INSTITUTO UNIVERSITÁRIO EGAS MONIZ

MESTRADO INTEGRADO EM MEDICINA DENTÁRIA

INTERN AND EXTERN CHANGES AFTER TREATMENT OF ICON INFILTRATION RESIN: A SYSTEMATIC REVIEW AND META-ANALYSIS

Trabalho submetido por
Madalena dos Santos Vargas Soveral
para a obtenção do grau de Mestre em Medicina Dentária

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Trabalho orientado por
Prof.ª Doutora Cristina Manso
Prof.ª Doutora Vanessa Machado

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Resumo

Introdução: As lesões de *white spot* são as primeiras alterações do esmalte devido à cárie dentária e tratamentos não-invasivos têm sido sugeridos para travar a progressão da lesão. O objetivo desta tese é analisar as alterações da superfície do esmalte com e sem lesão de *white spot* após aplicação da resina infiltrativa, nomeadamente profundidade de penetração, rugosidade, microdureza e resistência ao cisalhamento.

Materiais e Métodos: A pesquisa foi realizada no *Medline, Pubmed, Cochrane Central Register of Controlled Trials, Embase, Web of Science, Scholar, and LILACS* até maio de 2021. Estudos *in-vitro* que avaliam a profundidade de penetração, rugosidade, microdureza e resistência ao cisalhamento antes e depois da infiltração de resina foram incluídos. A qualidade metodológica foi avaliada através do Joanna Briggs Institute Clinical Appraisal Checklist for Experimental Studies. Meta-análises *pairwise* de rácio de médias avaliaram as alterações das propriedades do esmalte com e sem lesão *white spot.*

Resultados: De um total de 1604 artigos, 48 foram incluídos para avaliação quantitativa meta-analítica. A rugosidade de superfície do esmalte melhorou 35% (95% CI: 0.49-0.85, $p<0.0021$) no esmalte saudável e 54% (95% CI: 0.29-0.74, 0.0012) nas lesões de *white spot*. A microdureza reduziu 24% (95% CI: 0.73-0.80, $p<0.001$) no esmalte saudável e aumentou 68% (95% CI: 1.51-1.86, $p<0.001$) nas lesões de *white spot*. A força de cisalhamento reduziu 25% (95% CI: 0.60-0.95, $p<0.001$) no esmalte saudável e aumentou 89% (95% CI: 1.28-2.79, $p<0.001$) em lesões de *white spot*. A profundidade de penetração da resina infiltrativa levou à oclusão de 65,39% (95% CI: 56.11-74.66, $p=0.01$, I2=100%) da lesão de *white spot*.

Conclusões: A aplicação da resina infiltrativa promove a recuperação das propriedades do esmalte, tanto em esmalte são como em lesões de *white spot*. Futuramente, estudos com controlos apropriados são necessários bem como follow-ups a longo prazo.

Palavras-chaves: Resina infiltrativa; lesões de *white spot*; propriedades superficiais.

Abstract

Introduction: White spot lesion represents the first visual alteration in the enamel caused by caries. The progression of these lesions can be arrest with non-invasive treatments before cavitation. The thesis aims to analyze changes in the enamel after applying the infiltrant resin in white spot lesions, namely penetration depth, surface roughness, microhardness, and shear bond strength.

Materials and Methods: The search was conducted in Medline, Pubmed, Cochrane Central Register of Controlled Trials, Embase, Web of Science, Scholar, and LILACS until May 2021. In-vitro studies that assess depth penetration, roughness, microhardness, and shear strength before and after resin infiltration were included. Methodological quality was evaluated using the Joanna Briggs Institute Clinical Appraisal Checklist for Experimental Studies. Pairwise ratio of means meta-analyses allowed evaluating of the enamel properties, before and after resin infiltration, on enamel surfaces with and without white spot lesions.

Results: From a total of 1604 articles, 48 were included for meta-analytic quantitative evaluation. In the parameter of enamel surface roughness there was an improvement by 35% in sound enamel (95% CI: 0.49-0.85, p<0.0021) and 54% (95% CI: 0.29; 0.74, 0.0012) in white spot lesions. Enamel microhardness was reduced by 24% (95% CI: 0.73; 0.80, p<0.001) and increased by 68% (95% CI: 1.51; 1.86, p<0.001) in white spot lesions. Shear strength in enamel was reduced by 25% in sound enamel (95% CI: 0.60; 0.95, p<0.001) and increased by 89% (95% CI: 1.28; 2.79, p<0.001) in white spot lesions. At penetration depth, the application of infiltrating resin led to occlusion of 65.39% (95% CI: 56.11; 74.66, p=0.01, I2=100%) of the white spot lesion.

Conclusions: The application of infiltrating resin promotes recovery of enamel properties, both in healthy enamel and in white spot lesions. In the future, studies with defined protocols and appropriate controls are needed with long-term follow-ups.

Keywords: Infiltrative resin; white spot lesions; surface properties.

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Abbreviations list

(MMP)-20- Matrix metalloproteinase

ACA CCS- Caries Classification System for Clinical Practice

ADA- American Dental Association

BISGMA- Bisphenol A-glycidyl methacrylate

ECM- Eletrical Conductivity method

FOTI- Fiber-optic transillumination

HCL- Hydrochloric acid

ICDAS- International Caries Detection, and Assessment System

Ra- Roughness average

TEGDMA- Triethylene glycol dimethacrylate

WHO- World Health Organization

WSL- White spot lesions

1. Introduction

Enamel is a unique and one of the most complex tissues of mammals. Given this, a detailed knowledge of the development and mineralization of enamel is important to better understand the onset of the cariogenic process (Rathee & Jain, 2021).

1.1 Odontogenesis

The odontogenesis comprises the tooth development process encompassing its formation, eruption and integration. Collectively, the process of odontogenesis can be divided in 5 stages schematized in Figure 1.

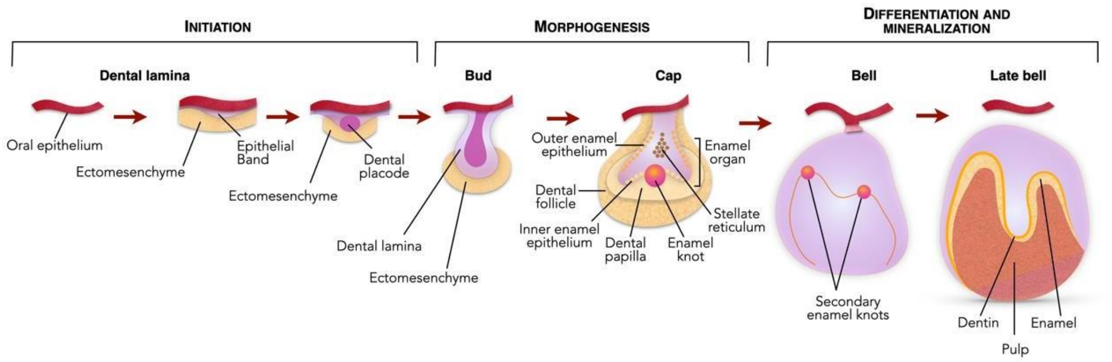

Figure 1. Stages of tooth development. The odontogenesis begin with initial stage, followed by a morphogenesis process (the bud and cap stages), ending with the differentiation and mineralization (bell & maturation and apposition stages)

During the late bell stage, different layers of distinguished cells begin to raise, through their form and final tissue of formation, as represented in figure 2. Particularly, the enamel is formed in a process defined as amelogenesis (Lacruz et al., 2017).

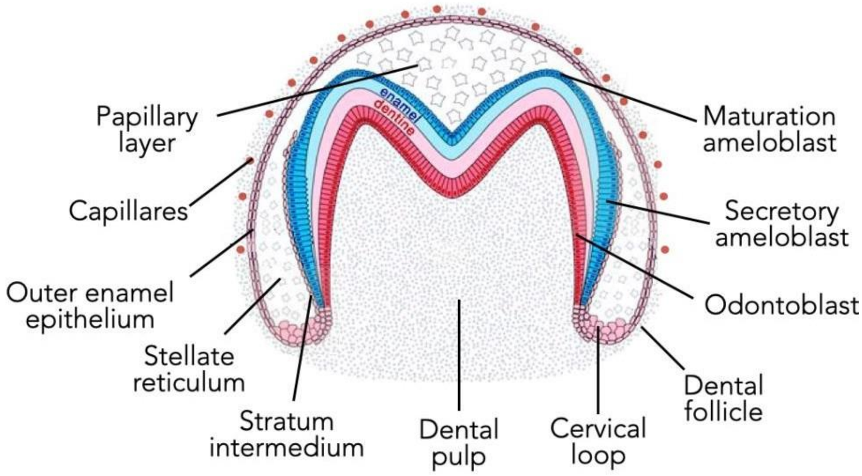

Figure 2- Representation of the final bell stage with the different structures and layers of the future tooth.

1.1.1 Amelogenesis

The amelogenesis is driven by ameloblasts, responsible for producing matrix proteins. These cells are responsible for creating and maintaining an extracellular environment favorable to mineral deposition (Lacruz et al., 2017). The enamel matrix is an ectodermal tissue, derived from the enamel organs' inner enamel epithelium, and comprised of proteins, carbohydrates, and a small portion of calcium hydroxyapatite crystals (Fehrenbach & Popowics, 2016; Lacruz et al., 2017).

Unlike other mesodermal products (dentin, cementum, and the alveolar process), enamel lacks collagen protein content (Fehrenbach & Popowics, 2016; Gil-Bona & Bidlack, 2020). Instead, ameloblasts produce non-collagenous unique proteins such as amelogenin, enamelin, ameloblastin, and tuftelin, as well as proteinases (that include matrix metalloproteinase (MMP)-20 and kallikrein-related peptidase) (Gil-Bona & Bidlack, 2020).

1.1.1.1 Proteins Involved in Amelogenesis

The organic component of the enamel matrix is fundamentally composed of proteins with carbohydrates and lipids. These protein content distinguishes this matrix from other mineral tissues and clearly expresses the enamel non-conjunctive origin (Nanci, 2018; Gil-Bona & Bidlack, 2020).

After the eruption, the enamel surface undergoes a post eruptive maturation process, where soluble components are substituted by less soluble elements. Compared to an initial composite of carbonate, water and magnesium, this structure suffers gradually changes to an amorphous tissue with lower porosity and water level, and with increased fluoride content (Abou Neel et al., 2016; Klimuszko et al., 2018). The post-eruptive characteristics are presented in the following section.

1.2. Enamel

Enamel is the hardest tissue in the human body which can withstand an assortment of aggressions (Baranova et al., 2020). This tissue is mainly composed of an inorganic content (92-96%), 4% of water and minimum content of organic components (Gomes et al., 2019; Baranova et al., 2020).

Regarding the inorganic matter, enamel is mainly composed of calcium (34-39% of its weight) and phosphorus (16-18% of its weight). Other minerals such as sodium, magnesium, potassium and zinc are also present in residual proportions. The mineral phase of enamel is in the form of hydroxyapatite crystals, $CA_4(PO_4)_6(OH)_2$, that compose approximately 80-90% of its volume (Lamont et al., 2018; Gomes et al., 2019). The hydroxyapatite crystals are characterized by an arrangement of ions around the central hydroxyl column. In the layout diagram, the hydroxyl ion is surrounded by a triangle of calcium II ions and a triangle of phosphate ions, surrounded by an hexagon of calcium I ions (Robinson et al., 2000).

The density of hydroxyapatite (in other words, the mineral content) is not homogenous, because it decreases from surface to the dentin and increases its porosity, fluid and organic content (Gomes et al., 2019). Also, enamel crystals are prone to ion substitutions that affect the behavior of apatite, namely when it comes to the level of solubility at low pH (Robinson et al., 2000). The integrity of enamel is secured by saliva and its constituents (calcium and phosphate ions) as its contact with the enamel surface permits the renovation of crystals, increasing its hardness and resistance (Farooq & Bugshan, 2021).

1.3. Dental caries

Dental caries is one of the two most prevalent conditions worldwide, estimated to affect 2.3 billion people and the primary dentition of more than 530 million children (Health Metrics and Evaluation, 2017). If caries lesions remain untreated and the risk factors unchanged, the patient's quality of life will be deteriorated (Nóbrega et al., 2019). In detail, pain and discomfort, severe infections associated with ulceration, fistula, abscess, oral mucosal conditions and disruption of the daily routine are likely to occur and to be associated with this worse perceived quality of life (Nóbrega et al., 2019).

The pathophysiology of dental caries is a well understood process and may be set out in two perspectives: 1) the hard tissue-related aspects, and 2) the microbiology content (Conrads & About, 2018). Fundamentally, a caries lesion represents the disruption of a dental hard tissue. This disruption is characterized by a demineralization process caused by acid release, a result of bacterial fermentation of dietary carbohydrates (Lamont et al., 2018). Often, caries lesions are identified in pits, grooves or occlusal surfaces, sites with higher accumulation of plaque (Paiva et al., 2017), yet the multifactorial profile of the patient will be decisive on the onset and progression of the lesions.

A diversity of factors can increase the risk towards caries, such as the cariogenic profile of bacteria present in plaque, low fluoride exposure, immunological components, socioeconomic status, inadequate oral health care and genetic factors (Pitts et al., 2017; Horst et al., 2018). Is the balance between the risk factors and protective ones that conditionate the appearance of the caries lesions, as shown in figure 3.

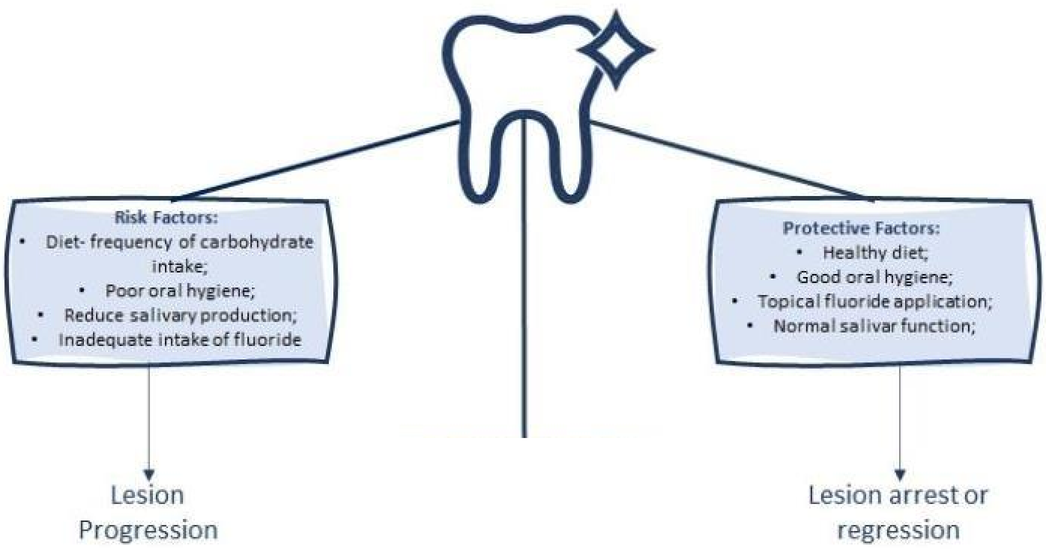

Figure 3. Representation of risk and protective factors associated with the development of caries. Adapted by the author from the article *Dental Caries by Nigel B. Pitts, 2017*.

1.3.1. Pathophysiology

Dental caries result from the action of bacterial-secreted acids in the enamel surface (Fejerskov, 2004; Nyvad & Takahashi, 2020). The disruption of the intra-oral balance is associated with an ecologic shift of dental biofilm environment (Nyvad & Takahashi, 2020). As abovementioned, this disease is multifactorial, yet the three main factors can be highlighted: 1) oral bacterium; 2) diet rich in carbohydrate intake; and, 3) teeth surface (Conrads & About, 2018).

The bacterial acid products', namely lactic acid, acetic acid, propionic and formic acid, are the result of the dietary fermentable carbohydrates' metabolism. The interaction between acid products with enamel is responsible for the enamel demineralization (Pitts et al., 2017). Furthermore, the pathophysiology of dental caries is a continuous process with different stages. Firstly, subclinical changes at a molecular level occur, and if the imbalance process remains, it leads to the destruction of the teeth (Cuenca & Pilar, 2013).

The bacterial activity can be divided into three stages: 1) dynamic stability; 2) acidogenic and; 3) aciduric phases. In the dynamic stability phase, there are a predominance of *Streptococcus no mutants* and *Actinomyces.* Also, the acidification periods are infrequent and saliva effectively restores its mineral content, favoring the remineralization process (Schwendicke et al., 2016). Then, the acidogenic phase occurs with the presence of a high content of sugar with a decreasing of the pH. This acidogenic environment will modify the phenotypic expression of *Streptococcus no mutants* and *actinomyces*, increasing the acid production. Consequently, more acidic conditions will cause an increase of more acidogenic and aciduric bacteria's (Schwendicke et al., 2016). The aciduric phase is marked by a continuous production of acid, and therefore allows the development of *Streptococcus mutans* and *Lactobacillus*. Underlying these conditions, the shift of bacterial content is extreme. N*on-mutans Streptococci* and *Actinomyces* are eliminated and replaced by acidic bacteria that will pronounce a fast net mineral loss (Cuenca & Pilar, 2013; Schwendicke et al., 2016). The interaction between the three stages and the mineral changes is represent in the figure 4.

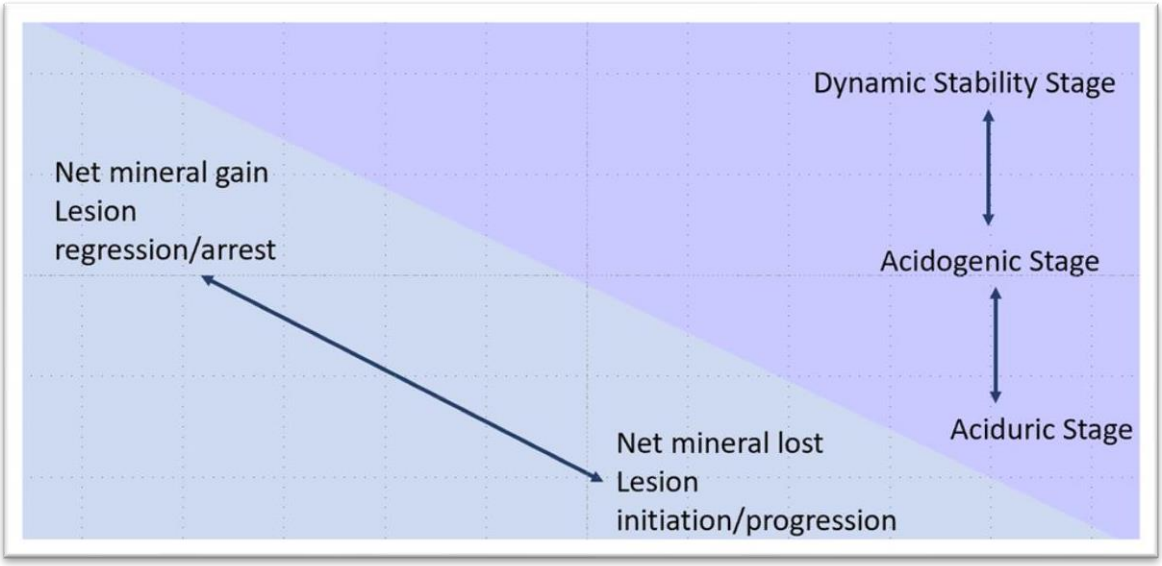

Figure 4. Representation of the dynamic stage of the caries lesion formation and arresting. Adapted by the author from *The Role of Bacteria in the Caries Process: Ecological Perspectives, Takahashi & Nyvad, 2011.*

Conversely, dental biofilm is a complex and highly organized structure of microorganisms and related subproducts, that are embedded inside the intercellular matrix (Bowen et al., 2018). In turn, a symbiotic relationship is established between microorganisms and the host. In other words, microorganisms benefit from nutrients provided by the host and, in return, prevents the dysbiosis of this complex community (Pitts et al., 2017; Lamont et al., 2018;).

The oral microbiota adhere to dental surfaces as organized and functional communities (Lamont et al., 2018). First, there is the formation of the acquired pellicle that provides a bonding site for the co-adhesion of secondary bacteria causing an increase of its complexity that will motivate the demineralization process (Pitts et al., 2017; Lamont et al., 2018; Schulz et al., 2020; Chawhuaveang et al., 2021).

As above mentioned, three main factors are associated with the formation of carious lesions such as: 1) diet (related to the carbohydrates frequency and intake pattern) (Setiawan et al., 2021); 2) tooth composition, structure, maturation and location (Lacruz et al., 2017) and 3) the host saliva composition and rate, a protector element (Zabokova, 2021).

Briefly, in physiologic conditions, the pH of the saliva is comprehended between 6.75-7.25. In about 3 to 5 minutes after eating carbohydrates, the pH drop and reach values below the critical one (pH 5.5), and become unsaturated. Therefore, the hydroxyapatite dissolves its minerals. Three biological mechanism are related with the overcome of the demineralization process: 1) the saliva pH increases; 2) the substrates are depleted; or 3) the saliva is supersaturated in minerals, and these minerals allow the deposition of the crystals in the tooth surface (Fejerskov, 2004; Cuenca & Pilar, 2013; Pachori et al., 2018).

1.3.2. Chemical Changes in the Cariogenic Process

Crystals in the tooth surface go through natural periods of mineral loss (demineralization) and mineral gain (remineralization) with ionic and molecular fluxes and pH variations (Farooq & Bugshan, 2021). Thus, the loss of mineral content from teeth cannot be seen as entirely pathologic.

After a food intake, the acid produced by the bacteria will diffuse into the tooth, causing a pH dropping and forming an undersaturated environment leading to a demineralization process (Pitts et al., 2017; Al-Obaidi et al., 2018). The increase of carbonate and magnesium and the decrease of fluoride causes an increasing of the enamel's porosity, which widen the spaces between the crystals, as the ions dissolve from the lesion body and distribute themselves through pores. Part of these minerals reprecipitate at the surface layer that surrounds the demineralize lesion. If the acid attack proceeds, it will result in a continuous loss of minerals, mainly phosphate and calcium and can lead to an irreversible cavity formation (Robinson et al., 2000; Abou Neel et al., 2016; Lacruz et al., 2017; Pitts et al., 2017; Du et al., 2020).

The calcium and the phosphate lost from the dissolution of the surface and subsurface can raise the degree of saturation and partially protect the surface layer. If the rate of remineralization, supported by the clearance of sugars, mouth swallowing, and saliva, exceeds the rate of transport of ions out of the tooth surface, the remineralization process starts. In that case, the biofilm goes back towards neutrality and becomes sufficiently saturated with calcium, phosphate and fluoride ions, so that a redeposition of minerals can occur (Changyu et al., 2019; Philip, 2019).

When saturated in the oral environment, the calcium and phosphate ions are deposited into the crystals and avoid the demineralization of the tooth and these ionic changes result in an enamel significantly more resistant to a subsequent acid challenge (Changyu et al., 2019; Philip, 2019).

It's fundamental to have a proper diagnostic and classification so that the demineralization process can be stopped as early as possible.

1.3.3. Caries diagnosis and classification

Several clinical manifestations of the caries disease were described in the literature, and over the past years the case definition has been improved. Nevertheless, regardless of diagnostic criteria, the tooth surface must be clean and dry, and the intra-oral examination must do with proper light and a community exploratory probe (Srilatha et al., 2019).

The caries lesion can be detect using the tactile, visual, and radiographic examination. There are other methods available, such as optical fiber transillumination (FOTI), the method electrical conductivity (ECM) or fluorescence, DIAGNOdent (Hogan et al., 2019; Macey et al., 2021). Furthermore, the caries lesion can be classified according to localization, depth, activity and, type of tissue affected (Cuenca & Pilar, 2013; Machiulskiene et al., 2020). In table 1, a summary is presented, that shows the different classifications of the carious lesions.

Table 1- Different classifications of the carious lesions is present (Cuenca & Pilar, 2013; Young et al., 2015; Machiulskiene et al., 2020).

<table>
<tr><th colspan="4">Location</th></tr>
<tr><td>Pits and fissures</td><td>Interproximal surfaces</td><td>Gingival margin</td><td>Smooth surfaces</td></tr>
<tr><td colspan="4">Place of origin</td></tr>
<tr><td>Enamel</td><td colspan="2">Dentin</td><td>Cement</td></tr>
<tr><td colspan="4">Activity</td></tr>
<tr><td colspan="2">Active-reflects the loss of minerals during exploration and this lesion progresses if no measures are applied</td><td colspan="2">Inactive-unable to progress due to reduced local bacterial metabolic activity</td></tr>
<tr><td colspan="4">Free surface</td></tr>
<tr><td>White spots/active caries- rough, whitish, opaque and dull</td><td>Inactive enamel caries- opaque, whitish with a hard, smooth and shiny surface</td><td>Active cavitated dentin lesion - light brown color with a soft consistency</td><td>Inactive dentin lesion - dark brown color with a hard touch</td></tr>
<tr><td colspan="4">Occlusal surface</td></tr>
<tr><td>Active non cavitated lesion- opaque and rough whitish appearance</td><td>Inactive non cavitated lesion - dark coloration of the fissure system, having a hard consistency and being more resistant</td><td>Active cavitated lesion - brown/yellow color with a soft consistency</td><td>Active cavitated lesion - dark brown color with hard consistency</td></tr>
<tr><td colspan="4">Appearance Timing</td></tr>
<tr><td>Primary lesion that develops on a surface without any restoration</td><td colspan="2">Secondary or recurrent - lesion located next to a restoration</td><td>Residual - injury caused by the presence of demineralized tissue left during restoration</td></tr>
</table>

.

Multiple's classifications were emerging with different criteria. In the Caries Classification System for Clinical Practice (ACA CCS) of the American Dental Association (ADA), caries lesions are characterize by its clinical evaluation without reference to a particular treatment protocol (Young et al., 2015; Macri & Chitlall, 2017). Furthermore, the World Health Organization (WHO) adopts the "iceberg of dental caries" model for conceptualizing dental caries with the type of therapy that offer the best option for the patient (Pitts, 2004; Cuenca & Pilar, 2013). Recently, the International Caries Detection, and Assessment System (ICDAS) protocol was developed (Pitts & Ekstrand, 2013; Akarsu et al., 2019).

The ICDAS is a two-step decision process. In the first step, the tooth's condition must be considered, namely if it is entirely healthy or has already undergone to any treatment. In the second step, the presence of caries, if there are any, is analyzed according to its degree of development (ex: 1: First visual change in enamel; 3: Localized enamel breakdown [without clinical visual signs of dentinal involvement] 4: Underlying dark shadow from dentin) (Ismail et al., 2015; Bhoopathi et al., 2017; Ekstrand et al., 2018; Adiningrat et al., 2020;). Using these methods, the dentist must be able to identify the first enamel alterations due to the demineralization process, so called white spot lesion (WSL), and start the respective treatments to stop and reverse the demineralization progress.

1.4 WSLs

WSLs are the first visible sign of a carious lesion and the prevalence of WSLs range between 25 to 98%, depending on the diagnostic criteria (Deveci et al., 2018a). WSLs represents the first sign of enamel structure disintegration and enlargement of the intercrystalline spaces (Khoroushi & Kachuie, 2017; Sadyrin et al., 2020). Then, the deposition of fluor on the enamel surface causes a low acid solution of the superficial tissues (hypermineralized surface). However, at the same time, the acid penetrates into the deeper layers of the enamel and leads to increased porosity in the sub-surface enamel area (Lacruz et al., 2017; Deveci et al., 2018a). Consequently, the refractive index of the demineralized zone decreases due to the increased presence of air and water (Deveci et al., 2018a), going from 1.63 in a healthy enamel to 1.33 and 1.00 for wet and dry WSLs, respectively (Sampson & Sampson, 2020).

On the other hand, the increase enamel porosity also causes change in the enamel texture, surface microhardness, and shear strength (Deveci et al., 2018a). Therefore, after the early detection of the WSL, it is essential to apply a treatment protocol in order to avoid a new demineralization and collapse of the enamel surface layer.

1.4.1 Management of WSLs

The first step in managing WSLs is not the conventional treatment for caries lesions (Araujo et al., 2020). Instead, risk factors and adequacy of preventive measures with educational and plaque control protocols should be assessed (Cuenca & Pilar, 2013; Colorado et al., 2020).

After a correct diagnosis, non-cavitated caries lesion may eligible for non-invasive procedures, and remineralization techniques have been proposed to this end. We have several materials for remineralization, such as topical fluoride and casein phosphopeptides-amorphous calcium phosphate. However, a new material, infiltrative resins, with the purpose of occluding the remain porous and enhancing the aesthetic properties has been developed. This thesis solely focused on infiltrative resins, reason why the remaining materials are not addressed.

1.4.1.1 Infiltrative Resins

Minimally invasive therapies for the management of smooth surface and proximal non-cavitated caries lesions have been emerged to treat early signs of non-cavitated carious lesions (Araujo et al., 2020). In the beginning of the 21st century, resin infiltration technique, using a light-curing infiltrating resin, emerged to creates a diffusion barrier inside the enamel lesion (Borges et al., 2017; Anand et al., 2019). Therefore, after resin infiltration and light curing, the occlusion of the enamel porosity occur and, consequently, blocks the acid diffusion process and protects the remnant enamel (Kielbassa et al., 2017; Zakizade et al., 2020).

The resin infiltration technique is indicated to lesions up to the first third of the dentin (D1), as show in figure 5. The main aim is to stop the progression of the incipient caries lesion and to mask the WSLs, improving the patient's dental aesthetics (Askar et al., 2018; Conh & Chaet, 2020).

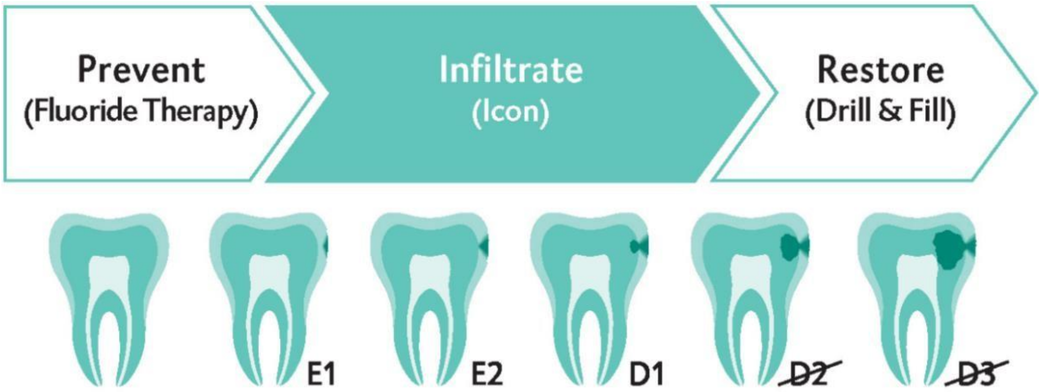

Figure 5. Representation of lesion that can be infiltrated with Icon. Image retrieved from DMG site. Authorization in the appendix 5.

Nowadays, ICON® has been continuous used in dental practice as an infiltrative resin kit to treat proximal and smooth surface caries lesions (*Icon Instructions for Use*, 2020). The ICON® is composed of three different components: 1) ICON-Etch, (hydrochloric acid, pyrogenic silicic acid, surface-active substances); 2) ICON-Dry, (99% ethanol); and 3) ICON-Infiltrant (Methacrylate-based resin matrix, initiators, additives) (*Icon Instructions for Use*, 2020).

The application of ICON-Etch removes the superficial pseudo-layer of enamel and increases the penetration capability to facilitate the infiltrant access to the body lesion (Lausch et al., 2015; Abbas et al., 2018). With an application of 15% hydrochloric acid for 2 minutes, it is possible to eliminate between 30-40µm of the superficial enamel pseudo-layer that covers the body of the lesion (Abbas et al., 2018; Attia, 2018; Andrade et al., 2019).

In the next step, the application of ICON-Dry decreases the contact angle, improves the penetration and eliminate all impurities present on the enamel surface. The ethanol confirms if the surface layer was removed correctly (Furuse et al., 2020). If the liquid is absorbed in a 3-5 seconds period and the lesion appears whitish, then the surface is ready to be infiltrate (Furuse et al., 2020).

After that, the infiltrated resin is applied for three minutes to creates a diffusion barrier inside the lesion that fills the remaining pores and replaces the lost ones with a methacrylate-based resin matrix containing bisphenol A-glycidil methacrylate (BISGMA) and triethylene glycol dimethacrylate (TEGDMA) (Enan et al., 2018). This matrix stabilizes the porous lesion body, seals the micro porosities, and blocks the access of acids to any remaining pores (Montasser et al., 2015; Behrouzi et al., 2020; Zakizade et al., 2020).

This resin infiltration technique also helps in aesthetic dental problems related to WSLs (Kim et al., 2011; Lawson, 2020), because enamel recovers the refractive index, and, therefore, reduce the light scattering and decrease the visual color differences (Paris et al., 2013). Nevertheless, the major limitation of the ICON® technique is its counter indication to treat initial enamel lesions in the pits and fissures of the occlusal surfaces. The main reason of this counter indication is the inadequate mechanical properties of ICON® to be applied on surfaces occlusal (Lausch et al., 2015; Anand et al., 2019).

Clinical evidence has shown that infiltrative resins can effectively mask the appearance of white enamel discoloration and has garnered increased attention due to its various advantages (Urquhart et al., 2019). Although it has been shown to be advantageous its effects on other characteristics, such as surface roughness, shear bond strength, and penetration depth are still unknown.

A systematic review estimated that microhardness can affect the properties of sound and WSLs (Zakizade et al., 2020). Notwithstanding our study revealed the effects of time and pH of the demineralized agent used, etching time, and tooth origin through meta-regression sensitivity analysis on this enamel characteristic. We also included we included 10 and 16 new studies on sound enamel and WSL, respectively (350% and 229% of the total number of included studies and more than 800 specimens (170% of the total number of specimens) comparing to previous systematic review.

With the recent increased of studies in this subject we present a systematic review assessing the effect of infiltrative resin on surface roughness, microhardness, shear bond strength and penetration depth in permanent teeth with and without enamel lesions.

1.5. Aims

This thesis aimed to analyze if there is an improvement of the surface properties, such as surface roughness, penetration depth, shear bond strength, and microhardness, after the application of an infiltrative resin in WSLs.

To address this objective, we defined the following research questions: ‘Do infiltrative resin in sound enamel and WSLs improve the surface roughness, microhardness and shear bond strength?” and “What is the penetration depth capacity of the infiltrative resin in WSLs?”. The PICO elements were:

- P (Population)- Teeth with white spot lesions or enamel demineralization or healthy teeth submitted to a demineralization procedure;
- I (Intervention)- Application of an infiltrative resin;
- C (Comparation)- Demineralized teeth or interested teeth;
- O (Outcome)- Disappearance or improvement of the intern and extern characteristics of the WSLs or enamel demineralization.

2. Article- EFFECT OF RESIN INFILTRATION ON ENAMEL: A SYSTEMATIC REVIEW AND META-ANALYSIS

Soveral, M., Machado, V., Botelho, J., Mendes, J. J., & Manso, C. (2021). Effect of Resin Infiltration on Enamel: A Systematic Review and Meta-Analysis. *Journal of Functional Biomaterials, 12(3)*, 48. https://doi.org/10.3390/jfb12030048

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Review

Effect of Resin Infiltration on Enamel: A Systematic Review and Meta-Analysis

Madalena Soveral [1], Vanessa Machado [1,2,*], João Botelho [1,2], José João Mendes [1] and Cristina Manso [1]

[1] Clinical Research Unit (CRU), Centro de Investigação Interdisciplinar Egas Moniz (CiiEM), Egas Moniz—Cooperativa de Ensino Superior, CRL, 2829-511 Almada, Portugal; madalenasvsoveral@gmail.com (M.S.); jbotelho@egasmoniz.edu.pt (J.B.); jmendes@egasmoniz.edu.pt (J.J.M.); mansocristina@gmail.com (C.M.)

[2] Evidence-Based Hub, Clinical Research Unit, Centro de Investigação Interdisciplinar Egas Moniz (CiiEM), Egas Moniz Cooperativa de Ensino Superior, CRL, 2829-511 Almada, Portugal

* Correspondence: vmachado@egasmoniz.edu.pt

Abstract: Subsurface enamel demineralization beneath an intact surface layer or white spots lesions (WSL) can and should be treated with non-invasive procedures to impede the development of a cavitated lesion. We aim to analyze if infiltrative resin improves enamel roughness, microhardness, shear bond strength, and penetration depth. MEDLINE [via Pubmed], Cochrane Central Register of Controlled Trials, Embase, Web of Science, Scholar, and LILACS were searched until May 2021. Methodological quality was assessed using the Joanna Briggs Institute Clinical Appraisal Checklist for Experimental Studies. Pairwise ratio of means (ROM) meta-analyses were carried out to compare the enamel properties after treatment with infiltrative resin on sound enamel and WSLs. From a total of 1604 articles, 48 studies were included. Enamel surface roughness decreased 35% in sound enamel (95%CI: 0.49–0.85, $I^2 = 98.2\%$) and 54% in WSLs (95%CI: 0.29–0.74, $I^2 = 98.5\%$). Microhardness reduced 24% in sound enamel (95%CI: 0.73–0.80, $I^2 = 99.1\%$) and increased by 68% in WSLs (95%CI: 1.51; 1.86, $I^2 = 99.8\%$). Shear bond strength reduced of 25% in sound enamel (95%CI: 0.60; 0.95, $I^2 = 96.9\%$) and increased by 89% in WSLs (95%CI: 1.28–2.79, $I^2 = 99.8\%$). Penetration depth was 65.39% of the WSLs (95%CI: 56.11–74.66, $I^2 = 100\%$). Infiltrative resins effectively promote evident changes in enamel properties in sound and WSLs. Future studies with long-term follow-ups are necessary to corroborate these results from experimental studies.

Keywords: resin infiltration; demineralization; white spot lesions; surface roughness; microhardness; shear bond strength; penetration depth

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1. Introduction

Dental caries is an oral condition estimated to affect 2.4 billion people worldwide in 2010 [1,2], while the frequency of white spot lesions (WSLs) varies between 2% and 97% [3–6]. WSLs were firstly described in 1908 by Black [7]. In the last decades, the prevalence of WSLs has increased as a side effect to fixed orthodontic appliances [8–11]. Consequently, multiple approaches have been proposed to prevent, manage and treat dental caries [12–14], while non-invasive therapies have emerged to treat early signs of WSLs [15–17].

Caries infiltration is a minimally invasive technique for the management of smooth surface and proximal non-cavitated caries lesions. Several remineralization products have been presented to this end, such as fluoride, casein phosphopeptide, amorphous calcium phosphate, and microabrasion [7,8]. Low-viscosity light-cured resins are another popular approach [9]. The infiltration of resins creates a diffusion barrier inside the enamel lesion body [18], retarding enamel dissolution [10,11], and the retention loss is unlikely to occur [19].

Clinical evidence points to the partial or total ability of infiltrative resins to mask enamel whitish discoloration [12], despite its clinical efficacy still warrants long-term confirmation [7,13–17]. A previous systematic review of in vitro studies has shown an increase of surface microhardness of WSLs after resin infiltration, and an opposite result in sound enamel [20]. Notwithstanding, there is still uncertainty regarding its efficacy on other characteristics (namely, surface roughness, shear bond strength, and penetration depth). Hence, appraising the available evidence on these characteristics in a systematic manner becomes clinically relevant to understand the potential of this minimally invasive procedure.

Considering the recent increased number of studies, here we present a systematic review assessing the effect of infiltrative resins on surface roughness, microhardness, shear bond strength and penetration depth in permanent teeth with and without enamel lesions.

2. Materials and Methods

2.1. Protocol and Registration

We registered and approved this systematic review protocol a priori at the National Institute for Health Research PROSPERO database, International Prospective Register of Systematic Review (Available online: www.crd.york.ac.uk, ID number: CRD42019140860) and we reported the review information according to the PRISMA guidelines [18] (Table S1).

2.2. Focused Question and Eligibility Criteria

To answer our main question, we developed a protocol with two PICO questions:

1. "Do infiltrative resin in sound enamel and WSLs improve the surface roughness, microhardness and shear bond strength?" and
2. "What is the penetration depth capacity of the infiltrative resin in WSLs?"

Each question had the following statements:

1. Teeth with sound enamel, and teeth with WSLs or teeth classified with ICDAS 1 or 2 (Population, P); Resin infiltration (Intervention, I); Initial condition or no treatment (Comparison, C); Disappearance or improvement of the surface roughness, microhardness, and shear bond strength (Outcome, O).
2. Teeth with WSLs or teeth classified with ICDAS 1 or 2 (Population, P); Resin infiltration (Intervention, I); Not applicable (Comparison, C); Penetration depth (Outcome, O).

In vitro studies that assess the enamel surface roughness, microhardness, shear bond strength and penetration depth before and after resin infiltration were eligible. In vivo studies were excluded because the methods used for clinical evaluation of those four characteristics mentioned in patients were substantially different from those used on in vitro studies, and there were innumerable variables that we are unable to control, such as the quality of patients' saliva, their cooperation, and the variation of the techniques and analyses performed. Although the teeth are considered healthy, we assume that they have changed their crystalline structure once they have been subjected to home care products, such as fluoridated toothpaste and oral rinsing solutions or mouthwash being subjected to remineralization with the incorporation of fluoride ions.

Regarding color, no assessment was made because Borges et al. in 2017 [21] systematically evaluated this characteristic in patients. Furthermore, editorial, letters, reviews, thesis, case reports, and case series were excluded. Most studies used profilometers (in Ra) to quantify the surface roughness, and therefore studies that quantified enamel surface roughness using other appliances were not included because it does not allow comparison.

2.3. Search Strategy

Seven electronic databases (MEDLINE [via Pubmed], Cochrane Central Register of Controlled Trials, Embase, Web of Science, Scholar, and LILACS) were searched systematically until May 2021. The following search strategies were adjusted to each database: ("infiltrative resin" OR "resin infiltration") AND ("white spot lesions" OR "white spots" OR "WSL" OR "Enamel demineralization"). In addition, we search manually in Journal of Dentistry, The Journal of Prosthetic Dentistry, Clinical Implant Dentistry and Related Research, Operative Dentistry, Community Dentistry, and Oral Epidemiology, Journal of Conservative Dentistry, and International Journal of Dentistry. The Grey literature was searched using the latter strategy in OpenGray. Any limitation of the publication period and language was applied. Authors were contacted, when necessary, for additional data clarification.

2.4. *Study Process*

Two independent researchers (M.S. and V.M.) screened the title and/or abstract of retrieved studies. Any disagreements were resolved by discussion with a third author (C.M.). The final selection of studies was independently performed by two authors (M.S. and V.M.) who reviewed the selected papers' full text based on the inclusion criteria mentioned above. For measurement reproducibility purposes, inter-examiner reliability following full-text assessment was calculated via kappa statistics.

A predefined table was used to extract necessary data from each eligible study, including the citation, publication status and year of publication, study design, inclusion/exclusion criteria, number of specimens per group, demineralization process, resin infiltration protocol, surface roughness, microhardness, shear bond strength and penetration depth measurement method. Concerning additional data clarifications, we attempted to contact the corresponding authors twice, with an interval time of 1 week.

2.5. *Methodological Quality Assessment*

Two researchers (M.S. and V.M.) independently assessed the methodological quality of the included studies, following the Joanna Briggs Institute Clinical Appraisal Checklist for Experimental Studies. This assessment tool was adapted from previously published systematic reviews [22–24]. The items on the checklist were as follows: (1) clearly mention aim, justification of sample size; (2) sample randomization; (3) blind treatment allocation; (4) possibility of comparison between control and treatment groups; (5) baseline equivalence of control and treatment groups; (6) clearly describe the preparation protocol; (7) clearly report the experimental protocol; (8) measurement method, and adequate statistical analysis. Each item was scored using a 2-point scale: 0—not reported or reported inadequately; and 1—reported and adequate. Any disagreements between the examiners were resolved through discussion with a third author (C.M.).

2.6. *Statistical Analysis*

For continuous data, mean values and standard deviations (SD) were collected to predefined tables prepared to determine the quantity of data. If median and interquartile range were reported in the selected studies, mean and SD were calculated following Hozo's formula [25]. The random-effect meta-analysis and forest plots were calculated in R version 3.4.1 (R Studio Team 2018) using 'meta' package [26], through DerSimonian-Laird random-effects meta-analysis. Firstly, we started by conducting an a priori sensitivity analysis comparing Standardized Mean Difference (SMD) versus Ratio of Means (RoM) meta-analyses. If there are similar results in terms of heterogeneity and significance, RoM was applied as it would allow easier and direct interpretation of the results (reported as percentage) [26]. To investigate sources of heterogeneity, meta-regression analysis was conducted for method, pH, and demineralization time. I^2 index and Cochrane's Q statistic were used to assess statistical heterogeneity ($p < 0.1$) and $\chi 2$ test calculated overall homogeneity [26]. Substantial heterogeneity was considered when I^2 statistics exceeded 50% [27]. All tests were two-tailed with alpha set at 0.05 except for the homogeneity test whose significance level cutoff was 0.10 due to the low power of the $\chi 2$ test with a limited amount of studies. Overall estimates were reported with 95% confidence interval (CI). For meta-analysis including 10 or more studies, we analyzed publication bias [28].

3. Results

3.1. Study Selection

The initial database search strategy retrieved 1604 possibly relevant articles. After exclusion of all duplicates, 175 articles were assessed for full paper review eligibility. Among these, 127 articles were excluded with the respective reasons for exclusion detailed in Table S2. A total of 48 articles fulfilled the inclusion criteria and were selected for further quantitative and qualitative analyses (Figure 1). Good inter-examiner agreement was obtained during full-text screening and article final selection (Cohen's Kappa: 0.92; 95% CI: 0.89; 0.94).

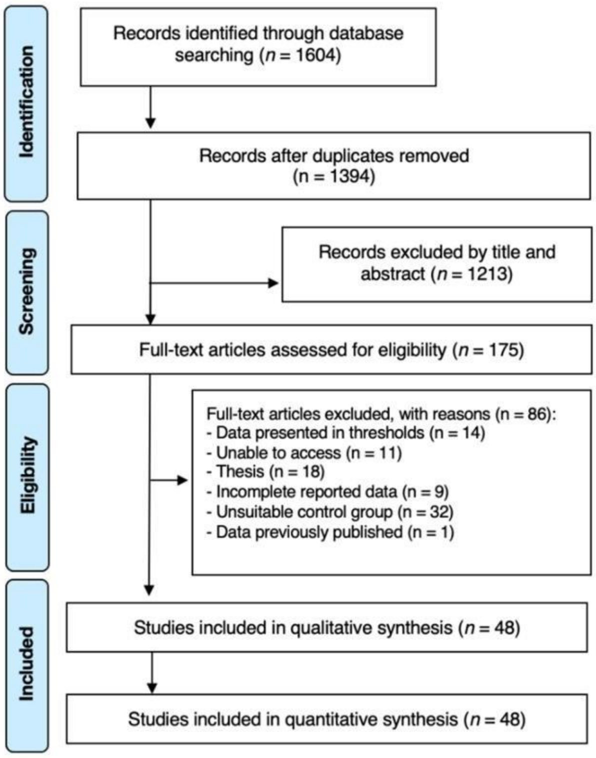

Figure 1. PRISMA flow-chart representing the results of the workflow to identify eligible studies.

3.2. Characteristics of the Studies

In this systematic review, twenty-three articles reported information about microhardness [27–49], ten evaluated surface roughness, [27,31,37,47,49–54], sixteen assessed the penetration depth [40,46,50,55–67] and eight explored shear bond strength after resin infiltration [32,52,68–73].

Overall, twelve studies included bovine teeth (*n* per group = 803) while twenty-five studies included human teeth (*n* per group = 865). Nine studies reported data without specimen demineralization previously to resin infiltration [47,54,55,57,59,61–64,74] and thirty-nine articles included the demineralization process before the infiltrative resin [21,27–44,48–53,56,58,60,65–67,69–73]. The demineralization process consists of emerging the teeth in a demineralization solution, with pH between 4 and 5 for a period of time that ranges from 1 min to 1200 h, to simulate the formation of WSLs (Table 1).

Nowadays there is only one commercial kit available, ICON® (DMG, Hamburg, Germany), that aims to infiltrate proximal and vestibular lesions [75]. Taking this into account, all studies used the ICON® protocol to do the infiltration of resin.

Table 1. Overview of the Included Studies.

Study	Funding	n	Specimen Origin	Exclusion CRITERIA	WSLs Preparation (pH for hours)	Outcome Reported
Pancu et al. 2011 (Romania) [42]	NR	10	Human (bicusps or molars)	NR	pH: 4.4 for 120 h	Microhardness (Vicker hardness- special device for microhardness testing with a squared diamond head)
Meyer-Lueckel et al. 2011 (Germany) [59]	DFG: PA 1508/1-1. HML and SP and royalties from DMG, Hamburg	20	Human (molars and premolars)	Active non-cavitated proximal WSL (ICDAS code 2)	Without demineralization	Penetration Depth (Confocal laser scanning microscopy (CLSM))
Paris et al. 2011 B (Germany) [62]	Institute for Immunology, UK-SH, Christian-Albrechts Universitat zu Kiel for providing the CLSM. The Charité—Universitatmedizin Berlin holds US and European patents	19	Human (molars and premolars)	Active non-cavitated proximal lesions scored as ICDAS 2	Without demineralization	Penetration Depth (confocal laser scanning microscope)
Paris et al. 2011 A (Germeny) [64]	DFG: PA 1508/1-2, as part partially by DMG.	16	Human (molars)	Cavitated lesions	Without demineralization	Penetration Depth (Confocal laser scanning microscopy CLSM)
Taher et al. 2012 (Saudi Arabia) [47]	No	10	Human (premolars)	Cracks, restorations, or developmental lesions	Without demineralization	Roughness; Microhardness (microscope with 200 magnification and application of applying a load of 300 g; profilometer)
Torres et al. 2012 (Brazil) [48]	NR	15	Bovine (incisors)	Damaged or not intact enamel	pH: 5 for 16 h	Microhardness (microhardness tester fitted with a 50-g load)
Attin et al. 2012 (Switzerland) [32]	Dentaurum, 3M ESPE, and DMG	12	Bovine (incisors)	NR	pH: NR for 504 h	Shear Bond Strength (universal testing machine)
Veli et al. 2014 (Turkey) [72]	No	20	Human (premolars)	Caries, hypoplastic areas, restorations, and surface abnormalities	pH: 4.8 for 504 h	Shear Bond Strength (universal testing machine)
Ekizer et al. 2012 (Turkey) [70]	No	20	Human (premolars)	Hypoplastic spots, cracks, or gross irregularities	pH: 4.3 for 6 h	Shear Bond Strength (universal testing machine)
Paris et al. 2013 (Germany)[43]	DFG: PA1508/1-2. HML and SP and royalties from DMG, Hamburg.	12	Bovine (incisors)	NR	pH: 4.95 for 1200 h	Microhardness (Vickers hardness with a force (F) of 0.981 N for 10 s)
Paris et al. 2013 (Germany)[61]	DFG: PA 1508/1-1	15	Human (molars and premolars)	Cavitated caries	Without demineralization	Penetration Depth (confocal laser scanning)
Mohammed et al. 2014 (Iraq) [76]	NR	56	Human (premolars)	NR	pH: 4.5 for 120 h	Roughness (profilometer)
Paris et al. 2014 (Germany) [63]	DFG: PA 1508/1-3	9	Human (molars and premolars)	ICDAS codes 0, 1, 2	Without demineralization	Penetration Depth (dual fluorescence confocal microscopy)
Lausch et al. 2014 (Germany) [57]	The Charité Universitätsmedizin Berlin and DMG	17	Human (molars and premolars)	Without active or cavitated WSL	Without demineralization	Penetration Depth (confocal laser scanning)
Gelani et al. 2014 (USA) [56]	No	42	Bovine (incisors)	WSP, cracks, or any other defect	pH:5 for 24 h	Penetration Depth (Confocal Laser Scanning Microscopy and Transverse Microradiography)
Dilber et al. 2014 (Turkey) [69]	NR	15	Human (mandibular lateral teeth)	Hypoplastic areas, cracks, or gross irregularities in enamel	ph:4.3 for 6 h	Shear Bond Strength (Universal testing machine)
Montasser et al. 2015 (Egypt) [41]	No	10	Human (NR)	NR	pH: 4.4 for 504 h	Microhardness (Vickers diamond indenter load of 200 g)
Arslan et al. 2015 (Turkey) [31]	NR	15	Human (central incisors)	NR	pH: 4.5 for 6 h	Roughness; Microhardness (profilometer; Vickers hardness tester with 2 N load)

Table 1. *Cont.*

Study	Funding	*n*	Specimen Origin	Exclusion CRITERIA	WSLs Preparation (pH for hours)	Outcome Reported
Min et al. 2015 (South Korea) [60]	Basic Science Research Program through the National Research Foundation of Korea (2013R1A1A2062505)	20	Bovine (permanent anterior teeth)	NR	pH:4.8 for 960 h	Penetration Depth (Optical coherence tomography Confocal laser scanning microscopy)
Vianna et al. 2015 (Brazil) [73]	No	15	Bovine (incisors)	NR	pH:5 for 56 h	Shear Bond Strength (universal testing machine)
Gurdogan et al. 2016 (Turkey) [38]	No	20	Bovine (incisors)	NR	pH: 4 for 2 h	Microhardness (Vickers Hardness tester with 100 gr force)
Abdel-Hakim et al. 2016 (Egypt) [28]	NR	6	Human (molars)	Caries, hypocalcifications, or restorations	pH: 4.4 for 480 h	Microhardness (Vickers michrohardness testing with 200 gm load)
El-zankalouny et al. 2016 (Egypt) [46]	No	7	Human (premolars)	Cracks, caries, or restorations	pH: 4.4 for 96 h	Microhardness; Penetration Depth (Vickers tester with f 50 g; stereomicroscope)
Abdellatif et al. 2016 (Egypt) [29]	NR	11	Human (anterior teeth)	NR	pH: 4.8 for 720 h	Microhardness (Vicker's microhardness test with load of 200 g)
Baka et al. 2016 (Turkey) [52]	NR	20	Human (premolars)	Hypoplastic areas, cracks, restorations, or gross irregularities	pH: 4.8 for 504 h	Roughness; Shear Bond Strengths (profilometer; a universal testing machine)
Neto et al. 2016 (Brazil) [30]	CAPES, Funcap, and CNPq (Brazilian agencies). Project PON 254/Ric	10	Human (molars)	NR	pH: 4.9 for 16 h	Microhardness (Knoop microhardness)
Horuztepe et al. 2017 (Turkey) [39]	No	45	Bovine (incisors)	Cracks or other surface defects	pH: 4.95 for 672 h	Microhardness (microindentation hardness tester with a 50-g load)
Mandava et al. 2017 (India) [40]	No	20	Human (maxillary central incisors)	Presence of cracks and defects	pH: 4.4 for 96 h	Microhardness; Penetration Depth (Vicker's microhardness tester with a 300 g load; confocal laser fluorescence microscope)
Aziznezhad et al. 2017 (Iran) [34]	Babol University grant	10	Human (premolars)	Not intact and time of extraction more than 3 months	pH: 4.5 for 6 h	Microhardness (Vickers device with 500 g load)
Prajapati et al. 2017 (India) [44]	No	10	Human (premolars)	Teeth with hypoplasia or incipient carious lesions/WSL	pH:4.4 for 504 h	Microhardness (Vickers microhardness tester with 100 g load)
Sava-Rosianu et al. 2017 (Romania) [65]	Project for young researchers—Programme II-C3-TC-2015	60	Human (premolar)	NR	NR	Penetration Depth (Confocal Laser Scanning Microscopy)
Attia et al. 2018 (Egypt) [77]	NR	20	Bovine (NR)	Cracks or defects in the surface	pH:5 for 24 h	Microhardness (micro-indentation hardness tester (with a 50-g load)
Nabil et al. 2018 (Egypt) [27]	NR	15	Human (anterior teeth)	Cracks and any developmental defects	pH: NR for 1 h	Roughness; Microhardness (profilometer; Vickers Tester with load of 200 g)
Enan et al. 2018 (Egypt) [37]	NR	10	Human (bicuspid)	Cracks and defects	pH: 4.95 for 160 h	Roughness; Microhardness (profilometer; universal testing machine)
Khalid et al. 2018 (Indonesia) [54]	University of Indonesia	10	Human (premolars)	Enamel surface that was attached orthodontic appliance; WSL, defects on the buccal side of enamel; restorations	Without demineralization	Roughness (profilometer)
Yazkan et al. 2018 (Turkey) [49]	Suleyman Demirel University Scientific Research Projects Foundation (2969-D-11)	16	Bovine (incisors)	Caries, fracture, or other defects	pH: 5 for 240 h	Roughness; Microhardness (profilometer; Vickers indenter, with load of 200 g)
Askar et al. 2018 (Germany) [55]	Deutsche Forschungsgemeinschaft (DFG; PA 1508/1-3), and DMG	15	Human (NR)	Active proximal lesions with ICDAS-2, 3 and 5	Without demineralization	Penetration Depth (confocal microscopy)
Aswani et al. 2019 (India) [51]	No	10	Human (anterior teeth)	NR	pH:4.4 for 144 h	Roughness (profilometer)
Enan et al. 2019 (Egypt) [53]	No	30	Human (premolars)	NR	pH:4.95 for 160 h	Roughness (profilometer)

Table 1. *Cont.*

Study	Funding	*n*	Specimen Origin	Exclusion CRITERIA	WSLs Preparation (pH for hours)	Outcome Reported
Arora et al. 2019 (India) [50]	No	30	Bovine (premolars)	Caries	pH: 4.5 for 96 h	Roughness; Penetration Depth (optical profilometer)
Theodory et al. 2019 (USA) [66]	Student Government for Graduate and Professional Students at the University of Iowa	15	Human (molars)	NR	pH: 4.3 for 2160 h	Penetration Depth (Confocal Laser Scanning Microscopy)
López et al. 2019 (Brazil) [59]	NR	8	Human (NR)	Cavity lesions, white stains, cracks, or structural alterations and restorations	pH: 5 for 0.5 h	Penetration Depth (Confocal Laser Scanning Microscopy)
Gulec et al. 2019 (Turkey) [71]	NR	20	Human (premolars)	Caries, attrition, fracture, restoration, congenital or surface anomalies, or surface	pH: 4.5 for 22 h	Shear Bond Strength (universal testing machine)
Borges et al. 2019 (Brazil) [68]	FAPESP(2010/16878-7, 2010/17757-9)	30	Bovine (incisors)	NR	pH:5 for 16 h	Shear Bond Strength (Scanning electron microscopy (SEM))
Ayad et al. 2020 (Egypt) [33]	NR	7	Bovine (anteriors)	NR	pH: 4.4 for 96 h	Microhardness (Vickers indenter, with a static load of 200 g)
Behrouzi P et al. 2020 (Iran) [35]	No	15	Human (maxillary central incisors)	Cracks, caries, or mineralization defects	pH: 4.5 for 96 h	Microhardness (Vickers hardness tester with 50 kg load)
El Meligy, 2020 (Saudi Arabia) [36]	No	27	Human (premolars)	ICDAS 1 and 2	pH: 4.5 for 399 h	Microhardness (transversal Vickers hardness with a force of 0.891 N)
Wang et al. 2020 (Brazil) [67]	FAPESP, 2012/13160-3, #2012/18579-2 and 2013/23310-5) CAPES—Brasil	13	Bovine (incisors)	NR	pH: 4.7 for 168 h	Penetration Depth (confocal laser scanning microscopy)

CAPES—Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; CLSM—Confocal Laser Scanning Microscope; CNPq-Conselho Nacional de Desenvolvimento Científico e Tecnológico; DFG—Deutsche Forschungsgemeinschaft; FAPESP—Fundação de Amparo à Pesquisa do Estado de São Paulo; FUNCAP—Fundação Cearense de Apoio ao Desenvolvimento Científico e Tecnológico; H—Hours; HML—Hendrik Meyer-Lueckel; ICDAS—International Caries Detection and Assessment System; NR—Not reported; WSL—white spots lesions; S.P—Sebastian Paris.

3.3. Methodological Quality of the Included Studies

Methodological appraisal of the included in-vitro studies using the Joanna Briggs Institute Clinical Appraisal Checklist for Experimental Studies tool is presented in Figure 2 and is detailed in Table S3. The assessment varied from 7 to 10 (one article with score 7, twenty-two with score 8, twenty-two with score 9 and three with score 10). All included studies showed a clear objective (n = 48, 100%) and treated the specimens from the control and experimental group using the same protocol (n = 48, 100%). Furthermore, all articles used an appropriate statistical analysis (n = 48, 100%) and presented reliable outcomes (n = 48, 100%). The majority carefully described the preparation protocol (n = 44, 91.7%), and the experimental protocol to characterize the several steps and materials applied (n = 39, 81.3%). On the opposite, most articles failed on sample size justification (n = 41, 85.4%), in the random assignment of treatment groups (n = 15, 31.3%), and only one study reported blindness regarding treatment allocation (n = 1, 2.1%).

3.4. Clinical Measures

An a priori sensitivity analysis was performed to compare whether both ROM and SMD approaches yielded results in terms of significance and heterogeneity results (Table S4). Overall, ROM and SMD meta-analyses presented similar significance and heterogeneity degrees, therefore supporting the use of a ROM meta-analytical approach (Table S4).

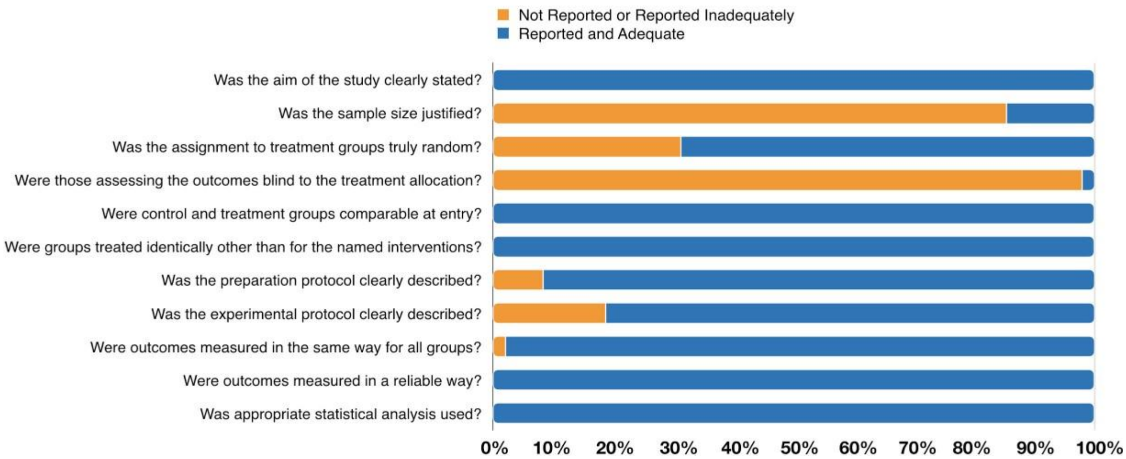

Figure 2. Assessment of the risk of bias in the included studies according to the percentage of the scores attributed to each evaluated study.

3.4.1. Enamel Surface Roughness

Surface roughness before and after resin application was analyzed in both sound enamel and in WSLs, only in human teeth samples (Tables 2 and 3). It is possible to attest that resin infiltration decreases the 35% (ROM = 0.65, 95% CI: 0.49; 0.85, $p < 0.0021$) the surface roughness in sound enamel and 54% in WSLs (ROM = 0.46, 95% CI: 0.29; 0.74, 0.0012) (Table 2, Figures S1 and S2). In both estimates' heterogeneity was considered high ($I^2 = 98.2\%$ and $I^2 = 98.5\%$, respectively) (Table 2). Furthermore, multivariate sensitivity analysis demonstrated pH and time of exposure to the demineralizing agent had an important impact on surface roughness (ROM = −1.37, 95% CI: −2.32; −0.42, $p < 0.005$; ROM = 0.01, 95% CI: 0.00; 0.01, $p < 0.001$, respectively) (Table 4).

Table 2. Sound enamel and white spot lesions according to surface roughness, enamel microhardness, bond strength and penetration depth.

Variable	*n* Studies	ROM	95% CI	*p*-Value	I^2 (%)	Egger Test
			Surface roughness			
Sound Enamel	5	0.65	0.49; 0.85	0.0021	98.2	-
WSL	8	0.46	0.29; 0.74	0.0012	98.5	-
			Enamel microhardness			
Sound Enamel	14	0.76	0.73; 0.8	<0.0001	99.1	0.8893
WSL	23	1.68	1.51;1.86	<0.0001	99.8	0.1352
			Shear Bond strength			
Sound Enamel	6	0.75	0.60; 0.95	<0.0001	96.9	-
WSL	8	1.89	1.28; 2.79	<0.0001	99.8	-
			Penetration depth			
Sound Enamel	15	65.39	56.11; 74.66	0.01	100.0	0.4712

CI—Confidence Interval; N—number; ROM—Ratio of Means; WSL—White Spot Lesions. Bold-face denotes significance.

Table 3. Sensitivity analysis of type of samples using meta-regressions.

Specimen Origin	*n*	B	95% CI	I^2 (%)	*p*-Value
		Surface Roughness of Sound Enamel			
Human	4	0.65	0.49; 0.85	98.8	-
Bovine	0	-	-	-	

Table 3. *Cont.*

Specimen Origin	*n*	B	95% CI	I^2 (%)	*p*-Value
		Surface Roughness of WSL			
Human	8	0.46	0.29; 0.74	98.5	-
Bovine	0	-	-	-	
		Enamel Microhardness of Sound Enamel			
Human	8	0.58	0.46; 0.72	99.0	0.0188
Bovine	6	0.80	0.69; 0.92	99.3	
		Enamel Microhardness of WSL			
Human	15	1.59	1.29; 1.96	99.5	0.1375
Bovine	8	1.96	1.64; 2.34	99.4	
		Shear Bond Strength of Sound Enamel			
Human	4	0.75	0.57; 0.99	97.2	0.9958
Bovine	2	0.75	0.41; 1.37	97.7	
		Shear Bond Strength of WSL			
Human	5	1.74	1.14: 2.65	98.7	0.6221
Bovine	3	2.20	0.93: 5.29	98.8	
		Penetration Depth			
Human	20	63.65	52.21; 75.09	99.3	0.5589
Bovine	6	71.22	48.57; 93.87	99.8	
ICDAS	16	62.37	46.12; 78.61	99.2	0.4500
WSLs	10	70.29	57.68;82.90	99.7	
Application of infiltrate for less than 1 min	4	49.17	33.36; 64.97	94.1	0.0270
Application of infiltrate for 3 min	18	65.36	55.77; 74.96	99.4	
Application of infiltrate for 5 min	4	81.45	63.88; 99.01	96.5	

CI—Confidence Interval; N—number; ROM—Ratio of Means; WSL—White Spot Lesions.

Table 4. Sensitivity analysis of pH and demineralization time using meta-regressions.

	Univariate			Multivariate		
Charateristics	**B**	**95% CI**	***p*-Value**	**B**	**95% CI**	***p*-Value**
		Surface roughness of WSLs				
pH	−0.51	−2.96; 1.93	0.6806	−1.37	−2.32; −0.42	0.00451
Demineralization time (hours)	0.00	−0.00; 0.01	1.8929	0.01	0.00; 0.01	<0.0001
		Enamel microhardness of WSLs				
pH	0.42	−3.42; 0.67	0.0641	0.42	−0.03; 0.00	0.0647
Demineralization time (hours)	0.00	−0.01; 0.00	0.6230	0.00	−0.01; 0.00	0.8729
		Shear Bond Strength of WSLs				
pH	−0.59	−6.98; 7.62	0.9781	−0.60	−2.02; 0.82	0.4098
Demineralization time (hours)	0.00	0.00; 0.01	0.0015	0.00	0.00; 0.01	0.0120
		Penetration depth of WSLs				
pH	−6.24	−54.77; 42.29	0.8010	−33.63	−0.88; 290.10	0.0432
Demineralization time (hours)	0.00	−0.02; 0.02	0.9969	0.00	−0.01; 0.01	0.8542
Time of application of resin infiltrate (minutes)	7.68	1.17; 14.18	0.0207	24.12	13.16; 35.07	<0.0001

CI—Confidence Interval.

3.4.2. Enamel Microhardness

Our results showed that resin infiltration significantly reduced by 24%, on average, the microhardness of sound enamel (ROM = 0.76, 95% CI: 0.73; 0.80, $p < 0.001$) and to increase by 68% the microhardness of enamel with WSLs (ROM = 1.68, 95% CI: 1.51; 1.86, $p < 0.001$) (Table 2, Figures S3 and S4). In both estimates, the heterogeneity was high (I^2 = 99.1% and I^2 = 99.8%, respectively), and there was no publication bias in both analyses (0.8893 and 0.1352, respectively) (Table 2, Figures S5 and S6). In particular, the enamel microhardness of sound enamel of human teeth was different compared to bovine teeth ($p < 0.0188$), showing that the enamel microhardness of sound enamel after resin application was lower in human teeth compared to bovine teeth (ROM = 0.58, 95% CI: 0.46; 0.72, and ROM = 0.80, 95% CI: 0.69; 0.92, $p < 0.0188$). Although without any significant difference ($p = 0.1375$), the same pattern was found in human and bovine teeth with WSLs (ROM = 1.59, 95% CI: 1.29; 1.96 and 1.96, 95% CI: 1.64; 2.34, respectively) (Table 3). Still, sensitivity analysis showed no differences based on pH and demineralization time, both using univariate and multivariate analysis ($p = 0.0188$) (Table 4).

3.4.3. Shear Bond Strength

In what concerns shear bond strength, resin infiltration was estimated to reduce 25% the bond strength in sound enamel (ROM = 0.75, 95% CI: 0.60; 0.95, $p < 0.001$) and to increase by 89% the bond strength in WSLs (ROM = 1.89, 95% CI: 1.28; 2.79, $p < 0.001$) (Table 2, Figures S7 and S8). In both estimates, heterogeneity was high ($I^2 = 96.9\%$ and $I^2 = 99.8\%$, respectively) (Table 2). In addition, there was no difference between human and bovine teeth in both analyses ($p = 0.6221$) (Table 3), and only the demineralization time had an important impact on bond strength of teeth with WSLs, both in univariate and multivariate analyses (ROM = 0.00, 95% CI: 0.00; 0.01, $p = 0.0015$ and ROM = 0.00, 95% CI: 0.00; 0.01, $p = 0.0120$, respectively) (Table 4).

3.4.4. Penetration Depth in Caries Lesions

Regarding the penetration depth, only studies with enamel lesions were included. Considering the sound enamel the baseline value as zero, resin infiltration was estimated to penetrate 65.4% of overall lesion (MRAW = 65.4, 95% CI: 56.11; 74.66, $p = 0.01$, $I^2 = 100\%$) (Table 2, Figure S9). In addition, the longer the application time, the greater the average penetration depth of the resin (Table 3, Figures S9 and S10).

4. Discussion

4.1. *Summary of the Main Results*

Overall, the present systematic review demonstrates that infiltrative resins effectively change the properties of both sound enamel and WSLs. In sound enamel, infiltrative resins reduced surface roughness, microhardness and shear bond strength. Regarding WSLs, infiltrative resins reduced enamel surface roughness, but increased its microhardness and shear bond strength. Furthermore, estimates point to an average penetration depth capacity of 65% by this type of resin.

4.2. *Quality of the Evidence and Potential Biases in the Review Process*

There are limitations inherent to the included studies. The protocols to create artificial WSLs differ in the pH of the demineralized agent used and etching time, and this could be a source of heterogeneity. Our sensitivity analyses via meta-regression confirmed that pH significantly influences surface roughness in WSLs and resin penetration depth after infiltration technique, and the etching time affected surface roughness and shear bond strength in WSLs. Thus, these protocol variations might affect the interaction with superficial crystals [78] and, therefore, might have contributed to the heterogeneity in the estimates. Additionally, our estimates included both studies on bovine and human teeth. Although this could undermine the consistency of the results, sensitivity analyses only showed an effect on microhardness in sound enamel specimens, and for the remaining analyses there was no significant impact. Nevertheless, future studies shall look for a harmonization of the protocol of WSL creation as well the specimen origin towards a consistent study methodology. In addition, most studies lacked an appropriate rationale for sample size calculation and group allocation of specimens, and these should be accounted for in future studies.

This systematic review also presents some strengths that are worth discussing. A strict protocol was followed with a guideline-based methodology and extensive scientific search. To the best of our knowledge, this is the first systematic review to demonstrate how much infiltrative resins can improve surface roughness, shear bond strength and penetration depth in permanent teeth with and without enamel lesions. Regarding microhardness, although one systematic review had estimated the impact of microhardness on WSLs and sound enamel [20], our approach explored for the first time the effect of pH of the demineralized agent used, etching time, and tooth origin through meta-regression sensitivity analysis on this enamel characteristic. In addition, we included 10 and 16 new studies on sound enamel and WSL, respectively (350% and 229% of the total number of included studies [20], and more than 800 specimens (170% of the total number of specimens) comparing to previous systematic review [20]. Furthermore, by using two meta-analytical approaches and the effort to detect and mitigate potential sources of heterogeneity, we are secure with the effect sizes across the included studies.

4.3. Agreements and Disagreements with Other Reviews or Studies and Clinical Relevance

Resin infiltration technique is a minimally invasive therapy to WSLs [78] with a pre-etching phase onto the lesion to improve penetration ability [28,77]. In addition, this penetrative role is enhanced by its methacrylate-based resin matrix containing BisGMA (bisphenol A diglycidil dimethacrylate) and TEGDMA (triethylene glycol dimethacrylate) [43,49], which confer low viscosity to the resin [35].

Analyzing our results on surface roughness, both sound enamel and WSLs decreased the roughness after resin-infiltration application (35% and 54%, respectively), and these results have clinical importance. The oral cavity constantly undergoes a dynamic demineralization-remineralization cycle that promotes natural healing processes [79]. On the one hand, oral biofilm and dietary acids can contribute to create porous lesions on enamel, and, on the other hand, saliva, sealants, antibacterials, fluoride, and a controlled diet with less sugar and starchy foods promote a non-demineralizing environment [80]. Hence, infiltrative resins may play a role not only interventional but also preventive in the enamel roughness resulting throughout life.

Microhardness is a linear enamel characteristic based on the local calcium content [41], and this parameter can be used to assess the increase or reduction of percentage of enamel porosity [28]. Although resin infiltration might increase the microhardness, the establishment of the polymeric chain does not always happen in the entire lesion [81]. Therefore, the inability of a strong intermolecular bond plus the non-infiltration of the resin in the entire enamel lesion can prevent the full recovery of the enamel microhardness. Our results confirmed that the resin infiltration cannot return the microhardness of WSLs to that of sound enamel, although it may restore 68% of it. This result is in agreement with one systematic review that had shown a 3.66 mean difference increase compared with untreated samples [20]. Furthermore, our results fully comply with this previous work with a similar level of heterogeneity. Yet, as above mentioned, our results explored other characteristics that until today had not been in an evidence-based manner.

Shear bond strength concerns the amount of force required to break the adhesive/adherend interface connection [82], and our results showed this characteristic decreases 25% in sound enamel and increases 89% in WSLs. These results are consistent with the literature [52,70]. Firstly, enamel lesions have a degree of porosity with high permeability, allowing the infiltration of the resin. This ultimately results in micromechanical interdigitation strengthening, and therefore increases shear bond strength [52,70]. Secondly, the decrease of shear bond strength on sound enamel may be justified by the low quality of the enamel surface and lack of resin tags for mechanical interlocking [52].

The resin infiltration of WSLs with low viscosity resin results in a hybrid enamel with resin tags that impregnates the interprismatic enamel and reinforces the hard tissue [60,83,84]. Despite its qualities, not the whole portion of the lesion is filled with the resin [40,65,66]. Furthermore, increasing time of application of resin infiltration improves depth penetration [59,63]. The 'Washburn equation' describes the time-dependent as an important characteristic to advantage the viscosity, surface tension, and contact angle and allows the resin penetration into porous solids [68]. Comprehensively, our results highlight 65,35% of overall enamel lesions were filled with resin, and the longer the application time, the greater the average penetration depth. Our results are in fully agreement with the literature [43,50,77].

The animal origin of the samples may explain the heterogeneity observed. Bovine teeth are often used in this type of studies, due to their similarities to human teeth [85]. Bovine teeth have a larger crystalline diameter, and their calcium distribution is more homogenous [86]. This species also has a lower fluoride concentration and increased porosity [87]. Nevertheless, the calcium/phosphorus ratio of the mineral removed from the enamel surfaces during demineralization, as well as the remineralization characteristics are similar [88]. Furthermore, caries progression in these two specimens is identical, and the inhibition and composition of biofilm formed are alike [89]. In addition, bovine enamel has approximately the same microhardness as human enamel [80], and no significant differences in bond strength between human and bovine enamel were found [90]. All in all, the reader must bear in mind the aforementioned differences and similarities when analyzing the results of the present review.

5. Conclusions

Resin infiltration significantly changes surface roughness, microhardness and shear bond strength in both sound enamel and WSLs. In sound enamel, infiltrative resins decrease 35% of surface roughness, 24% of microhardness and 25% of shear bond strength. In WSLs, enamel surface roughness reduced 54% after infiltrative resins application, but increased 68% and 89% its microhardness and shear bond strength, respectively. Furthermore, estimates point to an average penetration depth capacity of 65% in WSLs. These enamel characteristics can be affected by specimen, pH, and etching time. Future studies with homogeneous methodologies are warranted to confirm these results.

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References

1. Dorri, M.; Martinez-Zapata, M.J.; Walsh, T.; Marinho, V.C.; Sheiham deceased, A.; Zaror, C. Atraumatic Restorative Treatment versus Conventional Restorative Treatment for Managing Dental Caries. *Cochrane Database Syst. Rev.* **2017**. [CrossRef]
2. Kassebaum, N.J.; Bernabé, E.; Dahiya, M.; Bhandari, B.; Murray, C.J.L.; Marcenes, W. Global Burden of Untreated Caries: A Systematic Review and Metaregression. *J. Dent. Res.* **2015**, *94*, 650–658. [CrossRef] [PubMed]
3. Bishara, S.E.; Ostby, A.W. White Spot Lesions: Formation, Prevention, and Treatment. *Semin. Orthod.* **2008**, *14*, 174–182. [CrossRef]
4. Heymann, G.C.; Grauer, D. A Contemporary Review of White Spot Lesions in Orthodontics: White Spot Lesions in Orthodontics. *J. Esthet. Restor. Dent.* **2013**, *25*, 85–95. [CrossRef] [PubMed]
5. Julien, K.C.; Buschang, P.H.; Campbell, P.M. Prevalence of White Spot Lesion Formation during Orthodontic Treatment. *Angle Orthod.* **2013**, *83*, 641–647. [CrossRef]
6. Sangamesh, B.; Kallury, A. Iatrogenic Effects of Orthodontic Treatment—Review on White Spot Lesions. *Int. J. Sci. Eng. Res.* **2011**, *2*, 2–16.

7. Black, G.V. *Operative Dentistry: The Pathology of the Hard Tissues of the Teeth*, 1st ed.; Medico-Dnetal Publishing: Chicago, IL, USA, 1908.
8. Gorelick, L.; Geiger, A.M.; Gwinnett, A.J. Incidence of White Spot Formation after Bonding and Banding. *Am. J. Orthod.* **1982**, *81*, 93–98. [CrossRef]
9. Tufekci, E.; Dixon, J.S.; Gunsolley, J.C.; Lindauer, S.J. Prevalence of White Spot Lesions during Orthodontic Treatment with Fixed Appliances. *Angle Orthod.* **2011**, *81*, 206–210. [CrossRef]
10. Prevalence of White-Spot Lesions before and during Orthodontic Treatment with Fixed Appliances | European Journal of Orthodontics | Oxford Academic. Available online: https://academic.oup.com/ejo/article/35/5/664/495801 (accessed on 12 June 2021).
11. Sundararaj, D.; Venkatachalapathy, S.; Tandon, A.; Pereira, A. Critical Evaluation of Incidence and Prevalence of White Spot Lesions during Fixed Orthodontic Appliance Treatment: A Meta-Analysis. *J. Int. Soc. Prev. Community Dent.* **2015**, *5*, 433–439. [CrossRef] [PubMed]
12. Urquhart, O.; Tampi, M.P.; Pilcher, L.; Slayton, R.L.; Araujo, M.W.B.; Fontana, M.; Guzmán-Armstrong, S.; Nascimento, M.M.; Nový, B.B.; Tinanoff, N.; et al. Nonrestorative Treatments for Caries: Systematic Review and Network Meta-Analysis. *J. Dent. Res.* **2019**, *98*, 14–26. [CrossRef]
13. Giudice, G.L.; Lipari, F.; Lizio, A.; Cervino, G.; Cicciù, M. Tooth Fragment Reattachment Technique on a Pluri Traumatized Tooth. *J. Conserv. Dent. JCD* **2012**, *15*, 80–83. [CrossRef]
14. Jobim Jardim, J.; Henz, S.; Barbachan, E.; Silva, B. Restorative Treatment Decisions in Posterior Teeth: A Systematic Review. *Oral Health Prev. Dent.* **2017**, *15*, 107–115. [CrossRef]
15. Abdullah, Z.; John, J. Minimally Invasive Treatment of White Spot Lesions—A Systematic Review. *Oral Health Prev. Dent.* **2016**, *14*, 197–205. [CrossRef]
16. Bhat, S.; Hegde, S.; Bhat, V.; Ramya, K.; Jodalli, P. Assessment of Maternal Risk Factors and Its Relationship with Early Childhood Caries among Preschool Children in Mangaluru City. *J. Indian Soc. Pedod. Prev. Dent.* **2017**, *35*, 193. [CrossRef]
17. Domöjean, S.; Ducamp, R.; Löger, S.; Holmgren, C. Resin Infiltration of Non-Cavitated Caries Lesions: A Systematic Review. *Med. Princ. Pract.* **2015**, *24*, 216–221. [CrossRef]
18. Meyer-Lueckel, H.; Paris, S.; Kielbassa, A.M. Surface Layer Erosion of Natural Caries Lesions with Phosphoric and Hydrochloric Acid Gels in Preparation for Resin Infiltration. *Caries Res.* **2007**, *41*, 223–230. [CrossRef] [PubMed]
19. Dorri, M.; Dunne, S.M.; Walsh, T.; Schwendicke, F. Micro-Invasive Interventions for Managing Proximal Dental Decay in Primary and Permanent Teeth. *Cochrane Database Syst. Rev.* **2015**. [CrossRef] [PubMed]
20. Zakizade, M.; Davoudi, A.; Akhavan, A.; Shirban, F. Effect of Resin Infiltration Technique on Improving Surface Hardness of Enamel Lesions: A Systematic Review and Meta-Analysis. *J. Evid. Based Dent. Pract.* **2020**, *20*, 101405. [CrossRef] [PubMed]
21. Borges, A.B.; Caneppele, T.M.F.; Masterson, D.; Maia, L.C. Is Resin Infiltration an Effective Esthetic Treatment for Enamel Development Defects and White Spot Lesions? A Systematic Review. *J. Dent.* **2017**, *56*, 11–18. [CrossRef] [PubMed]
22. Aminoshariae, A.; Kulild, J. Master Apical File Size—Smaller or Larger: A Systematic Review of Microbial Reduction. *Int. Endod. J.* **2015**, *48*, 1007–1022. [CrossRef]
23. Dos Reis-Prado, A.H.; Abreu, L.G.; Tavares, W.L.F.; da Cunha Peixoto, I.F.; Viana, A.C.D.; de Oliveira, E.M.C.; Bastos, J.V.; Ribeiro-Sobrinho, A.P.; Benetti, F. Comparison between Immediate and Delayed Post Space Preparations: A Systematic Review and Meta-Analysis. *Clin. Oral Investig.* **2021**, *25*, 417–440. [CrossRef] [PubMed]
24. Ethem Yaylali, I.; Kececi, A.D.; Ureyen Kaya, B. Ultrasonically Activated Irrigation to Remove Calcium Hydroxide from Apical Third of Human Root Canal System: A Systematic Review of In Vitro Studies. *J. Endod.* **2015**, *41*, 1589–1599. [CrossRef]
25. Hozo, S.P.; Djulbegovic, B.; Hozo, I. Estimating the Mean and Variance from the Median, Range, and the Size of a Sample. *BMC Med. Res. Methodol.* **2005**, *5*, 13. [CrossRef] [PubMed]
26. Higgins, J.P.T.; Altman, D.G.; Gotzsche, P.C.; Juni, P.; Moher, D.; Oxman, A.D.; Savovic, J.; Schulz, K.F.; Weeks, L.; Sterne, J.A.C.; et al. The Cochrane Collaboration's Tool for Assessing Risk of Bias in Randomised Trials. *BMJ* **2011**, *343*, d5928. [CrossRef]
27. AL Again, N.A.; Atta, M.S.; Alhady, A.A.A. The Effect of Caries Infiltration Technique (Icons) on Surface Roughness and Microhardness of Enamel White Spot Lesions. *Al-Azhar J. Dent. Sci.* **2018**, *21*, 79–86. [CrossRef]
28. Abdel-Hakim, S.; Metwalli, N.; El-Askary, F.; Wassel, M. Microhardness, sem and color change analysis of artificial enamel lesions in primary teeth treated with resin infiltration, cpp-acp or fluoride gel: An in vitro study. *Egypt. Dent. J.* **2016**, *62*, 3735–3744.
29. Abdellatif, A.; Shalan, H.; Elsebaai, A. Effects of Resin Application on White Spot Lesions (Laboratory Study). *J. Clin. Pediatr. Dent.* **2016**, *46*, 120–126.
30. Andrade Neto, D.M.; Carvalho, E.V.; Rodrigues, E.A.; Feitosa, V.P.; Sauro, S.; Mele, G.; Carbone, L.; Mazzetto, S.E.; Rodrigues, L.K.; Fechine, P.B.A. Novel Hydroxyapatite Nanorods Improve Anti-Caries Efficacy of Enamel Infiltrants. *Dent. Mater. Off. Publ. Acad. Dent. Mater.* **2016**, *32*, 784–793. [CrossRef] [PubMed]
31. Arslan, S.; Zorba, Y.O.; Atalay, M.A.; Özcan, S.; Demirbuga, S.; Pala, K.; Percin, D.; Ozer, F. Effect of Resin Infiltration on Enamel Surface Properties and Streptococcus Mutans Adhesion to Artificial Enamel Lesions. *Dent. Mater. J.* **2015**, *34*, 25–30. [CrossRef]
32. Attin, R.; Stawarczyk, B.; Keçik, D.; Knösel, M.; Wiechmann, D.; Attin, T. Shear Bond Strength of Brackets to Demineralize Enamel after Different Pretreatment Methods. *Angle Orthod.* **2012**, *82*, 56–61. [CrossRef]

33. Ayad, A.; Mustafa, D.; Nour, K. Effect of Remineralizing Agents and Resin Infiltration on Resistance to Demineralization of Artificial Enamel Lesions. *Egypt. Dent. J.* **2020**, *66*, 2763–2771. [CrossRef]
34. Aziznezhad, M.; Alaghemand, H.; Shahande, Z.; Pasdar, N.; Bijani, A.; Eslami, A.; Dastan, Z. Comparison of the Effect of Resin Infiltrant, Fluoride Varnish, and Nano-Hydroxy Apatite Paste on Surface Hardness and Streptococcus Mutans Adhesion to Artificial Enamel Lesions. *Electron. Physician* **2017**, *9*, 3934–3942. [CrossRef]
35. Behrouzi, P.; Heshmat, H.; Hoorizad Ganjkar, M.; Tabatabaei, S.F.; Kharazifard, M.J. Effect of Two Methods of Remineralization and Resin Infiltration on Surface Hardness of Artificially Induced Enamel Lesions. *J. Dent. Shiraz Iran* **2020**, *21*, 12–17. [CrossRef]
36. El Meligy, O.A.E.S.; Alamoudi, N.M.; Eldin Ibrahim, S.T.; Felemban, O.M.; Al-Tuwirqi, A.A. Effect of Resin Infiltration Application on Early Proximal Caries Lesions in Vitro. *J. Dent. Sci.* **2021**, *16*, 296–303. [CrossRef]
37. Enan, E.T.; Tawfik, M.A.; Ali, A.I.; Anan, A.T. Surface properties of resin-infiltrated incipient enamel lesions after aging under thermal stresses. *Egypt. Dent. J.* **2018**, *64*, 2833–2840. [CrossRef]
38. Gurdogan, E.B.; Ozdemir-Ozenen, D.; Sandalli, N. Evaluation of Surface Roughness Characteristics Using Atomic Force Microscopy and Inspection of Microhardness Following Resin Infiltration with Icon®. *J. Esthet. Restor. Dent. Off. Publ. Am. Acad. Esthet. Dent. Al* **2017**, *29*, 201–208. [CrossRef]
39. Horuztepe, S.A.; Baseren, M. Effect of Resin Infiltration on the Color and Microhardness of Bleached White-Spot Lesions in Bovine Enamel (an in vitro Study). *J. Esthet. Restor. Dent. Off. Publ. Am. Acad. Esthet. Dent. Al* **2017**, *29*, 378–385. [CrossRef]
40. Mandava, J.; Reddy, Y.S.; Kantheti, S.; Chalasani, U.; Ravi, R.C.; Borugadda, R.; Konagala, R.K. Microhardness and Penetration of Artificial White Spot Lesions Treated with Resin or Colloidal Silica Infiltration. *J. Clin. Diagn. Res. JCDR* **2017**, *11*, ZC142–ZC146. [CrossRef]
41. Montasser, M.A.; El-Wassefy, N.A.; Taha, M. In Vitro Study of the Potential Protection of Sound Enamel against Demineralization. *Prog. Orthod.* **2015**, *16*, 12. [CrossRef]
42. Pancu, G.; Andrian, S.; Iovan, G.; Ghiorghe, A.; Topoliceanu, C.; Moldovanu, A.; Georgescu, A.; Pancu, I.; Stoleriu, S. Study regarding the assessment of enamel microhardness in incipient carious lesions treated by icon method. *Rom. J. Oral Rehabil.* **2011**, *3*, 94–100.
43. Paris, S. Micro-Hardness and Mineral Loss of Enamel Lesions after Infiltration with Various Resins: Influence of Infiltrant Composition and Application Frequency in Vitro—ScienceDirect. Available online: https://www.sciencedirect.com/science/article/abs/pii/S0300571213000869 (accessed on 10 March 2021).
44. Prajapati, D.; Nayak, R.; Pai, D.; Upadhya, N.; Bhaskar, V.K.; Kamath, P. Effect of Resin Infiltration on Artificial Caries: An in Vitro Evaluation of Resin Penetration and Microhardness. *Int. J. Clin. Pediatr. Dent.* **2017**, *10*, 250–256. [CrossRef] [PubMed]
45. Qasim, A. Assessement of White Spot Treated with (ICON) and Flouride Gel (An In Vitro Study). *Int. J. Enhanc. Res. Sci. Technol. Eng.* **2014**, *3*, 1–6.
46. El-zankalouny Shimaa, M.; Abd El Fattah Wegdan, M.; El-Shabrawy Sonia, M. Penetration depth and enamel microhardness of resin infiltrant and traditional techniques for treatment of artificial enamel lesions. *Alex. Dent. J.* **2016**, *41*, 20–25. [CrossRef]
47. Taher, N.M.; Alkhamis, H.A.; Dowaidi, S.M. The Influence of Resin Infiltration System on Enamel Microhardness and Surface Roughness: An in Vitro Study. *Saudi Dent. J.* **2012**, *24*, 79–84. [CrossRef] [PubMed]
48. Torres, C.R.G.; Rosa, P.C.F.; Ferreira, N.S.; Borges, A.B. Effect of Caries Infiltration Technique and Fluoride Therapy on Microhardness of Enamel Carious Lesions. *Oper. Dent.* **2012**, *37*, 363–369. [CrossRef] [PubMed]
49. Yazkan, B.; Ermis, R.B. Effect of Resin Infiltration and Microabrasion on the Microhardness, Surface Roughness and Morphology of Incipient Carious Lesions. *Acta Odontol. Scand.* **2018**, *76*, 473–481. [CrossRef] [PubMed]
50. Arora, T.C.; Arora, D.; Tripathi, A.M.; Yadav, G.; Saha, S.; Dhinsa, K. An In-Vitro Evaluation of Resin Infiltration System and Conventional Pit and Fissure Sealant on Enamel Properties in White Spot Lesions. *J. Indian Soc. Pedod. Prev. Dent.* **2019**, *37*, 133–139. [CrossRef]
51. Aswani, R.; Chandrappa, V.; Uloopi, K.; Chandrasekhar, R.; RojaRamya, K.S. Resin Infiltration of Artificial Enamel Lesions: Evaluation of Penetration Depth, Surface Roughness and Color Stability. *Int. J. Clin. Pediatr. Dent.* **2019**, *12*, 520–523. [CrossRef]
52. Baka, Z.M.; Akin, M.; Ileri, Z.; Basciftci, F.A. Effects of Remineralization Procedures on Shear Bond Strengths of Brackets Bonded to Demineralized Enamel Surfaces with Self-Etch Systems. *Angle Orthod.* **2016**, *86*, 661–667. [CrossRef]
53. Enan, E.T.; Aref, N.S.; Hammad, S.M. Resistance of Resin-Infiltrated Enamel to Surface Changes in Response to Acidic Challenge. *J. Esthet. Restor. Dent. Off. Publ. Am. Acad. Esthet. Dent. Al* **2019**, *31*, 353–358. [CrossRef]
54. Khalid, I.; Anggani, H.S.; Ismah, N. Differences in Enamel Surface Roughness Changes after Debonding Using Resin Infiltration System and Nano-Filled Resin Coating. *J. Int. Dent. Med. Res.* **2019**, *12*, 95–100.
55. Askar, H.; Schwendicke, F.; Lausch, J.; Meyer-Lueckel, H.; Paris, S. Modified Resin Infiltration of Non-, Micro- and Cavitated Proximal Caries Lesions in Vitro. *J. Dent.* **2018**, *74*, 56–60. [CrossRef]
56. Gelani, R.; Zandona, A.F.; Lippert, F.; Kamocka, M.M.; Eckert, G. In Vitro Progression of Artificial White Spot Lesions Sealed with an Infiltrant Resin. *Oper. Dent.* **2014**, *39*, 481–488. [CrossRef]
57. Lausch, J.; Paris, S.; Selje, T.; Dörfer, C.E.; Meyer-Lueckel, H. Resin Infiltration of Fissure Caries with Various Techniques of Pretreatment in Vitro. *Caries Res.* **2015**, *49*, 50–55. [CrossRef] [PubMed]

58. López López, E.A.; Dominguez, J.A.; Gomes, G.M.; Mora, C.A.P.; Bittencourt, B.F.; Gomes, J.C.; Gomes, O.M.M. Effect of Conditioning Protocols and Ultrasonic Application of an Infiltrant Resin in White Spot Lesions. *Braz. Dent. J.* **2019**, *30*, 58–65. [CrossRef]
59. Meyer-Lueckel, H.; Chatzidakis, A.; Naumann, M.; Dörfer, C.E.; Paris, S. Influence of Application Time on Penetration of an Infiltrant into Natural Enamel Caries. *J. Dent.* **2011**, *39*, 465–469. [CrossRef] [PubMed]
60. Min, J.H.; Inaba, D.; Kwon, H.K.; Chung, J.H.; Kim, B.I. Evaluation of Penetration Effect of Resin Infiltrant Using Optical Coherence Tomography. *J. Dent.* **2015**, *43*, 720–725. [CrossRef]
61. Paris, S.; Soviero, V.M.; Schuch, M.; Meyer-Lueckel, H. Pretreatment of Natural Caries Lesions Affects Penetration Depth of Infiltrants in Vitro. *Clin. Oral Investig.* **2013**, *17*, 2085–2089. [CrossRef]
62. Paris, S.; Bitter, K.; Naumann, M.; Dörfer, C.E.; Meyer-Lueckel, H. Resin Infiltration of Proximal Caries Lesions Differing in ICDAS Codes. *Eur. J. Oral Sci.* **2011**, *119*, 182–186. [CrossRef] [PubMed]
63. Paris, S.; Lausch, J.; Selje, T.; Dörfer, C.E.; Meyer-Lueckel, H. Comparison of Sealant and Infiltrant Penetration into Pit and Fissure Caries Lesions in Vitro. *J. Dent.* **2014**, *42*, 432–438. [CrossRef]
64. Paris, S.; Soviero, V.M.; Seddig, S.; Meyer-Lueckel, H. Penetration Depths of an Infiltrant into Proximal Caries Lesions in Primary Molars after Different Application Times in Vitro. *Int. J. Paediatr. Dent.* **2011**, *22*, 349–355. [CrossRef]
65. Sava-rosianu, R.; Podariu, A.; Negrutiu, M.; Szuhanek, C.; Sinescu, C. Low Viscosity Resin Penetration Degree in Incipient Caries Lesions. *Rev. Chim.* **2017**, *68*, 2588–2592. [CrossRef]
66. Theodory, T.G.; Kolker, J.L.; Vargas, M.A.; Maia, R.R.; Dawson, D.V. Masking and Penetration Ability of Various Sealants and ICON in Artificial Initial Caries Lesions In Vitro. *J. Adhes. Dent.* **2019**, *21*, 265–272. [CrossRef] [PubMed]
67. Wang, L.; de Almendra Freitas, M.C.C.; Prakki, A.; Mosquim, V.; González, A.H.M.; Rios, D.; Honório, H.M. Experimental Self-Etching Resin Infiltrants on the Treatment of Simulated Carious White Spot Lesions. *J. Mech. Behav. Biomed. Mater.* **2021**, *113*, 104146. [CrossRef] [PubMed]
68. Borges, A.B.; Abu Hasna, A.; Matuda, A.G.N.; Lopes, S.R.; Mafetano, A.P.V.P.; Arantes, A.; Duarte, A.F.; Barcellos, D.C.; Torres, C.R.G.; Pucci, C.R. Adhesive Systems Effect over Bond Strength of Resin-Infiltrated and de/Remineralized Enamel. *F1000Research* **2019**, *8*, 1743. [CrossRef]
69. Dilber, E.; Akın, M.; Yavuz, T.; Erdem, A. Effects of Different Demineralization-Inhibiting Methods on the Shear Bond Strength of Glass-Ceramics. *J. Prosthodont. Off. J. Am. Coll. Prosthodont.* **2015**, *24*, 407–413. [CrossRef] [PubMed]
70. Ekizer, A.; Zorba, Y.O.; Uysal, T.; Ayrikcila, S. Effects of Demineralizaton-Inhibition Procedures on the Bond Strength of Brackets Bonded to Demineralized Enamel Surface. *Korean J. Orthod.* **2012**, *42*, 17–22. [CrossRef] [PubMed]
71. Gulec, A. Assessment of the Resin Infiltration and CPP-ACP Applications before Orthodontic Brackets Bonding—PubMed. Available online: https://pubmed.ncbi.nlm.nih.gov/31434834/ (accessed on 11 March 2021).
72. Velİ, I.; Akin, M.; Baka, Z.M.; Uysal, T. Effects of Different Pre-Treatment Methods on the Shear Bond Strength of Orthodontic Brackets to Demineralized Enamel. *Acta Odontol. Scand.* **2016**, *74*, 7–13. [CrossRef]
73. Vianna, J.S.; Marquezan, M.; Lau, T.C.L.; Sant'Anna, E.F. Bonding Brackets on White Spot Lesions Pretreated by Means of Two Methods. *Dent. Press J. Orthod.* **2016**, *21*, 39–44. [CrossRef]
74. Paris, S.; Schwendicke, F.; Keltsch, J.; Dörfer, C.; Meyer-Lueckel, H. Masking of White Spot Lesions by Resin Infiltration in Vitro. *J. Dent.* **2013**, *41*, e28–e34. [CrossRef] [PubMed]
75. Paris, S.; Meyer-Lueckel, H. Resin Infiltration after Enamel Etching. In *Tooth Whitening*; Perdigão, J., Ed.; Springer International Publishing: Cham, Switzerland, 2016; pp. 211–222. ISBN 978-3-319-38847-2.
76. Mohamed, A.M.; Wong, K.H.; Lee, W.J.; Marizan Nor, M.; Mohd Hussaini, H.; Rosli, T.I. In Vitro Study of White Spot Lesion: Maxilla and Mandibular Teeth. *Saudi Dent. J.* **2018**, *30*, 142–150. [CrossRef]
77. Attia, R.M. Effect of PH Challenge on the Micro-Hardness of Artificially Induced de-Mineralized Enamel Treated with Resin Infiltrant and Fluoride Varnish. *Egypt. Dent. J.* **2018**, *64*, 2841–2850. [CrossRef]
78. Wong, A.; Subar, P.E.; Young, D.A. Dental Caries. *Adv. Pediatr.* **2017**, *64*, 307–330. [CrossRef] [PubMed]
79. Abou Neel, E.A.; Aljabo, A.; Strange, A.; Ibrahim, S.; Coathup, M.; Young, A.M.; Bozec, L.; Mudera, V. Demineralization–Remineralization Dynamics in Teeth and Bone. *Int. J. Nanomed.* **2016**, *11*, 4743–4763. [CrossRef] [PubMed]
80. Ten Cate, J.M.; Featherstone, J.D.B. Mechanistic Aspects of the Interactions Between Fluoride and Dental Enamel. *Crit. Rev. Oral Biol. Med.* **1991**, *2*, 283–296. [CrossRef]
81. Neres, É.; Moda, M.; Chiba, E.; Briso, A.; Pessan, J.; Fagundes, T. Microhardness and Roughness of Infiltrated White Spot Lesions Submitted to Different Challenges. *Oper. Dent.* **2017**, *42*, 428–435. [CrossRef] [PubMed]
82. Rasmussen, S.T. Analysis of Dental Shear Bond Strength Tests, Shear or Tensile? *Int. J. Adhes. Adhes.* **1996**, *16*, 147–154. [CrossRef]
83. Nakabayashi, N.; Nakamura, M.; Yasuda, N. Hybrid Layer as a Dentin-Bonding Mechanism. *J. Esthet. Dent.* **1991**, *3*, 133–138. [CrossRef]
84. Perdigão, J. Resin Infiltration of Enamel White Spot Lesions: An Ultramorphological Analysis. *J. Esthet. Restor. Dent. Off. Publ. Am. Acad. Esthet. Dent. Al* **2020**, *32*, 317–324. [CrossRef]
85. Yassen, G.H.; Platt, J.A.; Hara, A.T. Bovine Teeth as Substitute for Human Teeth in Dental Research: A Review of Literature. *J. Oral Sci.* **2011**, *53*, 273–282. [CrossRef]
86. Arends, J.; Jongebloed, W.L. Crystallites Dimensions of Enamel. *J. Biol. Buccale* **1978**, *6*, 161–171.

87. Mellberg, J.R. Hard-Tissue Substrates for Evaluation of Cariogenic and Anti-Cariogenic Activity in Situ. *J. Dent. Res.* **1992**, *71*, 913–919. [CrossRef] [PubMed]
88. Feagin, F.; Koulourides, T.; Pigman, W. The Characterization of Enamel Surface Demineralization, Remineralization, and Associated Hardness Changes in Human and Bovine Material. *Arch. Oral Biol.* **1969**, *14*, 1407–1417. [CrossRef]
89. Hara, A.T.; Queiroz, C.S.; Paes Leme, A.F.; Serra, M.C.; Cury, J.A. Caries Progression and Inhibition in Human and Bovine Root Dentine in Situ. *Caries Res.* **2003**, *37*, 339–344. [CrossRef]
90. Rüttermann, S.; Braun, A.; Janda, R. Shear Bond Strength and Fracture Analysis of Human vs. Bovine Teeth. *PLoS ONE* **2013**, *8*, e59181. [CrossRef] [PubMed]

2.1. General discussion

WSLs are the first sign of a caries lesion and consist in the demineralization of the enamel subsurface without cavitation (Paula et al., 2017; Deveci et al., 2018b). These enamel injuries are characterized as a white, chalky, opaque appearance commonly located in pits, fissures, and smooth surfaces of teeth (Aykut-Yetkiner, 2017; Höchli et al., 2017).

There are two treatment approaches for these type of enamel lesions. The first one comprehends restorative or conventional treatment involving caries lesion removal with rotary burs and/or hand instruments (Dorri et al., 2017). In contrast, the minimal invasive concept is based on managing the risk factors and in the disease prevention. In other words, the earliest signs of caries are management without treatment or with minimally enamel therapies (Wong et al., 2017). ICON® is an infiltrative resin that insert in the minimal invasive concept were the tooth surface is preserved as much as possible.

ICON® infiltration resin is a TEGMA low viscosity resin that penetrates into the porous lesion with several benefits. The protocol is simple and each step is program in order to enhance the repair of the lesion (Arora et al., 2019). As above mentioned, the pre-etching with HCL is used to remove around 40 μr of the tooth surface, improving the penetration ability of resin. It removes most of the hypermineralized surface layer, facilitating the infiltrant’s access to the lesion’s interior (El Meligy et al., 2021). After this step, ICON-Dry (99% of which is ethanol) is apply in order to decreases the contact angle and viscosity that also enhances resin penetration (Attia, 2018). In the final step, the TEGMA resin is apply. This approach seals the micro porosities, blocks the access of acids to any remaining pores, increases surface hardness, and provides significant mechanical support to tooth tissue (Arora et al., 2019).

The present study demonstrated that the application of the ICON® infiltrative resin is capable of effectively change the properties of both sound enamel and WSLs.

As shown in the table 2 of our article, it is possible to conclude that the ICON® application improves surface roughness with a decrease of the roughness average (Ra) in both sound and demineralized enamel (35% and 54%, respectively). The ability to contain the remaining hydroxyapatite crystals in the enamel lesion, by giving a uniform resin hydroxyapatite matrix, can explain this improvement (Enan et al., 2018). The impact of dental materials on surface roughness is material-dependent, where the materials are going to influence the final surface roughness (Arslan et al., 2015). Despite the improvement of the results, none of the studies had a surface roughness bellow 0,2 mm, the critical value for bacterial colonization. This values may be explain by the inability of resin infiltration to seal the total of lesions porous (Baka et al., 2016).

Other parameter studied was microhardness. This characteristic is calcium dependent (Montasser et al., 2015; Rathi et al., 2017). Changes in calcium concentration can be related to the percentage of the caries lesions progression or arresting (Abdel-Hakim et al., 2016).

With a diffusion barrier creation inside the caries lesion, by filling the remaining pores and replacing the lost one with a methacrylate-based resin matrix containing BISGMA and TEGDMA, the microhardness values are going to suffer fluctuations (Taher et al., 2012; Montasser et al., 2015). This material is supposed to stabilize the porous lesion body and increase microhardness when compared to untreated or remineralized carious lesions (Paris et al., 2013; Manoharan et al., 2019).

This systematic review showed that, in most studies, there is an increase in microhardness, by 68%, when compared with demineralized samples. The increase of microhardness can be explain by the filling of the enamel porosities with a barrier's formation. Still, there is a decrease when compared with the sound enamel and this phenomenon was explained by the reduced penetration depth of the resin (Paris et al., 2013; Deveci et al., 2018b).

Only one previously systematic review had shown similar results to ours regarding microhardness, with 3.66 mean increase when compared with untreated samples (Zakizade et al., 2020). Nevertheless, this previous review did not explore the impact of the type of tooth used (bovine versus human), pH and demineralization time protocols to create WSLs.

In the different studies´ protocols, WSLs were artificially created or were already with a caries lesion. This protocol aimed to analyze the infiltration resin's capacity to penetrate the lesions and how the time of application conditional this penetration.

In the table 2 of our article, it is possible to concluded, that there are an increment of the penetration depth by 65.35%. ICON® infiltrate resin composition has very low viscosity, a low contact angle to the enamel, and a high surface tension. All these features permit a complete penetration of the resin infiltrant into the body of the enamel lesions (Min et al., 2015; Swamy et al., 2017).

Despite its qualities not the whole portion of the lesion is filled with the infiltrate. The conventional HCl's high viscosity may explain this lack of infiltration that impossibilities a total diffusion by the lesion's enamel pores which cause an insufficient infiltration (Lausch et al., 2015).

As shown by Meyer-Lueckel et al., (2011) and Paris et al., (2013), the increasing time of application of ICON® infiltration resin causes an increase in resin penetration. The 'Washburn equation' describes the time-dependent influence of the material properties like viscosity, surface tension, and contact angle to the enamel on penetration abilities into porous solids that support our observations (Borges et al., 2019).

The last parameter studied was the shear bond strength were by measuring, analyzes the amount of force required to break the connection between a bonded restoration and the tooth surface with the failure occurring in or near the adhesive/adherend interface (Rasmussen, 1996; El Mourad, 2018).

When considering applying a fixed orthodontic therapy, we must assume that the brackets will be adhered to the tooth surface for a minimum of two years on average, and for this matter, the first step must be the treatment of the tooth surface (Gulec & Goymen, 2019).

Thus, several papers were made where numerous materials are compared to see which one showed a better improvement of the shear bond strength (El Mourad, 2018).

In our systematic review, it is possible to conclude that there is an improvement of the shear bond strength by 89% when resin infiltration is applied in the demineralized enamel. This result is consistent with the literature and may be assigned to the facility of the resin to penetrate the demineralized enamel, which results in micromechanical interdigitation strengthening (Ekizer et al., 2012; Baka et al., 2016; Kumar et al., 2017).

Despite that, the result is inconsistent when compared the sound enamel with the infiltrated one. Some studies, including Dilber et al., (2015), Velİ et al., (2016), Borges et al.,(2019) showed an improvement but Attin et al., (2012), Baka et al., (2016), Gulec, (2019) exhibit a smaller value. Our results show a decrease of 25% in this parameter when comparing to the sound enamel. The decrease of this value may be consisting with de low quality of the enamel surface and lack of resin tags for mechanical interlocking (Baka et al., 2016).

Despite the promising results, there are a few limitations inherent to the studies included. Although the sample preparation protocols are similar, there are differences in the pH values, etching time, and this could be a source of heterogeneity. Our sensitivity investigations through meta-regression affirmed that pH altogether impacts surface roughness in WSLs and resin penetration, and the etching time influenced surface roughness and shear bond strength in WSLs. This variances in the protocol can cause heterogeneity in the results. The use of human samples and bovine samples can also cause a diversity of results. Although this could compromise the consistency of the results, sensitivity analyses only showed an effect on microhardness in sound enamel specimens, and for the remaining analyses there was no significant impact. Nevertheless, future studies shall look for a harmonization of the protocol of WSL creation as well the specimen origin towards a consistent study methodology. Likewise, most investigations did not have a suitable sample estimation and gathering group allocation of specimens, and these ought to be represented in future examinations.

The animal origin of the samples may explain the heterogeneity observed. Bovine teeth are often used in this type of studies, due to its similarities to human teeth (Yassen et al., 2011a). Bovine teeth have larger crystalline diameter, and their calcium distribution is more homogenous (Arends & Jongebloed, 1978). This species also has a lower fluoride concentration and increased porosity (Mellberg, 1992). Nevertheless, the calcium/phosphorus ratio of the mineral removed from the enamel surfaces during demineralization, as well as the remineralization characteristics are similar (Feagin et al., 1969). Furthermore, caries progression in these two specimens is identical, and the inhibition and composition of biofilm formed are alike (Hara et al., 2003). Also, bovine enamel has approximately the same microhardness as human enamel (Yassen et al., 2011b), and no significant differences in bond strength between human and bovine enamel were found (Rüttermann et al., 2013). All in all, the reader must bear in mind the aforementioned differences and similarities when analyzing the results of the present review.

One systematic review had reported infiltrative resins to increase microhardness of demineralized enamel and to decrease in sound enamel (Zakizade et al., 2020). Our results fully comply with this previous work with a similar level of heterogeneity. Yet, our results are based on a substantially higher number of studies included and explored other characteristics that until today had not been in an evidence-based manner.

2.2. Futures Perspectives

Although the application of resin infiltration shows promising results in mechanical properties, several points must be filed not to compromise the results and sequentially the conclusions.

More in vitro studies are needed with more rigorous methods with stipulated and standardized protocols. When study in vitro properties, the type of tooth, animal or bovine, the demineralization process and time, the ICON® application protocol and the methods of analysis of the results must be consensual and well defined.

Other features such as surface substance loss, remineralization potential, microbial adhesion, conversion degree, modulus of elasticity, water sorption and solubility must be considered in future studies.

Long term studies are needed with wider follow-ups and well-conducted trials to robustly assess the efficacy of several interventions with limited evidence including CPP–ACP creams with fluoride, bioactive glass dentifrices, bleaching, microabrasion, and resin infiltration.

3. Conclusion

Resin infiltration significantly changes surface roughness, microhardness and shear bond strength in both sound enamel and WSLs. In concern of surface roughness there is an improvement by 35% in sound enamel and 54% in WSLs. In the microhardness parameters the results show a gain by 24% in sound enamel and 68% in WSLs. There was a reduction of values by 25% of the shear bond strength in sound enamel and a increase by 89% in WSLs. The penetration depth is estimated to be 65% in WSLs. These enamel characteristics can be affected by tooth specimen, pH and etching time.

4. Bibliography

Abbas, B. A., Marzouk, E. S., & Zaher, A. R. (2018). Treatment of various degrees of white spot lesions using resin infiltration—In vitro study. *Progress in Orthodontics*, *19*(1), 27. https://doi.org/10.1186/s40510-018-0223-3

Abdel-Hakim, S., Metwalli, N., El-Askary, F., & Wassel, M. (2016). Microhardness, sem and color change analysis of artificial enamel lesions in primary teeth treated with resin infiltration, CPP-ACP or fluoride gel: an in vitro study. *Egyptian dental journal*, *Vol. 62, 3735:3744, O.*

Abou Neel, E., Aljabo, A., Strange, A., Ibrahim, S., Coathup, M., Young, A., Bozec, L., & Mudera, V. (2016). Demineralization–remineralization dynamics in teeth and bone. *International Journal of Nanomedicine*, *Volume 11*, 4743–4763. https://doi.org/10.2147/ijn.s107624

Adiningrat, A., Kusmaharani, H., Utami, S., & Ratna Astuti, N. (2020). Evaluation of International Caries Detection and Assessment System (ICDAS)-related caries severity among caries risk groups in Pendul district: An observational study. *Journal of International Society of Preventive and Community Dentistry*, *10*(4), 498. https://doi.org/10.4103/jispcd.jispcd_46_20

Akarsu, S., Aktug Karademir, S., Akarsu, S., & Aktug Karademir, S. (2019). In Vitro Comparison of ICDAS And DIAGNOdent Pen in The Diagnosis and Treatment Decisions of Non-Cavitated Occlusal Caries. *Odovtos International Journal of Dental Sciences*, *21*(1), 67–81. https://doi.org/10.15517/ijds.v0i0.34896

Al-Obaidi, R., Salehi, H., Desoutter, A., Bonnet, L., Etienne, P., Terrer, E., Jacquot, B., Levallois, B., Tassery, H., & Cuisinier, F. J. G. (2018). Chemical & Nano-mechanical Study of Artificial Human Enamel Subsurface Lesions. *Scientific Reports*, *8*(1), 4047. https://doi.org/10.1038/s41598-018-22459-7

Anand, V., Arumugam, S. B., Manoharan, V., Kumar, S. A., & Methippara, J. J. (2019). Is Resin Infiltration a Microinvasive Approach to White Lesions of Calcified Tooth Structures?: A Systemic Review. *International Journal of Clinical Pediatric Dentistry*, *12*(1), 53–58. https://doi.org/10.5005/jp-journals-10005-1579

Andrade, R. M. P. M. B. de, Nogueira, R. D., Menezes-Oliveira, M. A. H., Lepri, C. P., & Geraldo-Martins, V. R. (2019). Use of Resin Infiltrate for the Treatment of White spot Lesions on Dental Enamel: Case Report. *Journal of Health Sciences*, *21*(2), 134. https://doi.org/10.17921/2447-8938.2019v21n2p134-138

Araujo, M. P., Innes, N. P., Bonifácio, C. C., Hesse, D., Olegário, I. C., Mendes, F. M., & Raggio, D. P. (2020). Atraumatic restorative treatment compared to the Hall Technique for occluso-proximal carious lesions in primary molars; 36-month follow-up of a randomised control trial in a school setting. *BMC Oral Health*, *20*(1), 318. https://doi.org/10.1186/s12903-020-01298-x

Sundström, B., Jongebloed, W., & Arends, J. (1978). Fluorosed Human Enamel. *Caries Research*, *12*(6), 329–338. https://doi.org/10.1159/000260352

Arora, T. C., Arora, D., Tripathi, A. M., Yadav, G., Saha, S., & Dhinsa, K. (2019). An In-Vitro evaluation of resin infiltration system and conventional pit and fissure sealant on enamel properties in white spot lesions. *Journal of the Indian Society of Pedodontics and Preventive Dentistry*, *37*(2), 133–139. https://doi.org/10.4103/1319-2442.261345

Arslan, S., Zorba, Y. O., Atalay, M. A., Özcan, S., Demirbuga, S., Pala, K., Percin, D., & Ozer, F. (2015). Effect of resin infiltration on enamel surface properties and Streptococcus mutans adhesion to artificial enamel lesions. *Dental Materials Journal*, *34*(1), 25–30. https://doi.org/10.4012/dmj.2014-078

Askar, H., Schwendicke, F., Lausch, J., Meyer-Lueckel, H., & Paris, S. (2018). Modified resin infiltration of non-, micro- and cavitated proximal caries lesions in vitro. *Journal of Dentistry*, *74*, 56–60. https://doi.org/10.1016/j.jdent.2018.03.010

Attia, R. (2018). Effect of pH challenge on the micro-hardness of artificially induced de-mineralized enamel treated with resin infiltrant and fluoride varnish. *Egyptian Dental Journal*, *64*(3), 2841–2850. https://doi.org/10.21608/edj.2018.77340

Attin, R., Stawarczyk, B., Keçik, D., Knösel, M., Wiechmann, D., & Attin, T. (2012). Shear bond strength of brackets to demineralize enamel after different pretreatment methods. *The Angle Orthodontist*, *82*(1), 56–61. https://doi.org/10.2319/012311-48.1

Aykut-Yetkiner, A., Kara, N., Ateş, M., Ersin, N., & Ertuğrul, F. (2014). Does Casein Phosphopeptid Amorphous Calcium Phosphate Provide Remineralization on White Spot Lesions and Inhibition of Streptococcus mutans? *Journal of Clinical Pediatric Dentistry*, *38*(4), 302–306. https://doi.org/10.17796/jcpd.38.4.b4q401v6m4818215

Baka, Z. M., Akin, M., Ileri, Z., & Basciftci, F. A. (2016). Effects of remineralization procedures on shear bond strengths of brackets bonded to demineralized enamel surfaces with self-etch systems. *The Angle Orthodontist*, *86*(4), 661–667. https://doi.org/10.2319/041515-247.1

Baranova, J., Büchner, D., Götz, W., Schulze, M., & Tobiasch, E. (2020). Tooth Formation: Are the Hardest Tissues of Human Body Hard to Regenerate? *International Journal of Molecular Sciences*, *21*(11), 4031. https://doi.org/10.3390/ijms21114031

Bartlett, J. D. (2013). Dental Enamel Development: Proteinases and Their Enamel Matrix Substrates. *ISRN Dentistry*, *2013*, 1–24. https://doi.org/10.1155/2013/684607

Bhoopathi, R. H., Patil, P. U., Kamath, B. V., Gopal, D., Kumar, S., & Kulkarni, G. (2017). Caries Detection with ICDAS and the WHO Criteria: A Comparitive Study. *Journal of clinical and diagnostic research*. https://doi.org/10.7860/JCDR/2017/29017.10929

Borges, A. B., Abu Hasna, A., Matuda, A. G. N., Lopes, S. R., Mafetano, A. P. V. P., Arantes, A., Duarte, A. F., Barcellos, D. C., Torres, C. R. G., & Pucci, C. R. (2019). Adhesive systems effect over bond strength of resin-infiltrated and de/remineralized enamel. *F1000Research*, *8*, 1743. https://doi.org/10.12688/f1000research.20523.1

Borges, A. B., Caneppele, T. M. F., Masterson, D., & Maia, L. C. (2017). Is resin infiltration an effective esthetic treatment for enamel development defects and white spot lesions? A systematic review. *Journal of Dentistry*, *56*, 11–18. https://doi.org/10.1016/j.jdent.2016.10.010

Bowen, W. H., Burne, R. A., Wu, H., & Koo, H. (2018). Oral Biofilms: Pathogens, Matrix and Polymicrobial Interactions in Microenvironments. *Trends in microbiology*, *26*(3), 229–242. https://doi.org/10.1016/j.tim.2017.09.008

Changyu, S., Jin, B., Mu, Z., Lu, H., Zhao, Y., Wu, Z., Yan, L., Zhang, Z., Zhou, Y., Pan, H., Liu, Z., & Tang, R. (2019). Repair of tooth enamel by a biomimetic mineralization frontier ensuring epitaxial growth. *Science Advances*, *5*(8), eaaw9569. https://doi.org/10.1126/sciadv.aaw9569

Chawhuaveang, D. D., Yu, O. Y., Yin, I. X., Lam, W. Y.-H., Mei, M. L., & Chu, C.-H. (2021). Acquired salivary pellicle and oral diseases: A literature review. *Journal of Dental Sciences*, *16*(1), 523–529. https://doi.org/10.1016/j.jds.2020.10.007

Colorado, V., Franco Cortés, Á. M., Ochoa Acosta, E. M., & Bran Muñoz, V. (2020). Assessment of an educational strategy and application of an oral health preventive protocol in early childhood. *Revista Facultad de Odontología*, *32*(1), 6–17. https://doi.org/10.17533/udea.rfo.v32n1a1

Conh, C., & Chaet, R. (2020). *The Science and Benefits of Caries Infiltration* (1º, Vol. 1–1). ADA American Dental Association.

Conrads, G., & About, I. (2018). Pathophysiology of Dental Caries. *Monographs in Oral Science*, *27*, 1–10. https://doi.org/10.1159/000487826

Sala, C. E., Sala, E. C., & García, P. B. (2013). *Odontología preventiva y comunitaria: Principios, métodos y aplicaciones (Spanish Edition)* (4th ed.). Elsevier Masson.

Deveci, C., Çınar, Ç., & Tirali, R. E. (2018a). Management of White Spot Lesions. Em *Dental Caries—Diagnosis, Prevention and Management*. IntechOpen. https://doi.org/10.5772/intechopen.75312

Deveci, C., Çınar, Ç., & Tirali, R. E. (2018b). Management of White Spot Lesions. Em Z. Akarslan (Ed.), *Dental Caries—Diagnosis, Prevention and Management*. InTech. https://doi.org/10.5772/intechopen.75312

Dilber, E., Akın, M., Yavuz, T., & Erdem, A. (2015). Effects of Different Demineralization-Inhibiting Methods on the Shear Bond Strength of Glass-Ceramics. *Journal of Prosthodontics: Official Journal of the American College of Prosthodontists*, *24*(5), 407–413. https://doi.org/10.1111/jopr.12230

Dorri, M., Martinez-Zapata, M. J., Walsh, T., Marinho, V. C., Sheiham deceased, A., & Zaror, C. (2017). Atraumatic restorative treatment versus conventional restorative treatment for managing dental caries. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.CD008072.pub2

Ekizer, A., Zorba, Y. O., Uysal, T., & Ayrikcila, S. (2012). Effects of demineralizaton-inhibition procedures on the bond strength of brackets bonded to demineralized enamel surface. *Korean Journal of Orthodontics*, *42*(1), 17–22. https://doi.org/10.4041/kjod.2012.42.1.17

Ekstrand, K. R., Gimenez, T., Ferreira, F. R., Mendes, F. M., & Braga, M. M. (2018). The International Caries Detection and Assessment System - ICDAS: A Systematic Review. *Caries Research*, *52*(5), 406–419. https://doi.org/10.1159/000486429

El Meligy, O. A. E. S., Alamoudi, N. M., Eldin Ibrahim, S. T., Felemban, O. M., & Al-Tuwirqi, A. A. (2021). Effect of resin infiltration application on early proximal caries lesions in vitro. *Journal of Dental Sciences*, *16*(1), 296–303. https://doi.org/10.1016/j.jds.2020.04.005

El Mourad, A. M. (2018). Assessment of Bonding Effectiveness of Adhesive Materials to Tooth Structure using Bond Strength Test Methods: A Review of Literature. *The Open Dentistry Journal*, *12*, 664–678. https://doi.org/10.2174/1745017901814010664

Enan, E., Tawfik, M., Ali, A., & Anan, A. (2018). Surface properties of resin-infiltrated incipient enamel lesions after aging under thermal stresses. *Egyptian Dental Journal*, *64*(3), 2833–2840. https://doi.org/10.21608/edj.2018.77339

Farooq, I., & Bugshan, A. (2021). The role of salivary contents and modern technologies in the remineralization of dental enamel: A narrative review. *F1000Research*, *9*, 171. https://doi.org/10.12688/f1000research.22499.3

Feagin, F., Koulourides, T., & Pigman, W. (1969). The characterization of enamel surface demineralization, remineralization, and associated hardness changes in human and bovine material. *Archives of Oral Biology*, *14*(12), 1407–1417. https://doi.org/10.1016/0003-9969(69)90258-1

Fehrenbach, M. J., & Popowics, T. (2016). *Illustrated dental embryology, histology, and anatomy* (4. ed). Elsevier.

Fejerskov, O. (2004). Changing paradigms in concepts on dental caries: Consequences for oral health care. *Caries Research*, *38*(3), 182–191. https://doi.org/10.1159/000077753

Furuse, A. Y., Fernandes Neto, C., Guimarães, G. M. de F., Terrabuio, B. R., Rizzante, F. A. P., & Wang, L. (2020). Color evaluation of white spot lesions treated with resin infiltration after water or grape juice storage. *Brazilian Journal of Oral Sciences*, *19*, e201674. https://doi.org/10.20396/bjos.v19i0.8658336

Gamber, D. C. F. (2010). *Icon. DMG - High quality dental materials for dentists and dental technicians*. Icon. DMG America. https://www.dmg-america.com/en/products/product/icon/- consulted in 27.06.2021

Gil-Bona, A., & Bidlack, F. B. (2020). Tooth Enamel and Its Dynamic Protein Matrix. *International Journal of Molecular Sciences*, *21*(12), 4458. https://doi.org/10.3390/ijms21124458

Gomes, D., Santos, A. M. C., Neves, G. A., & Menezes, R. R. (2019). A brief review on hydroxyapatite production and use in biomedicine. *Cerâmica*, *65*(374), 282–302. https://doi.org/10.1590/0366-69132019653742706

Gulec, A., & Goymen, M. (2019). Assessment of the resin infiltration and CPP-ACP applications before orthodontic brackets bonding. *Dental Materials Journal*, *38*(5), 854–860. https://doi.org/10.4012/dmj.2019-021

Hara, A. T., Queiroz, C. S., Paes Leme, A. F., Serra, M. C., & Cury, J. A. (2003). Caries progression and inhibition in human and bovine root dentine in situ. *Caries Research*, *37*(5), 339–344. https://doi.org/10.1159/000072165

Health Metrics and Evaluation (IHME). (2017). *Global Burden of Disease Study 2017*. United States of America.

Höchli, D., Hersberger-Zurfluh, M., Papageorgiou, S. N., & Eliades, T. (2017). Interventions for orthodontically induced white spot lesions: A systematic review and meta-analysis. *European Journal of Orthodontics*, *39*(2), 122–133. https://doi.org/10.1093/ejo/cjw065

Hogan, R., Pretty, I. A., & Ellwood, R. P. (2019b). Fibre-Optic Transillumination: FOTI. *Detection and Assessment of Dental Caries*, 139–150. https://doi.org/10.1007/978-3-030-16967-1_14

Horst, J. A., Tanzer, J. M., & Milgrom, P. M. (2018). Fluorides and Other Preventive Strategies for Tooth Decay. *Dental Clinics of North America*, *62*(2), 207–234. https://doi.org/10.1016/j.cden.2017.11.003

Ismail, A. I., Pitts, N. B., & Tellez, M. (2015). The International Caries Classification and Management System (ICCMS^{TM}) An Example of a Caries Management Pathway. *BMC Oral Health*, *15*(Suppl 1), S9. https://doi.org/10.1186/1472-6831-15-S1-S9

Khoroushi, M., & Kachuie, M. (2017). Prevention and Treatment of White Spot Lesions in Orthodontic Patients. *Contemporary Clinical Dentistry*, *8*(1), 11–19. https://doi.org/10.4103/ccd.ccd_216_17

Kielbassa, A. M., Ulrich, I., Schmidl, R., Schüller, C., Frank, W., & Werth, V. D. (2017). Resin infiltration of deproteinised natural occlusal subsurface lesions improves initial quality of fissure sealing. *International Journal of Oral Science*, *9*(2), 117–124. https://doi.org/10.1038/ijos.2017.15

Kim, S., Kim, E.-Y., Jeong, T.-S., & Kim, J.-W. (2011). The evaluation of resin infiltration for masking labial enamel white spot lesions. *International Journal of Paediatric Dentistry*, *21*(4), 241–248. https://doi.org/10.1111/j.1365-263X.2011.01126.x

Klimuszko, E., Orywal, K., Sierpinska, T., Sidun, J., & Golebiewska, M. (2018). Evaluation of calcium and magnesium contents in tooth enamel without any pathological changes: in vitro preliminary study. *Odontology*, *106*(4), 369–376. https://doi.org/10.1007/s10266-018-0353-6

Kumar, H., Palamara, J. E. A., Burrow, M. F., & Manton, D. J. (2017). An investigation into the effect of a resin infiltrant on the micromechanical properties of hypomineralised enamel. *International Journal of Paediatric Dentistry*, *27*(5), 399–411. https://doi.org/10.1111/ipd.12272

Lacruz, R. S., Habelitz, S., Wright, J. T., & Paine, M. L. (2017). Dental Enamel Formation and Implications for Oral Health and Disease. *Physiological Reviews*, *97*(3), 939–993. https://doi.org/10.1152/physrev.00030.2016

Lamont, R. J., Koo, H., & Hajishengallis, G. (2018). The oral microbiota: Dynamic communities and host interactions. *Nature reviews. Microbiology*, *16*(12), 745–759. https://doi.org/10.1038/s41579-018-0089-x

Lausch, J., Paris, S., Selje, T., Dörfer, C. E., & Meyer-Lueckel, H. (2015). Resin infiltration of fissure caries with various techniques of pretreatment in vitro. *Caries Research*, *49*(1), 50–55. https://doi.org/10.1159/000366082

Lawson, N. (2020). Resin Infiltration as Treatment for an Anterior Tooth Discoloration of Developmental Origin. *Oral Health Group*. https://doi.org/10.31525/ct1-nct03841370

Macey, R., Walsh, T., Riley, P., Glenny, A.-M., Worthington, H. V., O'Malley, L., Clarkson, J. E., & Ricketts, D. (2021). Visual or visual-tactile examination to detect and inform the diagnosis of enamel caries. *Cochrane Database of Systematic Reviews*, *2021*(6). https://doi.org/10.1002/14651858.CD014546

Machiulskiene, V., Campus, G., Carvalho, J. C., Dige, I., Ekstrand, K. R., Jablonski-Momeni, A., Maltz, M., Manton, D. J., Martignon, S., Martinez-Mier, E. A., Pitts, N. B., Schulte, A. G., Splieth, C. H., Tenuta, L. M. A., Ferreira Zandona, A., & Nyvad, B. (2020). Terminology of Dental Caries and Dental Caries Management: Consensus Report of a Workshop Organized by ORCA and Cariology Research Group of IADR. *Caries Research*, *54*(1), 7–14. https://doi.org/10.1159/000503309

Macri, D., & Chitlall, A. (2017). Caries Classification. *Publications and Research*. https://doi.org/10.1186/1472-6831-15-s1-s9

Manoharan, V., Arun Kumar, S., Arumugam, S. B., Anand, V., Krishnamoorthy, S., & Methippara, J. J. (2019). Is Resin Infiltration a Microinvasive Approach to White Lesions of Calcified Tooth Structures?: A Systemic Review. *International Journal of Clinical Pediatric Dentistry*, *12*(1), 53–58. https://doi.org/10.5005/jp-journals-10005-1579

Mellberg, J. R. (1992). Hard-tissue substrates for evaluation of cariogenic and anti-cariogenic activity in situ. *Journal of Dental Research*, *71 Spec No*, 913–919. https://doi.org/10.1177/002203459207100S25

Meyer-Lueckel, H., Chatzidakis, A., Naumann, M., Dörfer, C. E., & Paris, S. (2011). Influence of application time on penetration of an infiltrant into natural enamel caries. *Journal of Dentistry*, *39*(7), 465–469. https://doi.org/10.1016/j.jdent.2011.04.003

Min, J. H., Inaba, D., Kwon, H. K., Chung, J. H., & Kim, B. I. (2015). Evaluation of penetration effect of resin infiltrant using optical coherence tomography. *Journal of Dentistry*, *43*(6), 720–725. https://doi.org/10.1016/j.jdent.2015.03.006

Montasser, M. A., El-Wassefy, N. A., & Taha, M. (2015). In vitro study of the potential protection of sound enamel against demineralization. *Progress in Orthodontics*, *16*, 12. https://doi.org/10.1186/s40510-015-0080-2

Nanci, A., & TenCate, A. R. (2018). *Ten Cate's oral histology: Development, structure, and function* (9th edition). Elsevier.

Nóbrega, A. V. D., Moura, L. D. F. A. D. D., Andrade, N. S., Lima, C. C. B., Dourado, D. G., & Lima, M. D. D. M. D. (2019). Impacto da cárie dentária na qualidade de vida de pré-escolares mensurado pelo questionário PedsQL. *Ciência & Saúde Coletiva*, *24*(11), 4031–4042. https://doi.org/10.1590/1413-812320182411.04712018

Nyvad, B., & Takahashi, N. (2020). Integrated hypothesis of dental caries and periodontal diseases. *Journal of Oral Microbiology*, *12*(1), 1710953. https://doi.org/10.1080/20002297.2019.1710953

Pachori, A., Kambalimath, H., Bhambhani, G., & Malhotra, G. (2018). Evaluation of Changes in Salivary pH after Intake of Different Eatables and Beverages in Children at Different Time Intervals. *International Journal of Clinical Pediatric Dentistry*, *11*(3), 177–182. https://doi.org/10.5005/jp-journals-10005-1507

Paiva, M. A. A. de, MangueiraLeite, D. F. B., Farias, I. A. P., Costa, A. de P. C., & Sampaio, F. C. (2017). Dental Anatomical Features and Caries: A Relationship to be Investigated. Em *Dental Anatomy*. IntechOpen. https://doi.org/10.5772/intechopen.71337

Paris, S., Schwendicke, F., Keltsch, J., Dörfer, C., & Meyer-Lueckel, H. (2013). Masking of white spot lesions by resin infiltration in vitro. *Journal of Dentistry*, *41*, e28–e34. https://doi.org/10.1016/j.jdent.2013.04.003

Paris, S., Schwendicke, F., Seddig, S., Müller, W.-D., Dörfer, C., & Meyer-Lueckel, H. (2013). Micro-hardness and mineral loss of enamel lesions after infiltration with various resins: Influence of infiltrant composition and application frequency in vitro. *Journal of Dentistry*, *41*(6), 543–548. https://doi.org/10.1016/j.jdent.2013.03.006

Paula, A. B. P., Fernandes, A. R., Coelho, A. S., Marto, C. M., Ferreira, M. M., Caramelo, F., do Vale, F., & Carrilho, E. (2017). Therapies for White Spot Lesions—A Systematic Review. *Journal of Evidence Based Dental Practice*, *17*(1), 23–38. https://doi.org/10.1016/j.jebdp.2016.10.003

Philip, N. (2019). State of the Art Enamel Remineralization Systems: The Next Frontier in Caries Management. *Caries Research*, *53*(3), 284–295. https://doi.org/10.1159/000493031

Pitts. (2004). Modern concepts of caries measurement. *Journal of Dental Research*, *83 Spec No C*, C43-47. https://doi.org/10.1177/154405910408301s09

Pitts, N., & Ekstrand, K. (2013). International Caries Detection and Assessment System (ICDAS) and its International Caries Classification and Management System (ICCMS)—Methods for staging of the caries process and enabling dentists to manage caries. *Community Dentistry and Oral Epidemiology*, *41*. https://doi.org/10.1111/cdoe.12025

Pitts, N., Zero, D., Marsh, P., Ekstrand, K., Weintraub, J., Gomez, F., Tagami, J., Twetman, S., Tsakos, G., & Ismail, A. (2017). Dental caries. *Nature Reviews Disease Primers*, *3*. https://doi.org/10.1038/nrdp.2017.30

Rasmussen, S. T. (1996). Analysis of dental shear bond strength tests, shear or tensile? *International Journal of Adhesion and Adhesives*, *16*(3), 147–154. https://doi.org/10.1016/0143-7496(95)00029-1

Rathee, M., & Jain, P. (2021). Review of the Embryology of the Teeth. *Neurographics*, *8*(5), 369–393. https://doi.org/10.3174/ng.1600049/

Rathi, N., Baid, R., Baliga, S., & Thosar, N. (2017). Comparative evaluation of Nano-Hydroxyapatite preparation and Calcium Sucrose Phosphate on microhardness of deciduous teeth after iron drop exposure—An in-vitro study. *Journal of Clinical and Experimental Dentistry*, *9*(4), e579–e583. https://doi.org/10.4317/jced.53677

Robinson, C., Shore, R., Brookes, S., Strafford, S., Wood, S., & Kirkham, J. (2000). The Chemistry of Enamel Caries. *Critical Reviews in Oral Biology & Medicine*, *11*(4), 481–495. https://doi.org/10.1177/10454411000110040601

Rüttermann, S., Braun, A., & Janda, R. (2013). Shear bond strength and fracture analysis of human vs. Bovine teeth. *PloS One*, *8*(3), e59181. https://doi.org/10.1371/journal.pone.0059181

Sadyrin, E., Swain, M., Mitrin, B., Rzhepakovsky, I., Nikolaev, A., Irkha, V., Yogina, D., Lyanguzov, N., Maksyukov, S., & Aizikovich, S. (2020). Characterization of Enamel and Dentine about a White Spot Lesion: Mechanical Properties, Mineral Density, Microstructure and Molecular Composition. *Nanomaterials*, *10*(9), 1889. https://doi.org/10.3390/nano10091889

Sampson, V., & Sampson, A. (2020). Diagnosis and treatment options for anterior white spot lesions. *British Dental Journal*, *229*(6), 348–352. https://doi.org/10.1038/s41415-020-2057-x

Schulz, A., Lang, R., Behr, J., Hertel, S., Reich, M., Kümmerer, K., Hannig, M., Hannig, C., & Hofmann, T. (2020). Targeted metabolomics of pellicle and saliva in children with different caries activity. *Scientific Reports*, *10*(1), 697. https://doi.org/10.1038/s41598-020-57531-8

Schwendicke, F., Frencken, J. E., Bjørndal, L., Maltz, M., Manton, D. J., Ricketts, D., Van Landuyt, K., Banerjee, A., Campus, G., Doméjean, S., Fontana, M., Leal, S., Lo, E., Machiulskiene, V., Schulte, A., Splieth, C., Zandona, A. F., & Innes, N. P. T. (2016). Managing Carious Lesions: Consensus Recommendations on Carious Tissue Removal. *Advances in Dental Research*, *28*(2), 58–67. https://doi.org/10.1177/0022034516639271

Setiawan, I., Sagita, A., Suryatmojo, I., Herawati, D. M. D., Sufiawati, I., & Widyaputra, S. (2021). Correlation between carbohydrate intake and dental caries in obese individuals. *Dental Journal (Majalah Kedokteran Gigi)*, *54*(1), 46. https://doi.org/10.20473/j.djmkg.v54.i1.p46-51

Srilatha, A., Doshi, D., Kulkarni, S., & Reddy, M. (2019). Conventional diagnostic aids in dental caries. *Journal of Global Oral Health*, *2*, 53–58. https://doi.org/10.25259/JGOH_42_2019

Swamy, D. F., Barretto, E. S., Mallikarjun, S. B., & Dessai, S. S. R. (2017). In vitro Evaluation of Resin Infiltrant Penetration into White Spot Lesions of Deciduous Molars. *Journal of Clinical and Diagnostic Research : JCDR*, *11*(9), ZC71–ZC74. https://doi.org/10.7860/JCDR/2017/28146.10599

Taher, N. M., Alkhamis, H. A., & Dowaidi, S. M. (2012). The influence of resin infiltration system on enamel microhardness and surface roughness: An in vitro study. *The Saudi Dental Journal*, *24*(2), 79–84. https://doi.org/10.1016/j.sdentj.2011.10.003

Urquhart, O., Tampi, M. P., Pilcher, L., Slayton, R. L., Araujo, M. W. B., Fontana, M., Guzmán-Armstrong, S., Nascimento, M. M., Nový, B. B., Tinanoff, N., Weyant, R. J., Wolff, M. S., Young, D. A., Zero, D. T., Brignardello-Petersen, R., Banfield, L., Parikh, A., Joshi, G., & Carrasco-Labra, A. (2019). Nonrestorative Treatments for Caries: Systematic Review and Network Meta-analysis. *Journal of Dental Research*, *98*(1), 14–26. https://doi.org/10.1177/0022034518800014

Velİ, I., Akin, M., Baka, Z. M., & Uysal, T. (2016). Effects of different pre-treatment methods on the shear bond strength of orthodontic brackets to demineralized enamel. *Acta Odontologica Scandinavica*, *74*(1), 7–13. https://doi.org/10.3109/00016357.2014.982703

Wong, A., Subar, P. E., & Young, D. A. (2017). Dental Caries. *Advances in Pediatrics*, *64*(1), 307–330. https://doi.org/10.1016/j.yapd.2017.03.011

Yassen, G. H., Platt, J. A., & Hara, A. T. (2011a). Bovine teeth as substitute for human teeth in dental research: A review of literature. *Journal of Oral Science*, *53*(3), 273–282. https://doi.org/10.2334/josnusd.53.273

Yassen, G. H., Platt, J. A., & Hara, A. T. (2011b). Bovine teeth as substitute for human teeth in dental research: A review of literature. *Journal of Oral Science*, *53*(3), 273–282. https://doi.org/10.2334/josnusd.53.273

Young, D. A., Nový, B. B., Zeller, G. G., Hale, R., Hart, T. C., Truelove, E. L., Ekstrand, K. R., Featherstone, J. D. B., Fontana, M., Ismail, A., Kuehne, J., Longbottom, C., Pitts, N., Sarrett, D. C., Wright, T., Mark, A. M., & Beltran-Aguilar, E. (2015). The American Dental Association Caries Classification System for Clinical Practice: A report of the American Dental Association Council on Scientific Affairs. *The Journal of the American Dental Association*, *146*(2), 79–86. https://doi.org/10.1016/j.adaj.2014.11.018

Zabokova Bilbilova, E. (2021). Dietary Factors, Salivary Parameters, and Dental Caries. *Dental Caries*. Published. https://doi.org/10.5772/intechopen.92392

Zakizade, M., Davoudi, A., Akhavan, A., & Shirban, F. (2020). Effect of Resin Infiltration Technique on Improving Surface Hardness of Enamel Lesions: A Systematic Review and Meta-analysis. *Journal of Evidence Based Dental Practice*, *20*(2), 101405. https://doi.org/10.1016/j.jebdp.2020.101405

5. Attachments

Appendix S1. PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	3-4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4-9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	3-4
RESULTS			

Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	4-9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	12-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

NA – Not applicable

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix S2. List of potentially relevant studies not included in the systematic review, along with the reasons for exclusion.

N	Year	Reference	Exclusion reason
1	1976	Robinson C, Hallsworth AS, Weatherell JA, Künzel W. Arrest and Control of Carious Lesions: A Study Based on Preliminary Experiments with Resorcinol-Formaldehyde Resin. Journal of Dental Research. 1976;55(5):812-818. doi:10.1177/00220345760550051601	Data presented in thresholds
2	2009	Kugel G, Arsenault P, Papas A. Treatment modalities for cariess management, including a new resin infiltration system. Compend Contin Educ Dent. 2009 Oct;30 Spec No 3:1-10; quiz 11-2. PMID: 19894293.	Unable to access
3	2010	Mueller J1, Yang F, Neumann K, K. A. (n.d.). Effects of Different Finishing Procedures and Materials on Surface Roughness of Infiltrated Subsurface Bovine Enamel Lesions. Quintessence Int 42, 42(2):, 135-147.	Thesis
4	2011	Mueller J, Yang F, Neumann K, Kielbassa AM. Surface tridimensional topography analysis of materials and finishing procedures after resinous infiltration of subsurface bovine enamel lesions. Quintessence Int. 2011 Feb;42(2):135-47. PMID: 21359248.	Unable to access

5	2011	Wiegand A, Stawarczyk B, Kolakovic M, Hämmerle CH, Attin T, Schmidlin PR. Adhesive performance of a cariess infiltrant on sound and demineralised enamel. J Dent. 2011 Feb;39(2):117-21. doi: 10.1016/j.jdent.2010.10.010. Epub 2010 Oct 17. PMID: 20959133.	Unable to access
6	2011	Bidarkar, Atul. "In vitro prevention of secondary demineralization by Icon (infiltration concept)." MS (Master of Science) thesis, University of Iowa, 2011. https://doi.org/10.17077/etd.1u6479b8	Thesis
7	2012	Naidu E, Stawarczyk B, Tawakoli PN, Attin R, Attin T, Wiegand A. Shear bond strength of orthodontic resins after cariess infiltrant preconditioning. Angle Orthod. 2013 Mar;83(2):306-12. doi: 10.2319/052112-409.1. Epub 2012 Aug 22. PMID: 22908947.	Data presented in thresholds
8	2012	Jia L, Stawarczyk B, Schmidlin PR, Attin T, Wiegand A. Effect of cariess infiltrant application on shear bond strength of different adhesive systems to sound and demineralized enamel. J Adhes Dent. 2012 Dec;14(6):569-74. doi: 10.3290/j.jad.a25685. PMID: 22724105.	Incomplete data
9	2012	Yang F, Mueller J, Kielbassa AM. Surface substance loss of subsurface bovine enamel lesions after different steps of the resinous infiltration technique: a 3D topography analysis. Odontology. 2012 Jul;100(2):172-80. doi: 10.1007/s10266-011-0031-4. Epub 2011 Jun 16. PMID: 21678019.	Incomplete data
10	2012	Bailey, Melissa Wu, "Effectiveness of Resin Infiltration and Mi Paste Cpp-Acp in Masking White Spot Lesions" (2012). Loma Linda University Electronic Theses, Dissertations & Projects. 72. http://scholarsrepository.llu.edu/etd/72	Incomplete data
11	2012	Lincoln, T. A. (2012). The Surface Properties of Teeth Treated with Resin Infiltration or Amorphous Calcium Phosphate. May.	Thesis
12	2012	Hanashiro, F. S. (2012). Avaliação in vitro das superfícies vestibulares desmineralizadas e restauradas com resina infiltrante [Universidade de São Paulo]. https://doi.org/10.11606/T.23.2012.tde-13042013-120154	Thesis
13	2012	De Araújo, Larissa Sgarbosa Napoleão; Gaglianone, Lívia Aguilera; Marchi, Giselle Maria; Aguiar, Flávio Henrique Baggio; Araújo, Giovana Spagnolo Albamonte; Puppin-Rontani, R. M. (2012). Tratamento de lesão cariosa proximal através da infiltração com resina de baixa viscosidade. Revista Dental Press de Estética . Jan-Mar2012, Vol. 9 Issue 1, P76-84. 9p. 13 Color Photographs, 4 Black and White Photographs.	Unable to acess
14	2013	Araújo GS, Sfalcin RA, Araújo TG, Alonso RC, Puppin-Rontani RM. Evaluation of polymerization characteristics and penetration into enamel cariess lesions of experimental infiltrants. J Dent. 2013 Nov;41(11):1014-9. doi: 10.1016/j.jdent.2013.08.019. Epub 2013 Sep 1. PMID: 24004967.	Incomplete data
15	2013	Yuan H, Li J, Chen L, Cheng L, Cannon RD, Mei L. Esthetic comparison of white-spot lesion treatment modalities using spectrometry and fluorescence. Angle Orthod. 2014 Mar;84(2):343-9. doi: 10.2319/032113-232.1. Epub 2013 Aug 28. PMID: 23984991.	Data presented in thresholds
16	2013	Taher NM. Atomic force microscopy and tridimensional topography analysis of human enamel after resinous infiltration and storage in water. Saudi Med J. 2013 Apr;34(4):408-14. Erratum in: Saudi Med J. 2015 Jul;36(7):885. PMID: 23552595.	Unsuitable control group
17	2013	Yetkiner, E., Özcan, M., Wegehaupt, F. J., Wiegand, A., Eden, E., & Attin, T. (2013). Effect of a low-viscosity adhesive resin on the adhesion of metal brackets to enamel etched with hydrochloric or phosphoric acid combined with conventional adhesives. The Journal of Adhesive Dentistry, 15(6), 575-57581. https://doi.org/10.3290/j.jad.a29607	Unsuitable control group
18	2014	Tostes MA, Santos E Jr, Camargo SA Jr. Effect of resin infiltration on the nanomechanical properties of demineralized bovine enamel. Indian J Dent. 2014 Jul;5(3):116-22. doi: 10.4103/0975-962X.140819. PMID: 25565739; PMCID: PMC4213871.	Data presented in thresholds
19	2014	Borges AB. The concept of resin infiltration technique and its multiple applications. J Contemp Dent Pract. 2014 May 1;15(3):i. PMID: 25307827.	Unable to access
20	2014	Resin infiltration effects in a cariess-active environment. J Calif Dent Assoc. 2014 Jun;42(6):372. PMID: 25080756.	Unable to access
21	2014	Subramaniam P, Girish Babu KL, Lakhotia D. Evaluation of penetration depth of a commercially available resin infiltrate into artificially created enamel lesions: An in vitro study. J Conserv Dent. 2014 Mar;17(2):146-9. doi: 10.4103/0972-0707.128054. PMID: 24778511; PMCID: PMC4001271.	Incomplete data

22	2014	Chay PL, Manton DJ, Palamara JE. The effect of resin infiltration and oxidative pre-treatment on microshear bond strength of resin composite to hypomineralised enamel. Int J Paediatr Dent. 2014 Jul;24(4):252-67. doi: 10.1111/ipd.12069. Epub 2013 Oct 17. PMID: 24134408.	Unsuitable control group
23	2014	Crombie F, Manton D, Palamara J, Reynolds E. Resin infiltration of developmentally hypomineralised enamel. Int J Paediatr Dent. 2014 Jan;24(1):51-5. doi: 10.1111/ipd.12025. Epub 2013 Feb 15. PMID: 23410530.	Unsuitable control group
24	2014	Ou XY, Zhao YH, Ci XK, Zeng LW. Masking white spots of enamel in cariess lesions with a non-invasive infiltration technique in vitro. Genet Mol Res. 2014 Aug 29;13(3):6912-9. doi: 10.4238/2014.August.29.14. PMID: 25177972.	Incomplete data
25	2014	Arnold WH, Bachstaedter L, Benz K, Naumova EA. Resin infiltration into differentially extended experimental carious lesions. Open Dent J. 2014;8:251-256. Published 2014 Dec 29. doi:10.2174/1874210601408010251	Extension of the lesions- Not Enought Studies
26	2014	Alexandru Ogodescu, Adrian Manescu, Ana Emilia Ogodescu, Alessandra Giuliani, Carmen Todea, "Micro-CT application for infiltration technology in paedodontics and orthodontics," Proc. SPIE 8925, Fifth International Conference on Lasers in Medicine: Biotechnologies Integrated in Daily Medicine, 892508 (14 January 2014); https://doi.org/10.1117/12.2044116	Data presented in thresholds
27	2014	Munhoz, T. (2014). Effect of bonding protocol on shear bond strength of orthodontic brackets: An in vitro study. Revista Materia, 19(3), 212-217. https://doi.org/10.1590/S1517-70762014000300004	Unsuitable control group
28	2014	MACIEL, Patricia Pereira. Avaliação da hibridização do esmalte dentário através de fluxo eletrocinético. 2014. 84 f. Dissertação (Mestrado em Odontologia) - Universidade Federal da Paraíba, João Pessoa, 2014.	Thesis
29	2014	Pérez, R., Quijada, V., & Uribe, S. (2014). Revista Clínica de Periodoncia , Implantología y Rehabilitación Oral Confocal laser microscopy analysis of resin infiltration in fluorotic teeth. 7(2), 53-58.	Unsuitable control group
30	2015	Montasser MA, El-Wassefy NA, Taha M. In vitro study of the potential protection of sound enamel against demineralization. Prog Orthod. 2015;16:12. doi: 10.1186/s40510-015-0080-2. Epub 2015 May 22. PMID: 26061985; PMCID: PMC4440871.	Data presented in thresholds
31	2015	Natarajan AK, Fraser SJ, Swain MV, Drummond BK, Gordon KC. Raman spectroscopic characterisation of resin-infiltrated hypomineralised enamel. Anal Bioanal Chem. 2015 Jul;407(19):5661-71. doi: 10.1007/s00216-015-8742-y. Epub 2015 May 13. PMID: 25967150.	Data presented in thresholds
32	2015	Skucha-Nowak M. Attempt to assess the infiltration of enamel made with experimental preparation using a scanning electron microscope. Open Med (Wars). 2015 Apr 3;10(1):238-248. doi: 10.1515/med-2015-0036. PMID: 28352701; PMCID: PMC5152982.	Data presented in thresholds
33	2015	Askar H, Lausch J, Dörfer CE, Meyer-Lueckel H, Paris S. Penetration of micro-filled infiltrant resins into artificial cariess lesions. J Dent. 2015 Jul;43(7):832-8. doi: 10.1016/j.jdent.2015.03.002. Epub 2015 Mar 10. PMID: 25769265.	Unsuitable control group
34	2015	Ulrich I, Mueller J, Wolgin M, Frank W, Kielbassa AM. Tridimensional surface roughness analysis after resin infiltration of (deproteinized) natural subsurface carious lesions. Clin Oral Investig. 2015 Jul;19(6):1473-83. doi: 10.1007/s00784-014-1372-5. Epub 2014 Dec 9. PMID: 25483122.	Different type of analyze
35	2015	Mews L, Kern M, Ciesielski R, Fischer-Brandies H, Koos B. Shear bond strength of orthodontic brackets to enamel after application of a cariess infiltrant. Angle Orthod. 2015 Jul;85(4):645-50. doi: 10.2319/013014-82.1. Epub 2014 Aug 26. PMID: 25157972.	Unsuitable control group
36	2015	Mugisa, I. (2015). Microhardness and cariess resistance of an infiltrant resin in a novel artificial mouth. August 2010.	Thesis
37	2015	Gabrielle, T., & Ara, F. (2015). "Influência de solventes nas propriedades físico -químicas de infiltrantes resinosos experimentais" " Influence of solvents on the physicochemical properties of experimental resin infiltrants."	Thesis
38	2015	Freitas, M. C. C. de A. (2015). Efeito de um infiltrante resinoso no tratamento de lesões de mancha branca: análise in vitro e in situ [Universidade de São Paulo]. https://doi.org/10.11606/T.25.2015.tde-28102015-092917	Thesis

39	2015	Tereza, G. P. G. (2015). Influência da remoção do excesso de materiais adesivos sobre o esmalte erodido, na resistência a desafio erosivo in vitro [Universidade de São Paulo]. https://doi.org/10.11606/D.25.2015.tde-25112015-094345	Thesis
40	2016	Farias de Lacerda AJ, Ferreira Zanatta R, Crispim B, Borges AB, Gomes Torres CR, Tay FR, Pucci CR. Influence of de/remineralization of enamel on the tensile bond strength of etch-and-rinse and self-etching adhesives. Am J Dent. 2016 Oct;29(5):289-293. PMID: 29178743.	Unable to access
41	2016	Skucha-Nowak M, Machorowska-Pieniążek A, Tanasiewicz M. Assessing the Penetrating Abilities of Experimental Preparation with Dental Infiltrant Features Using Optical Microscope: Preliminary Study. Adv Clin Exp Med. 2016 Sep-Oct;25(5):961-969. doi: 10.17219/acem/63007. PMID: 28028962.	Incomplete data
42	2016	Inagaki LT, Alonso RC, Araújo GA, de Souza-Junior EJ, Anibal PC, Höfling JF, Pascon FM, Puppin-Rontani RM. Effect of monomer blend and chlorhexidine-adding on physical, mechanical and biological properties of experimental infiltrants. Dent Mater. 2016 Dec;32(12):e307-e313. doi: 10.1016/j.dental.2016.09.028. Epub 2016 Oct 28. PMID: 28327302.	Unsuitable control group
43	2016	Ionta, F. Q., Boteon, A. P., Moretto, M. J., Júnior, O. B., Honório, H. M., Silva, T. C., Wang, L., & Rios, D. (2016). Penetration of resin-based materials into initial erosion lesion: A confocal microscopic study. Microscopy Research and Technique, 79(2), 72-80. https://doi.org/10.1002/jemt.22607	Unsuitable control group
44	2016	Al-Dabagh, D. J. N., & Balasim, M. (2016). The Influence of Cariess Infiltrant Combined with and without Conventional Adhesives on Sealing of Sound Enamel : In Vitro Study. Journal of Baghdad College of Dentistry, 28(2), 119-125. https://doi.org/10.12816/0028233	Unable to access
45	2016	Commander, L., Corps, D., States, U., & Health, P. (2016). كتابة.Pdf. June.	Thesis
46	2016	Dos Reis, B. C., Lacerda, A. J. F. de, Canepele, T. M. F., Borges, A. B., Yui, K. C. K., Torres, C. R. G., & Pucci, C. R. (2016). Evaluation of bond strength of composite resin to enamel demineralized, exposed to remineralization and subjected to cariess infiltration. Brazilian Dental Science, 19(1), 48. https://doi.org/10.14295/bds.2016.v19i1.1212	Unsuitable control group
47	2016	Vianna, Julia Sotero; Marquezan, Mariana; Thiago Chon Leon Lau; San'Anna, E. F. (2016). Colagem de braquetes em lesões de mancha branca pré-tratadas por meio de dois métodos. Dental Press Journal of Orthodontics . Mar/Apr2016, Vol. 21 Issue 2, P39-44. 6p.	Unable to acess
48	2016	Elhiny, O. A., Elattar, H. S., & Salem, G. A. (2016). CODEN (USA): PCHHAX. 8(18), 100-106.	Unsuitable control group
49	2016	Elhiny, O., & Salem, G. (2016). Will Resin Infiltration With Icon Prevent Enamel Demineralization Around Orthodontic Brackets? International Journal of Advanced Research, 4(9), 1661-1667. https://doi.org/10.21474/ijar01/1626	Unsuitable control group
50	2016	Arnold WH, Meyer AK, Naumova EA. Surface Roughness of Initial Enamel Cariess Lesions in Human Teeth After Resin Infiltration. Open Dent J. 2016;10:505-515. Published 2016 Sep 23. doi:10.2174/1874210601610010505	Different type of analyze
51	2017	Piątek-Jakubek K, Nowak J, Bołtacz-Rzepkowska E. Influence of infiltration technique and selected demineralization methods on the roughness of demineralized enamel: An in vitro study. Adv Clin Exp Med. 2017 Nov;26(8):1179-1188. doi: 10.17219/acem/66209. PMID: 29264873.	Unsuitable control group
52	2017	Swamy DF, Barretto ES, Mallikarjun SB, Dessai SSR. In vitro Evaluation of Resin Infiltrant Penetration into White Spot Lesions of Deciduous Molars. J Clin Diagn Res. 2017 Sep;11(9):ZC71-ZC74. doi: 10.7860/JCDR/2017/28146.10599. Epub 2017 Sep 1. PMID: 29207838; PMCID: PMC5713860.	Unsuitable control group
53	2017	Schneider H, Park KJ, Rueger C, Ziebolz D, Krause F, Haak R. Imaging resin infiltration into non-cavitated carious lesions by optical coherence tomography. J Dent. 2017 May;60:94-98. doi: 10.1016/j.jdent.2017.03.004. Epub 2017 Mar 10. PMID: 28286174.	Data presented in thresholds
54	2017	Lausch J, Askar H, Paris S, Meyer-Lueckel H. Micro-filled resin infiltration of fissure cariess lesions in vitro. J Dent. 2017 Feb;57:73-76. doi: 10.1016/j.jdent.2016.12.010. Epub 2016 Dec 30. PMID: 28043846.	Incomplete data

55	2017	Sfalcin RA, Correr AB, Morbidelli LR, Araújo TGF, Feitosa VP, Correr-Sobrinho L, Watson TF, Sauro S. Influence of bioactive particles on the chemical-mechanical properties of experimental enamel resin infiltrants. Clin Oral Investig. 2017 Jul;21(6):2143-2151. doi: 10.1007/s00784-016-2005-y. Epub 2016 Nov 12. PMID: 27838844.	Unsuitable control group
56	2017	Zamorano, X., Valenzuela, V., Daniels, A. and Iturain, A. (2017) SEM Comparison of Penetration in Artificial White Spots Lesion between an Infiltrant Resin and Two Adhesive Systems. Open Journal of Stomatology, 7, 147-157. https://doi.org/10.4236/ojst.2017.73010	Unsuitable control group
57	2017	Easterly, D. E. (2017). An Investigation of Surface Characteristics of Enamel Treated An Investigation of Surface Characteristics of Enamel Treated with Infiltrative Resin: A Scanning Electron Microscopy Study with Infiltrative Resin: A Scanning Electron Microscopy Study. https://scholarscompass.vcu.edu/etd	Thesis
58	2017	RIBEIRO, Mariana Dias Flor. Avaliação das propriedades físicas e antibacterianas de infiltrantes experimentais contendo sal de iodônio e quitosana. 2017. 1 recurso online (56 p.). Dissertação (mestrado) - Universidade Estadual de Campinas, Faculdade de Odontologia de Piracicaba, Piracicaba, SP. Disponível em: <http://www.repositorio.unicamp.br/handle/REPOSIP/331395>. Acesso em: 1 set. 2018.	Thesis
59	2017	SOUZA, Caroline Mathias Carvalho de. Influência da incorporação de um sal de ônio sobre propriedades físicas de infiltrantes experimentais contendo diferentes diluentes. 2017. 1 recurso online (61 p.). Dissertação (mestrado) - Universidade Estadual de Campinas, Faculdade de Odontologia de Piracicaba, Piracicaba, SP. Disponível em: <http://www.repositorio.unicamp.br/handle/REPOSIP/331942>. Acesso em: 1 set. 2018.	Thesis
60	2017	Hariyati, 2017. (2017). Инновационные подходы к обеспечению качества в здравоохраненииNo Title. Вестник Росздравнадзора, 6, 5-9.	Thesis
61	2018	Freitas MCCA, Nunes LV, Comar LP, Rios D, Magalhães AC, Honório HM, Wang L. In vitro effect of a resin infiltrant on different artificial cariess-like enamel lesions. Arch Oral Biol. 2018 Nov;95:118-124. doi: 10.1016/j.archoralbio.2018.07.011. Epub 2018 Aug 6. PMID: 30099240.	Unsuitable control group
62	2018	Abbas BA, Marzouk ES, Zaher AR. Treatment of various degrees of white spot lesions using resin infiltration-in vitro study. Prog Orthod. 2018 Aug 6;19(1):27. doi: 10.1186/s40510-018-0223-3. PMID: 30079435; PMCID: PMC6081872.	Unsuitable control group
63	2018	Alizae Marny Mohamed, Kiong Hung Wong, Wan Jen Lee, Murshida Marizan Nor, Haizal Mohd Hussaini, Tanti Irawati Rosli, In vitro study of white spot lesion: Maxilla and mandibular teeth, The Saudi Dental Journal, Volume 30, Issue 2, 2018, Pages 142-150, ISSN 1013-9052, https://doi.org/10.1016/j.sdentj.2017.12.001.	Unsuitable control group
64	2018	Yazkan B, Ermis RB. Effect of resin infiltration and microabrasion on the microhardness, surface roughness and morphology of incipient carious lesions. Acta Odontol Scand. 2018 Oct;76(7):473-481. doi: 10.1080/00016357.2018.1437217. Epub 2018 Feb 15. PMID: 29447057.	Unsuitable control group
65	2018	Wisam W. Alhamadi et al. (2018), Effect of Resin Infiltrant Pretreatment on Shear Bond Strength of Metal Orthodontic Brackets in Vitro Study. Int J Dent & Oral Heal. 4:7, 105-110.	Unsuitable control group
66	2018	Yadak, A., EL-Sayed, H., & Genaid, T. (2018). Micro-Leakage and Penetration of a Resin Infiltrant Versus Two Conventional Fissure Sealants in Induced Occlusal Fissure. Researchgate.Net, December.	Data presented in thresholds
67	2018	Emanuela, J., & Dos, D. (2018). Universidade Estadual De Campinas Janaina Emanuela Damasceno Dos Santos Avaliação Das Propriedades Físico-Químicas E Da Profundidade De Penetração De Infiltrantes Avaliação Das Propriedades Físico-Químicas E Da.	Thesis
68	2018	Jorne, A. (2018). Instituto universitário egas moniz. 6-7.	Thesis
69	2018	Nassar, A. A. M. (2018). Effect of three different esthetic treatments on the microardness and surface roughness of (ICON) treated teeth. Al-Azhar Journal of Dental Science, 21(5), 539-543. https://doi.org/10.21608/ajdsm.2018.71698	Data presented in thresholds
70	2018	Attia, R. (2018). Effect of resin infiltrant and fluoride varnish on micro-hardness of de-mineralized enamel submitted to pH challenge. Egyptian Dental Journal, 64(1), 499-508. https://doi.org/10.21608/edj.2018.78053	Values present in other article

71	2019	Torres CRG, Zanatta RF, Fonseca BM, Borges AB. Fluorescence properties of demineralized enamel after resin infiltration and dental bleaching. Am J Dent. 2019 Feb;32(1):43-46. PMID: 30834731.	Unable to acess
72	2019	Wu L, Geng K, Gao Q. Effects of different anti-cariess agents on microhardness and superficial microstructure of irradiated permanent dentin: an in vitro study. BMC Oral Health. 2019 Jun 14;19(1):113. doi: 10.1186/s12903-019-0815-4. PMID: 31200708; PMCID: PMC6570839.	Unsuitable control group
73	2019	Al Tuwirqi AA, Alshammari AM, Felemban OM, Ali Farsi NM. Comparison of Penetration Depth and Microleakage of Resin Infiltrant and Conventional Sealant in Pits and Fissures of Permanent Teeth In Vitro. J Contemp Dent Pract. 2019 Nov 1;20(11):1339-1344. PMID: 31892688.	Unable to access
74	2019	Chen M, Li JZ, Zuo QL, Liu C, Jiang H, Du MQ. Accelerated aging effects on color, microhardness and microstructure of ICON resin infiltration. Eur Rev Med Pharmacol Sci. 2019 Sep;23(18):7722-7731. doi: 10.26355/eurrev_201909_18981. PMID: 31599398.	Unsuitable control group
75	2019	Yadav P, Desai H, Patel K, Patel N, Iyengar S. A comparative quantitative & qualitative assessment in orthodontic treatment of white spot lesion treated with 3 different commercially available materials - In vitro study. J Clin Exp Dent. 2019 Sep 1;11(9):e776-e782. doi: 10.4317/jced.56044. PMID: 31636868; PMCID: PMC6797449.	Data presented in thresholds
76	2019	Aswani R, Chandrappa V, Uloopi KS, Chandrasekhar R, RojaRamya KS. Resin Infiltration of Artificial Enamel Lesions: Evaluation of Penetration Depth, Surface Roughness and Color Stability. Int J Clin Pediatr Dent. 2019 Nov-Dec;12(6):520-523. doi: 10.5005/jp-journals-10005-1692. PMID: 32440067; PMCID: PMC7229383.	Unsuitable control group
77	2019	Arora TC, Arora D, Tripathi AM, Yadav G, Saha S, Dhinsa K. An In-Vitro evaluation of resin infiltration system and conventional pit and fissure sealant on enamel properties in white spot lesions. J Indian Soc Pedod Prev Dent 2019;37:133-9	Unsuitable control group
78	2019	Zhu, C., Chen, L., Ou, L., Geng, Q., Jiang, W., Lv, X., Wu, X., Ci, H., Liu, Q., Yao, Y., Pentadbiran, P., Persekutuan, K., Kami, R., Ketua, S., Kementerian, S., Persekutuan, J., Pentadbiran, S., Kerajaan, S., Berkanun, B., … Flynn, D. (2019). No Titleกระบวนการสื่อสารกบการยอมรับปรัชญาเศรษฐกิจพอเพียงของเกษตรกร ในจงั หวดั เชียงใหม่. Αγαη, 8(2), 2019. https://doi.org/10.22201/fq.18708404e.2004.3.66178	Thesis
79	2019	RUSSI, Tereza Maria Amorim Zaranza de Carvalho. Avaliação Microbiológica da Superfície de Infiltrante Resinoso Submetido a Diferentes Sistemas de Polimento. 2019.Dissertação (Mestrado Acadêmico em Ciências Odontológicas) - Centro Universitário Christus, Fortaleza, 2019.	Thesis
80	2019	PEDREIRA, Priscila Regis Matos. Influência da incorporação de óxido de bário e zircônia nas propriedades físico-químicas de infiltrantes experimentais e comercial. 2019. 1 recurso online (66 p.). Dissertação (mestrado) - Universidade Estadual de Campinas, Faculdade de Odontologia de Piracicaba, Piracicaba, SP.	Thesis
81	2019	Ozyurt, E., Arisu, H. D., & Turkoz, E. (2019). In vitro comparison of the effectiveness of a resin infiltration system and a dental adhesive system in dentinal tubule penetration Dentinal Penetration of Dental Resins. Clinical and Experimental Health Sciences, 36290600. https://doi.org/10.33808/clinexphealthsci.599847	Dentin tubule penetration- Not Enought Studies
82	2019	Abd Alhady, A., & Mohamed, H. (2019). Evaluation of the thickness and depth of penetration of Icon into the artificial enamel white spot lesion. Egyptian Dental Journal, 65(4), 3795-3803. https://doi.org/10.21608/edj.2019.76028	Data presented in thresholds
83	2020	Fahmy, R. S., Maher, K., & Refai, W. (2020). EFFECT OF RESIN INFILTRATION CONCEPT ON BONDING STRENGTH OF EFFECT OF RESIN INFILTRATION CONCEPT ON BONDING Ragi Samy Fahmy *, Kareem Maher Mohamed ** and Wael Mohamed Mobarak Refai ***. October.	Unsuitable control group
84	2020	Simunovic Anicic, M.; Goracci, C.; Juloski, J.; Miletic, I.; Mestrovic, S. The Influence of Resin Infiltration Pretreatment on Orthodontic Bonding to Demineralized Human Enamel. Appl. Sci. 2020, 10, 3619. https://doi.org/10.3390/app10103619	Unsuitable control group

Appendix S3. Joanna Briggs Institute Clinical Appraisal Checklist for Experimental Studies

SELECTION	1	2	3	4	5	6	7	8	9	10	11	OVERALL
Pancu et al. 2011	1	0	0	0	1	1	1	1	1	1	1	8
Meyer-Lueckel et al. 2011	1	0	0	0	1	1	1	1	1	1	1	8
Paris et al. 2011 A	1	0	1	0	1	1	1	1	1	1	1	9
Paris et al. 2011 B	1	0	0	0	1	1	1	1	1	1	1	8
Taher et al. 2012	1	0	0	0	1	1	1	1	1	1	1	8
Torres et al. 2012	1	0	0	0	1	1	1	1	1	1	1	8
Attin et al. 2012	1	0	1	0	1	1	0	1	1	1	1	8
Ekizer et al. 2012	1	1	0	1	1	1	1	0	1	1	1	9
Paris et al. 2013	1	0	1	0	1	1	1	0	1	1	1	8
Paris et al. 2013	1	0	1	0	1	1	1	1	1	1	1	9
Mohammed et al. 2014	1	0	1	0	1	1	1	1	1	1	1	9
Veli et al. 2014	1	1	1	0	1	1	1	1	1	1	1	10
Paris et al. 2014	1	0	1	0	1	1	1	0	1	1	1	8
Lausch et al. 2014	1	0	1	0	1	1	1	1	1	1	1	9
Gelani et al. 2014	1	0	0	0	1	1	1	1	1	1	1	8
Dilber et al. 2014	1	1	1	0	1	1	1	0	1	1	1	9
Arslan et al. 2015	1	0	1	0	1	1	1	1	1	1	1	9
Montasser et al. 2015	1	0	1	0	1	1	1	1	0	1	1	8
Min et al. 2015	1	0	0	0	1	1	1	1	1	1	1	8
Vianna et al. 2015	1	1	1	0	1	1	1	1	1	1	1	10
Baka et al. 2016	1	1	1	0	1	1	1	1	1	1	1	10
Gurdigan et al. 2016	1	0	1	0	1	1	1	0	1	1	1	8
Abdel-Hakim et al. 2016	1	0	1	0	1	1	1	1	1	1	1	9
El-zankalouny et al. 2016	1	0	1	0	1	1	1	1	1	1	1	9
Abdellatif et al. 2016	1	0	0	0	1	1	1	1	1	1	1	9
Neto et al. 2016	1	0	1	0	1	1	1	0	1	1	1	8
Horuztepe et al. 2017	1	0	1	0	1	1	1	1	1	1	1	9
Mandava et al. 2017	1	0	1	0	1	1	1	1	1	1	1	9
Aziznezhad et al. 2017	1	0	1	0	1	1	1	1	1	1	1	9
Prajapati et al. 2017	1	1	0	0	1	1	1	1	1	1	1	8
Rosianu et al. 2017	1	0	1	0	1	1	0	1	1	1	1	8
Yazkan et al. 2018	1	0	1	0	1	1	1	1	1	1	1	9
Khalid et al. 2018	1	0	1	0	1	1	1	1	1	1	1	9
Enan et al. 2018	1	0	1	0	1	1	1	1	1	1	1	9
Nabil et al. 2018	1	0	0	0	1	1	0	1	1	1	1	7
Attia et al. 2018	1	0	0	0	1	1	1	1	1	1	1	8
Askar et al. 2018	1	0	1	0	1	1	1	0	1	1	1	8
Enan et al. 2019	1	0	1	0	1	1	1	0	1	1	1	8
Aswani et al. 2019	1	0	0	0	1	1	1	1	1	1	1	8

Arora et al. 2019	1	0	0	0	1	1	1	1	1	1	1	8
Theodory et al. 2019	1	0	1	0	1	1	1	0	1	1	1	8
López et al. 2019	1	0	1	0	1	1	1	1	1	1	1	9
Gulec et al. 2019	1	1	1	0	1	1	0	1	1	1	1	9
Borges et al. 2019	1	0	0	0	1	1	1	1	1	1	1	8
Ayad et al. 2020	1	0	1	0	1	1	1	1	1	1	1	9
Behrouzi P et al. 2020	1	0	1	0	1	1	1	1	1	1	1	9
El Meligy, 2020	1	0	1	0	1	1	1	1	1	1	1	9
Wang et al. 2020	1	0	1	0	1	1	1	1	1	1	1	9

1. Was the aim of the study clearly stated?; 2. Was the sample size justified?; 3. Was the assignment to treatment groups truly random?; 4. Were those assessing the outcomes blind to the treatment allocation?; 5. Were control and treatment groups comparable at entry?; 6. Were groups treated identically other than for the named interventions?; 7. Was the preparation protocol clearly described?; 8. Was the experimental protocol clearly described?; 9. Were outcomes measured in the same way for all groups?; 10. Were outcomes measured in a reliable way?; 11. Was appropriate statistical analysis used?.

Appendix S4. Comparison between SMD and ROM results.

Variable	N	SMD	95% CI	I^2 (%)	N	ROM	95% CI	I^2 (%)
Surface roughness								
Sound enamel	**5**	**-7.78**	**-13.22; -2.33**	**98.1**	5	**0.65**	**0.49; 0.85**	98.2
WSL	**8**	**-2.43**	**-3.01; -1.67**	**95.2**	8	**0.46**	**0.29; 0.74**	98.5
Enamel microhardness								
Sound enamel	**14**	**-3.35**	**-4.80; -1.91**	**97.4**	14	**0.76**	**0.73; 0.8**	99.1
WSL	**23**	**4.08**	**2.76; 5.41**	**96.6**	23	**1.68**	**1.51;1.86**	**99.8**
Bond strength								
Sound enamel	6	-0.89	-1.92; 0.14	92.2	6	0.75	0.60; 0.95	96.9
WSL	**8**	**3.40**	**1.33; 5.48**	**97.1**	8	**1.89**	**1.28; 2.79**	**99.8**

Appendix S5. Authorization for image use referring to figure 5.

Jillian Foley <jfoley@dmg-america.com>
para mim

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jfoley@dmg-america.com | www.dmg-america.com

Appendix S6. Authorization for the thesis structure alteration.

Reitoria_Autorização para alteração da estrutura da tese

MM Maria Manuel Marnoto <mmarnoto@egasmoniz.edu.pt>
06/09/2021 14:19

Para: madalenasvsoveral@gmail.com Cc: mansocristina@gmail.com; Gil Alcoforado

Ex.ma Aluna,

Em nome do Senhor Professor Doutor Gil Alcoforado, Magnífico Reitor do IUEM a sua solicitação se encontra deferida pela Reitoria.

A Reitoria congratula a Madalena e toda a equipa de investigação pela publicação do artigo.

Com os meus melhores cumprimentos,

Secretária da Reitoria do IUEM
Maria Manuel Marnoto
INSTITUTO UNIVERSITÁRIO EGAS MONIZ
e-mail: iuem@egasmoniz.edu.pt
ou
mmarnoto@egasmoniz.edu.pt