with the 30% HP [95]. The outermost surface of enamel is the aprismatic enamel, [96]. This aprismatic structure is highly mineralised and therefore more resistant to demineralisation [97]. In *in-vitro* studies, enamel specimens are usually lapped and polished to create a flat surface for experimentation. This removes aprismatic enamel, and exposes the weaker and less mineralised prismatic enamel to testing, therefore, results might be an overestimation of what would happen in real life [97]. Incorporating the aprismatic enamel in a laboratory experiment to closely resemble the clinical situation is challenging; it is naturally present in different thicknesses between individuals and within different tooth sites, making it nearly impossible to standardise [98].

Light activated whitening has been shown to be more aggressive than whitening with no light activation [99-102]. For instance, diode laser assisted whitening using 30% HP caused significantly greater enamel damage in the form mineral loss and loss of interprismatic enamel, when compared to whitening using 40% HP with no light activation source [99].

In an attempt to improve upon whitening agents and minimise surface loss, the addition of casein phosphopeptide–amorphous calcium phosphate (CPP-ACP) as a remineralisation agent proved to stabilise the level of calcium and phosphate in saliva, therefore, enhancing its buffering capacity [103, 104]. The significant benefit remineralising agents have, proven by various clinical and laboratory studies, justifies the strong recommendation for their use during or after tooth whitening [99, 105-108].

Colour change

The effect of dental whitening agents depends upon pH, environmental temperature, added catalysts, and choice of light activation source [109]. According to a recent systematic review, 10% CP showed similar whitening efficacy with lower risk of tooth sensitivity when compared to whitening using greater concentrations [110]. Whitening agents take 5-15 minutes to penetrate enamel, cross the dentine layer, and ultimately reach the pulp [111, 112], and as the rate of change is reached, the additional increase in concentration would only cause an increased risk in tooth sensitivity and gingival irritation [112, 113].

Controversy in relation to the relevance of light activation sources to the whitening process is still evident. According to a review published in 2014, the use of light activation sources have no impact on the whitening efficacy or in accelerating the whitening process [12]. Conversely,

results of a randomised clinical trial showed that halogen light significantly improved the level of whitening compared to laser [114]. Whitening was performed using 38% HP for a maximum of four 15 minute intervals until teeth were lightened by six Vita® shade tabs. Dominguez *et al.*, additionally, claims that the light activation source is more relevant to the whitening process than the choice of whitening agent, as whitening using 35% HP activated using light-emitting diode (LED) produced the best whitening result in comparison to laser or halogen [115].

Colour stability depends greatly on diet and smoking habits as they contribute to the development of extrinsic stains [116]. In a study comparing smokers and non-smokers, results revealed the same level of whiteness a week after tray-based tooth whitening, however, a month later smokers showed darker teeth than non-smokers, indicating the same initial results but different long term whitening stability [117].

In cases of intrinsic staining such as dental fluorosis, enamel microabrasion prior to whitening showed great long term success in three case reports with 11, 20, and 23 year follow ups [118]. The process of microabrasion eliminated the porous enamel subsurface which entraps stains and causes light scattering; allowing the whitening agent to reach deeper into enamel and produce better whitening results than whitening protocols not including microabrasion [119]. Bristo *et al*., proposed abrading enamel surface using a fine diamond bur under water cooling for 5-10 seconds, followed by a 60 second prophylaxis using a 6.6% hydrochloric acid slurry with silicon carbide microparticles. This technique increased the degree of penetration of whitening agents, improving whitening efficacy and long term stability [120].

Sensitivity

Whitening induced tooth sensitivity is poorly understood in the literature [121]. Some believe that it is caused by high concentrations of whitening agents, leading to higher levels of by-products released and diffused through dentinal tubules [75, 122, 123]. Others attribute sensitivity to the glycerine carrier used in most whitening gels, as its hydrophilic nature causes dehydration of the tooth structure [18, 124].

A relationship between post-whitening tooth sensitivity and the presence of enamel craze lines (i.e. enamel infractions) was studied in a non-randomised controlled clinical trial. The study included 460 teeth (49% of teeth had enamel craze lines) which were subjected to in-office whitening using 15% HP. Results showed 15% of teeth with craze lines and 11% of teeth with

no craze lines presented with post whitening tooth sensitivity, indicating a positive but weak correlation between the presence of enamel craze lines and tooth sensitivity [125].

Others report that lower concentrations of whitening agents applied for prolonged periods (10% CP for a total treatment time of 112 hours; 8hrs/day for 14 days) are significantly more harmful to enamel and would consequently cause higher sensitivity levels than high concentrations applied for a short duration (45% CP for a total treatment time of 7 hours; 30 min./day for 14 days) [91]. Soares *et al.* reported that whitening using 35% HP for 5 minutes and 17.5% HP for 45 minutes similarly produced significantly less damage to enamel compared to 35% HP applied for 45 minutes, concluding that post whitening sensitivity is dependent upon both whitening duration and concentration [126]. Therefore, in an attempt to minimise harmful side effects inflicted by high whitening concentrations, researchers have investigated the benefits of separating whitening cycles [127], reducing whitening cycles from 3/15 minute to 2/15 minute cycles [128], and incorporating sugar-free gum containing CPP-ACP to reduce post whitening sensitivity.

Attempts to minimise the severity of post whitening sensitivity through the incorporation of desensitising agents have been reported. These attempts, however, did not reduce the risk or severity of tooth sensitivity post whitening [129]. According to a randomised triple blind clinical trial, post whitening sensitivity did not significantly differ after whitening using a 10% CP product with 3% potassium nitrate and 0.2% sodium fluoride in comparison to a desensitising free 10% CP whitening product [130]. In addition, a randomised controlled clinical study revealed no significant difference in sensitivity levels after chewing a pack of 12 sugar free CPP-ACP containing gum for 10 min/hr upon review 24 hours after whitening using 15% HP. [131]. A similar study tested the effect of chewing 5 pieces of sugar free CPP-ACP containing gum for 10 min/day for one week prior to tooth whitening using 30% HP. Results revealed no reduction in post-whitening sensitivity levels [132]. A cross-sectional clinical study by Pereira *et al.* tested the buffering capacity caused by gum chewing through stimulating salivary flow using sugar free gum with and without CPP-ACP. Results showed no difference between sugar free gum with and without CPP-ACP [133]. The absence of significant results after chewing CPP-ACP containing gum might be attributed to its very low concentration, which was reported to be 0.6% [132].

Cyclic whitening

Understanding the impact of extended whitening duration will provide greater awareness of the long term effects on enamel of repetitive whitening. As mentioned previously, adverse

effects of whitening agents depend on the technique followed, the concentration of whitening agent, and the duration of treatment. Repeated whitening was reported to cause adverse effects, ranging from demineralisation and formation of enamel defects to a more serious side effect such as hyperkeratosis, hyperplasia, and dysplasia [134]. Concerns were expressed in the literature regarding abuse of whitening products, as it has been reported that repeating a whitening cycle using 35% HP one week later, significantly reduces enamel microhardness [135].

In an attempt to study the impact of an extended whitening cycle beyond manufacturers recommendations, human enamel specimens were whitened with an undisclosed active agent concentration of 44% and exceeded the recommended whitening duration by 9 days. Mineral and elemental content measured revealed an irreversible damage in enamel microstructure [136].

In a clinical study, periodontally compromised teeth scheduled for extraction were whitened for 14, 21, and 90 days. Scanning electron microscopic images showed demineralisation of enamel and exposure of prisms after 14 days, with a deeper level of mineral loss leading to exposed prisms, down to enamel rods and frequently to dentine after 90 days [38].

One must, however bear in mind differences between whitening duration and cyclic whitening. Extending the duration of whitening has been predominantly tested in the literature, revealing damaging effects on enamel's chemical composition, physical behaviour, in addition to the overall systemic effects of continuous digestion of small amounts of HP or CP [38, 134, 136]. Cyclic whitening, on the other hand, has been rarely investigated. There are no published studies relating to the monthly repetition of a commonly prescribed tray-based whitening protocol using 10% CP for 2 weeks, for instance, or any other protocol for that matter. The time interval in between whitening cycles might possibly restore the enamel to its baseline values, or similar to reported results of longer whitening durations, long term, repeated whitening of enamel might lead to permanent damage.

Remineralisation of whitened enamel

CPP-ACP

In an attempt to accelerate the mineral uptake and remineralisation process of enamel, reduce dentine hypersensitivity, and even counteract the harmful effects of xerostomia, casein phosphopeptide-amorphous calcium phosphate (CPP-ACP) [137] has been added to a number of different dental products, such as toothpastes [138], mouth rinses [139] restorative materials [140, 141] chewing gums [142, 143], and more recently in tooth whitening products [144-146]. CPP-ACP was introduced in 2002 as a 10% CPP-ACP paste (GC Tooth Mousse™, GC Corporation, Melbourne, Australia), which is derived from milk protein 'casein', and due to its high affinity it binds and aggregates with calcium and phosphate ions in an amorphous state and chemically bonds to hydroxyapatite present in hard tissue, maintaining the saturation of calcium and phosphate ions, thus, hindering the demineralisation process caused by bacterial or erosive attacks [145].

In an attempt to maximize whitening efficiency while minimizing sensitivity, the combined effect of using CPP-ACP with tooth whitening agents was tested by either applying 10% GC Tooth Mousse™ on enamel before or after whitening. This resulted in a significant reduction in post-whitening sensitivity with no impact on whitening efficacy [147-150]. The application of CPP-ACP paste before, after, or before and after whitening enamel with 35% HP have additionally prevented significant hardness and roughness changes in bovine enamel following a 14 day whitening protocol [151]. Results were confirmed using human enamel samples, revealing a significant improvement in enamel remineralisation and microhardness values upon application of CPP-ACP paste (GC Tooth Mousse™) after whitening [99, 152].

According to a clinical study, roughness values of whitened enamel decreased by 50% after being remineralised using CPP-ACP, nano-hydroxyapatite, or novamin for 5 minutes after each whitening cycle [153].According to SEM images, a uniform layer of these bioactive pastes enhanced the remineralisation process and reparative capacity following the structural damage caused by whitening presenting as depressions and prismatic exposures, therefore creating a smoother and more uniform surface.

The long track record of CPP-ACP used before and after whitening treatments demonstrate its effectiveness in reducing negative side effects caused by peroxides, however, its effect on enamel exposed to an acidic, neutral, or alkaline whitening agent has not been reported so far.

Nano-hydroxyapatite

Hydroxyapatite is a calcium phosphate compound that can be either synthesized or extracted naturally from bovine teeth or bones for example [154]. In an attempt to maximize the benefits of dental products such as toothpastes, scientists incorporated nano-hydroxyapatite (nHA) particles for remineralisation, ability to reduce *Streptococcus mutans* virulence adsorption, and remove extrinsic stains by virtue of its abrasive nature [155-157].

Enamel building blocks are 97% HA crystals which are 20-40nm in size. If an attempt to repair enamel was undertaken after an erosive or abrasive attack it would be logical to do so using nano-sized HA (nHA) particles as they have proven to self-assemble, creating enamel like structures in aqueous solutions, which is a unique nanoscale advantage [158, 159]. Li *et al* reported the strong affinity, biocompatibility, and reparative capacity of 20 nm sized artificial nHA applied to eroded human enamel, which was not evident following the application of ACP or larger sizes of HA particles [160]. This could be explained by the high surface to core atoms present in nano-particles, meaning that in nano-sized particles there are more surface atoms with fewer bonds than atoms located deep into the core. This creates a more reactive particle with a higher potential to create new and strong bonds [161]. For this reason, the larger number of unbound surface atoms in a nano-particle, in comparison to micro or macro atomic scales, allow the creation of more bonds with surrounding structures, therefore, forming a more strongly adhered compound [159, 161].

Multiple clinical studies have been conducted using nHA toothpastes since the 1980s. A three-year clinical study, using 5% nHA toothpaste revealed a reduction in caries incidence by up to 56% in 181 school children [155]. More studies supporting the use of nHA in dental products were published afterwards. For instance, in comparison to fluoride, nHA containing pastes proved to be more effective in occluding dentinal tubules, thus, reducing dentine sensitivity, and in restoring surface roughness to pre-whitened conditions [107, 162-164]. An additional reported advantage of nHA is its ability to shift the oral flora to a more favourable condition. Saliva sampling collected to determine bacterial ratios before and after a 5 minute application of nHA paste revealed that it adheres to tooth and plaque surfaces and selectively adsorbs harmful bacteria such as *Streptococcus mutans* and *Porphyromonas gingivalis*, which in addition to reducing the incidence of caries, may potentially help prevent the occurrence of plaque related periodontal disease by smoothing plaque retentive rough enamel surfaces [108, 165, 166]. This was not the case however in a study where a serum with an undisclosed concentration of nHA was applied for 2-3 minutes then rinsed off after 20 minutes (n-HAP

Repairing Serum; PrevDent International BV, Netherlands). The procedure was repeated for 10 days, and revealed no significant effect in restoring enamel surface roughness [167].

According to the literature, significant improvements following the application of nHA required 90 minutes [108], 2 weeks [107], 2 to 5 weeks [156], and 2 months [165], which supports the argument that the application duration of nHA is an important factor to consider.

Regardless of the early development of nHA containing products, and the applications, benefits, and limitations reported in the literature to date, the amount of research on nHA is underwhelming, and overshadowed by other materials that have similar mechanisms of action. This leaves room for research to potentially improve currently used products with nHA additives.

Impact of dietary acids on whitened enamel

The effects of dietary acids upon whitened enamel are reported to include significant reduction in microhardness, enamel mineral loss, and formation of surface porosities [135, 168]. Whitened bovine enamel exposed to beverages containing dietary acids with pH values ranging between 2.75 and 3.29, for 7, 14, and 21 days were structurally more vulnerable to erosive attacks when compared with un-whitened enamel. Repeated exposures to HP and dietary acids negatively affected enamel hydroxyapatite crystals, through dissolving the calcium ions and leaching off mineral crystals [135, 169]. This was confirmed by de Araujo *et al*., who reported higher levels of mineral loss in enamel whitened for 6 hours/daily for a total of 3 weeks, using 10% CP, followed by immersion in a cola soft drink for 1 hour after each whitening cycle in comparison to a control group stored in artificial saliva for the duration of the experiment [169].

In an effort to formulate a clearer image of the true impact of dietary acids on whitened enamel, samples were exposed to either 38% HP or orange juice [170]. Researchers reported a statistically significant difference in microhardness (from 161 to 156.8) in the group exposed to orange juice, while whitened enamel exhibited no difference in micro-hardness values. One explanation could be that the short duration of whitening (15 minutes) inflicted minimum damage, or the whitening gel possibly contained remineralising additives, hence, micro hardness values did not change. A similar study comparing hardness values and surface topography in enamel specimens exposed to either 6% HP (pH of 5.5) or orange juice (pH of 3.8) revealed a 84% hardness reduction and significant topographical changes in enamel exposed to orange juice, with no significant difference observed in the whitened group [171]. This being the case, and since the cumulative effects of whitening and dietary acids are rarely

studied, it is it is likely that the combined effect of HP and dietary acids are more harmful to enamel than their separate effects.

Whitening stability and stain absorption

Patients are advised to minimise or eliminate dietary components that may cause enamel staining before, during, and after any whitening treatment, and for that reason, investigations on the susceptibility of whitened enamel to staining have been abundantly reported. Whitened enamel has a higher tendency for stain absorption, when compared to un-whitened enamel [97]. The effect of whitening on enamel roughness varied according to the literature, mostly reporting that whitened enamel surfaces become rougher after whitening, with higher susceptibility to stain absorption and retention compared to the control group [84, 172, 173]. This was corroborated by a laboratory study using coffee as the staining agent for whitened and un-whitened bovine enamel [174].

Immersion of bovine enamel samples in red wine for 48 hours, either immediately, 24 hours, or one week after whitening with 35% HP exhibited similar levels of stain uptake regardless of the time frame separating whitening and staining treatments [175]. Additionally, an *in-situ* study where small enamel slabs were mounted in intra oral devices and whitened using 35% HP and then stained either immediately or 7 days after whitening, showed no significant differences in enamel whiteness indices after being exposed to coffee [176].

This led to investigation of the impact of staining during and after whitening to help. According to Attia *et al.*, the immersion of human and bovine enamel in coffee during a 16% CP whitening treatment had no significant impact on the shade of whitened enamel [177]. Spectrophotometric evaluation of human enamel whitened using 10%, 15%, or 20% CP for 6 hours per day, for 3 days, followed by immersion in coffee or red wine for 15 minutes, revealed that during whitening no significant pigment uptake was noted (Côrtes et al., 2013). It has been theorised that storage in artificial saliva and subsequent whitening treatments might have reduced or eliminated the effects of coffee and red wine. Upon conclusion of the whitening treatment, enamel was immersed for one last time in coffee or red wine, and the colour uptake was measured 7, 15, and 30 days, post immersion. Readings revealed a significant stain uptake in both groups, more so in the red wine group. This was explained by the acidic nature of red wine, causing an increase in enamel roughness and susceptibility to stain uptake.

Colour stability of whitened enamel in a 12-month *in-vitro* colorimetric evaluation revealed a significant increase in L* (lightness levels), and decrease in b* (yellowness values)

immediately after whitening. There were no observed changes in the a* value, indicating no significant colour alterations along the red-green axis. [178]. Enamel was whitened using 6% HP WhitestripsTM (Procter & Gamble, Egham, UK), 15% CP lluminé (Dentsply, DeTrey, Konstanz, Germany), or 38% HP Opalescence Xtra Boost (Ultradent Products, South Jordan, Utah, USA) for 21 days. Colour measurements were obtained immediately after whitening and 3, 6, and 12 months post-whitening. During the observation period, *L** levels decreased gradually, however, they were still greater at 12 months post whitening than they were at baseline. The reduction in lightness was attributed to the organic constituents in artificial saliva, which were suggested to cause lightness reduction and colour regression. The *b** values, however, were constant throughout the 12-month follow-up period. This was explained by the possible irreversible degradation of organic matter in enamel, leading to a constant reduction in yellowness. Overall enamel colour change (ΔE), however, was reported to significantly decrease when comparing readings obtained immediately after whitening to readings obtained 6 months later. At 6 months post whitening a 45% reduction in ΔE was recorded in one study [41]. According to another clinical study, colorimetric readings of ΔE regression was up to 51% and 65% after one week and 6 weeks post whitening respectively [179]. The variation in colour relapse observed in clinical studies, was attributed to the frequency in consuming dietary pigments, smoking habits, and the level of oral hygiene [178].

Differences in findings between clinical and laboratory studies might be caused by the choice of storage solution, the elimination of aprismatic enamel by the lapping and polishing processes, or due to the possible variation in enamel microstructure according to its location and depth within the tooth from which it was harvested [180].

Developments in whitening agents

Plant extract

In an effort to effectively replace commercially available whitening agents with natural, less cytotoxic whitening products, a whitening HP gel also containing fruit organic acids (oxalic, citric, tartaric, malic, succinic, and fumaric) with pH values ranging from 4.5 to 7, was compared to hydrogen peroxide gel. Cytotoxic effects on fibroblasts and colour change of resin composites were evaluated following exposure to either the fruit acid gel or the HP gel. Similar levels of whitening were achieved however, fruit organic acids were less cytotoxic than HP [181].

The addition of vegetable-derived enzymes as a means for enhancing whitening efficacy and reducing enamel structural changes post-whitening was reported in the literature [182, 183]. Sweet potato enzymes including polyphenol peroxidase (PO), catalase (CAT), and superoxide dismutase (SOD) were added to two concentrations of HP (10% and 35%) and tested on 32 artificially stained teeth [183]. Sweet potato extract contains a number of antioxidant molecules, which according to studies, are highly effective free radical scavengers that target chromogens [184-186]. In comparison to HP without the additive antioxidants, spectrophotometric and SEM images of the experimental group revealed significantly increased tooth whiteness levels and reduced enamel structural breakdown [183]. The added antioxidant to HP reduced its high activation energy and increased the rate of free radical release. Lowering the activation energy increases the rate of free radical release, producing the desired whitening effect in less contact time, and ultimately causing less damage to enamel microstructure [183]. Although, the aforementioned *in-vitro* studies showed improved results that could potentially advance the field of dental whitening, these techniques have not been clinically tested, and therefore results can only be viewed as potentially promising.

Chemical additives

There are extensive novel dental whitening products with chemical additives [187], bioactive additives [137, 145, 146], and natural organic additives [181, 188]. In an attempt to elevate the pH value of HP, creating an alkaline environment that inhibits or delays the decomposition of HP, researchers formulated a new complex. This complex was composed of 5% HP, sodium tripolyphosphate (STPP), and urea, and was compared to a 10% HP and urea whitening agent [187]. This randomised double-blind clinical trial revealed that lower concentrations of HP in the (HP (5%) + STPP + urea) complex were as effective in whitening according to spectrometer measurements as a (10%HP + urea) complex. This highlights the potential to maximise whitening efficiency using lower concentrations of HP in the presence of chemical additives, which would help clinicians and patients achieve desired whitening results mostly obtained through the application of higher concentrations of HP.

The incorporation of calcium peroxide nano-particles allows active whitening ingredients to deeply penetrate enamel micro- and nano-structures, resulting in an increased surface contact and ultimately a greater whitening effect [189]. Another development was the incorporation of calcium phosphate microspheres as CP carriers in an attempt to reduce structural damage and tooth sensitivity [190]. The carrier system proved to be promising, showing similar diffusion

rates of CP through enamel. The introduction of these new additives and carrier systems can potentially maximise the whitening effect and reduce or even eliminate any potential side effects. The ongoing research to optimise dental whitening techniques and products along with the new possibilities nanotechnology provide will aid in serving this purpose.

Conclusion

The effectiveness of vital dental whitening depends on many factors, such as the concentration/pH of the whitening agent, application duration, chemical additives, and re-mineralising agents used. Developing new whitening products and technologies such as nano-additives and alternative carrier systems is showing promising results, and might prove efficient in maximising whitening benefits by accelerating the whitening reaction and/or minimising expected reversible/irreversible enamel structural damage.

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