ARE ASTHMA AND AIRWAY ALLERGY ASSOCIATED WITH INCREASED ROOT RESORPTION FOLLOWING ORTHODONTIC TREATMENT?
A SYSTEMATIC REVIEW

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Submitted to the Hamdan Bin Mohammed College of Dental Medicine
Mohammed Bin Rashid University of Medicine and Health Sciences
in Partial Fulfillment of the Requirements for the Degree of
Master of Science in Orthodontics
2020

ABSTRACT

Are asthma and airway allergy associated with increased root resorption following orthodontic treatment?

A systematic review

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Aim: Asthma and airway allergy have been implicated with root resorption development following orthodontic treatment. The objective of this study was to investigate systematically the relevant literature.

Materials and Methods: Search without restrictions for published and unpublished literature and hand searching took place. Data on root resorption in patients with asthma or allergy having undergone comprehensive orthodontic treatment were reviewed. The risk of bias was assessed using the Newcastle-Ottawa Scale.

Results: From the initially retrieved records, three cohort and two case-control studies met the inclusion criteria. The studies reported conflicting results and the risk of bias assessment revealed shortcomings in various domains.

Conclusions: The information regarding the association of asthma and airway allergy with root resorption following orthodontic treatment is contradictory and further research is warranted. However, until more data become available good practice would suggest that it is important to identify patients with asthma or airway allergy and consider the possible implications.

DEDICATION

First and foremost, Thanking My Almighty God, for His grace and blessings.

With great gratitude and appreciation, I would like to dedicate this thesis to my beloved parents and brothers, I could never have done anything without their huge support, passionate encouragement and continuous prayers.

To my dear husband Ziad and loving children Yasir and Sarah for their endless patience and great endurance for my absence throughout the three years I spent in this program, I am humbled and appreciative for all what they have sacrificed for me.

I am deeply indebted to my respected teachers, Associate Professor Eleftherios G. Kaklamanos and Professor Athanasios E. Athanasiou; no words can express my gratitude for them.

I would like to extend my thanks and great appreciation to all the other professors for their invaluable help and support throughout the program.

DECLARATION

I declare that all the content of the thesis is my own work. There is no conflict of interest with any other entity or organization.

Name: Reem Kais Al-Saqi

Signature:

ACKNOWLEDGEMENTS

I would like to express my special thanks and appreciation to Professor in Orthodontics Athanasios E. Athanasiou, who gave me the chance to fulfill my dream to become an orthodontist and whose constant motivation and guidance made me improve significantly during the years of my residency.

My deepest gratitude and acknowledgement to my thesis supervisor Associate Professor in Orthodontics Eleftherios G. Kaklamanos for his sincere guidance and invaluable support in order to complete my research dissertation. I was tremendously fortunate to have his continuous academic support. He has always been and always will be a constant source of inspiration to me.

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1. INTRODUCTION

Orthodontic tooth movement is achieved by the application of varying degrees of magnitude, frequency, and duration of mechanical forces. The applied forces result in inflammatory-like processes leading to structural changes in the periodontal tissues effected through bone resorption and apposition (Shroff, 2016; Proffit et al., 2019). These pathways involve cell to cell and cell to matrix interactions that are modified by a variety of systemic hormones, growth factors and cytokines. Recent studies have shown that osteoblasts and osteoclasts are the main cells controlling orthodontic tooth movement (Shroff, 2016; Proffit et al., 2019).

The main goal of orthodontic treatment is to have a long-term esthetic, healthy and functional occlusion (Proffit et al., 2019). Despite the multiple benefits of orthodontic treatment, sometimes adverse effects may affect the hard or the soft tissues. For example, the procedures of bonding and removal of the fixed appliances have been associated with changes in the enamel surface. Other changes like external root resorption, changes in enamel color, decalcifications, bone fenestrations and dehiscences, or gingival recessions can also be encountered during or after the completion of orthodontic treatment (Graber et al., 2004; Justus, 2015).

The external root resorption associated with orthodontic tooth movement is an inflammatory process, considered to be a common adverse effect of orthodontic treatment. As the teeth displace in the alveolus, cell necrosis might occur. The removal of these necrotic areas is a prerequisite before tooth movement can proceed.

During the removal of the necrotized tissues, the cementum and dentine may also be removed leading to external resorption of the roots (Dindaroğlu and Doğan, 2016).

Clinical practice and research evidence have shown that the amount of external root resorption during orthodontic treatment varies among individuals and may be affected by several factors such as orthodontic treatment type and duration, root length and morphology, as well as findings from the dental history like trauma (Iglesias-Linares et al., 2016). Moreover, systemic conditions like allergy, asthma, arthritis, and diabetes could be involved in the pathogenesis of root resorption associated with orthodontic tooth movement (Davidovitch et al., 1996).

Overall, the etiology of the phenomenon is complex and multifactorial. It is thought that a combination of the biological variability of a person, ethnicity, genetic predisposition, nutrition, hormones, medications, mechanical factors, parafunctional habits and different pathological and physiological conditions are implicated (Proffit et al., 2019).

Although the exact biological and mechanical factors responsible for aggravating resorption of the root tissues or inhibiting their repair after the application of an orthodontic force are still difficult to identify, it has been suggested that the inflammatory mediators involved in asthma and airway allergy might exert a synergistic effect (McNab et al., 1999). Asthma and airway allergy are common conditions that may occur during adolescence, when orthodontic treatment might be required (Machado et al., 2012).

Understanding the effect of asthma and airway allergy on the degree of external root resorption related to orthodontic treatment and considering the possible implications related to the proposed treatment could be of benefit to the clinician.

However, relevant information has not been summarized in an evidenced-based manner.

The aim of the present systematic review was to systematically investigate and critically appraise the quality of the available evidence from human studies regarding the effect of asthma and airway allergy on external root resorption associated with orthodontic treatment.

2. REVIEW OF THE LITERATURE

Throughout the years the interest about the adverse effects associated with orthodontic treatment has increased (Graber et al., 2004; Justus, 2015). However, the association of a phenomenon with a specific aspect of treatment, or the demonstration of a causative mechanism is not always easy to prove mainly because of the intricacy involved in the provocation of such side effects, individual differences, and challenging nature of the methodology of inspecting a cause-effect relationship.

2.1. Root resorption as an iatrogenic effect of orthodontic treatment

Orthodontically induced external apical root resorption is considered as one of the most common, undesirable, unpredictable and unavoidable pathologic sequelae that may occur during the course of orthodontic treatment (Murata et al., 2013; Sondeijker et al., 2019). It was related to Orthodontics firstly in 1914, by Ottolenghi and since then, it has instigated the researchers to search uninterruptedly for the possible causes of this serious problem (Pastro et al.,2018).

According to Oliveira et al. (2011), dental external apical root resorptions (DEARRs) are part of the biological cost of orthodontic treatment and as such they should not be considered as neither pathologic nor physiologic, but as unpredictable yet clinically acceptable irreversible loss of apical root material (cementum and dentine). The development of excessive root resorption during orthodontic treatment is considered as an adverse effect of the mechanical force–induced movement of teeth and can compromise the benefits of a successful orthodontic outcome (Nishioka et al., 2006). Little is known about the long-term prognosis of the affected teeth regarding their vitality, periodontal status (it was calculated that 3 mm of external apical root

resorption was equal to 1 mm of periodontal attachment loss), prosthetic abutments suitability, masticatory function resistance and mobility, as severe root resorption might also lead to tooth loss (Sondeijker et al., 2019).

2.2. Prevalence of root resorption after orthodontic treatment

Histological investigations usually indicate an extremely high (over 90%) occurrence of external apical root resorption associated with orthodontically moved teeth (Topkara et al., 2012; Sondeijker et al., 2019). Following buccal movement of maxillary premolars with a clinically relevant force of 50 cN, starting from the third week, some apical root resorption areas had reached halfway or more to the pulp (Kurol et al., 1996). External apical root resorption can also be visible on standard routine diagnostic radiographs. However, the severity reported after radiological investigations is much lower (Topkara et al., 2012) and the prevalence has been found to vary considerably among individuals after orthodontic treatment (Li et al., 2020).

Around 48–66 % of orthodontically treated patients demonstrate mild to moderate external apical root resorption (Sondeijker et al., 2019) and moderate to severe apical root resorption (>2mm to <1/3 of the root length) has been found in 12–17% of orthodontically treated patients (Hollender et al., 1980; Linge and Linge, 1991), while excessive apical root resorption (more than 4mm or >1/3 of the root length) is considered to be rare with an incidence of 1–5% (Levander and Malmgren, 1988; Davidovitch, 1996). However other studies have reported greater numbers, with the prevalence of severe apical root resorption of the incisors after orthodontic treatment to be 14.5% (Marques et al., 2011).

Radiographic examination is necessary to identify and observe external apical root resorption and there is no consensus regarding the timing or type of the radiographs

but usually panoramic radiographs are taken before, during and after orthodontic treatment (Sondeijker et al., 2019). Since external apical root resorption is a three-dimensional topographical change, two-dimensional radiography, such as intraoral (periapical) and extraoral (panoramic) radiographs, have inherent limitations in the precision and reliability of their measurements especially for the panoramic radiographs and predominantly in the anterior region because of the reduced visibility due to the bony structures' superimposition of the vertebrae and the skull (Sondeijker et al., 2019). In contrast, the three-dimensional, cone beam computed tomography (CBCT) which was introduced the last decade, has demonstrated a relatively higher accuracy in diagnosis and measurement of external apical root resorption (Li et al., 2020). Furthermore, the original treatment plan of more than 25% of cases were changed in some studies when using CBCT images compared to the conventional 2D images (De Grauwe et al., 2019).

Dudic et al. (2009), compared panoramic radiography (OPT) with CBCT in evaluating orthodontically induced apical root resorption and observed substantial differences between the two methods. 56% percent and 31% of the teeth showed no resorption by OPT and CBCT, respectively; 33.5% and 49% of the teeth showed mild resorption, whereas 8% and 19% showed moderate resorption by OPT and CBCT, respectively.

However, CBCT imaging should not be considered as a standard and routine method for diagnosis and treatment planning, due to its high ionizing radiation dose in comparison with conventional 2D radiographs based on the principle As Low As Reasonably Achievable (ALARA) (van Vlijmen et al., 2012). On the other hand, considerable differences in CBCT radiation dose exist depending on the exposure

protocol as there are as many as 15-fold difference between high-resolution and low-dose protocol with a similar field of view (Samandara et al., 2018).

According to the recent SEDENTEXCT and DIMITRA guidelines, small-field-of-view (FOV) CBCT can be indicated for the pretreatment evaluation of dental pathologies like external root resorption (De Grauwe et al., 2019).

2.3. Risk factors associated with root resorption during orthodontic treatment

Knowing the associated risk factors would allow clinicians to expect the frequency, location, and severity of root resorption before the beginning of orthodontic treatment (Nanekrungsan et al., 2012). Standardized studies to investigate the association between orthodontic tooth movement, the duration of applied force and early induced root resorption (Owman-Moll, 1995) and the type and magnitude of the applied force (Owman-Moll et al., 1996) led to ambiguous results and considerable individual variations. Since the adolescent patients, who were examined in these two investigations, were pretty homogeneous regarding age, dental development, and malocclusion, the differences recorded indicated a noticeable individual variation. Hence, root resorption related to orthodontic treatment seems to be a multifactorial problem (Sondeijker et al., 2019). Currently, there is lack of consensus on the causal factors of this phenomenon, the inability to foresee the susceptibility of individuals to orthodontic root resorption and why teeth resorb to various degrees in different individuals. Root resorption may not be caused by the same risk factors but many parameters have been involved in the greater prevalence of root resorption during orthodontic treatment and are believed to be caused by complex and multifactorial interactions between biological factors (Brezniak and Wasserstein, 2002; Sondeijker et al., 2019) and mechanical factors (Levander and Malmgren, 1988; Linge and Linge,

1983; Kaley and Phillips, 1991; Costopoulos and Nanda, 1996; Sondeijker et al., 2019).

2.3.1. Biological or patient related factors

Biological or patient related factors reported in the literature as risk factors for root resorption development associated with orthodontic treatment include: individual susceptibility and genetics (Harris et al., 1997; Topkara et al., 2012), gender (Massler and Perreault, 1954; Massler and Malone, 1954; McFadden et al., 1989; Linge and Linge, 1983), advanced age (Reitan et al., 1994), hormonal imbalances (hypothyroidism, hypopituitarism and hyperpituitarism) (Engstrom et al., 1988), pretreatment external root resorption (Massler and Malone, 1954; Goldson and Henrikson, 1975; Kalley and Phillips, 1991), dental anomalies (ectopia, taurodontism, and agenesis) (Kjaer, 1995; Lee et al., 1999), tooth-root morphology (pipette-shaped, blunt, abrupt deflection or narrow roots) (Levander and Malmgen, 1988; Kjær, 1995; Mirabella and Årtun, 1995a; Lee et al., 1999) parafunctional oral habits (clenching, bruxism, onychophagia, the habit of biting objects, lip dysfunction, tongue thrusting and thumb sucking habit) (Odenrick et al., 1985; Linge and Linge, 1991), type of malocclusion (Motokawa et al., 2013), severity of malocclusion (Topkara et al., 2012), occlusal trauma (Cakmak et al. 2014), trauma to the teeth (Malmegren et al., 1982; Andreasen, 1988), endodontically treated teeth (Wickwire et al., 1974; Remington et al., 1989; Spurrier et al., 1990; Mirabella and Årtun, 1995a,b), gingivitis, allergy, asthma, arthritis, and diabetes (Davidovitch et al., 1995; Davidovitch, 1996), chronic alcoholism, alveolar bone density, root proximity to cortical bone (Topkara et al., 2012) and pre-existing inflammatory conditions

(Davidovitch et al., 1995). Drugs and medication have also been suggested to play a role (Kaklamanos et al., 2019; Makrygiannakis et al., 2019).

2.3.2. Mechanical or treatment related factors

Mechanical or treatment related factors reported in the literature as risk factors for root resorption development associated with orthodontic treatment include: direction of tooth movement into the labial or cortical bone (Malmgren et al., 1994); long treatment duration and increased magnitude of the applied force (Kvam, 1967; Harry and Sims, 1982; Vardimon et al., 1991; Eross et al., 2015); the inclusion of extraction in the treatment plan (the incidence of root resorption was 3.72 times higher in patients treated with extractions than those treated without) (Nishioka, 2006; Pastro, 2018); the amount of apical displacement, treatment type and the method of force application (Topkara et al., 2012); the type of tooth movement (Roscoe et al., 2015) including crown tipping (Weiland, 2003; Chan and Darendeliler, 2005; Barbagallo et al., 2008), root torqueing (Bartley et al., 2011), rotational movement around the long axis of the tooth (Wu et al., 2011), extrusive (Montenegro et al., 2012) and intrusive tooth movements (Harry and Sims, 1982; Harris et al., 2006); appliance type (the incidence of root resorption was 2.30 times higher for Begg appliances compared with edgewise appliance) (Nishioka et al., 2006); the application of continuous forces (Levander and Malmgren, 1994) and the use of inter-maxilary elastics (Linge and Linge, 1983).

The recent introduction of clear aligners in the orthodontic armamentarium has raised the question whether the prevalence of root resorption is different in patients treated with this approach. A recent study on clear aligners assessed the upper and lower anterior teeth and first molars using panoramic radiographs and found that 46% of the

teeth presented measurable root reduction after treatment (Li et al., 2020). This prevalence of apical root resorption appears equal to or less than that reported in fixed appliances. However, a study using cone CBCT to measure apical root resorption found that patients with clear aligners suffered from expressively less incisor root resorption than that those treated with fixed appliances (Li et al., 2020).

2.4. Pathogenetic mechanisms of root resorption

Bone mass in humans is preserved by bone remodeling which is the determinant of skeletal homeostasis. The processes of bone resorption and deposition are joint with complex mechanisms. When one process is decelerated or accelerated the other follows (Harada and Rodan, 2003). Nevertheless, the action of resorption is faster than deposition and generally involves at least 3 months to rebuild bone that was resorbed in 2-3 weeks. Therefore, when increased resorption concurs with bone formation, bone loss will still happen due to the difference in the rate of action between these two processes (Harada and Rodan, 2003). The basic mechanism of orthodontic tooth movement triggered by orthodontic strain while maintaining the periodontal support, is a phenomenon that depends directly on the coordinated activity of osteoblasts, osteocytes, and osteoclasts and is achieved by a balance between alternating processes of osteoclastic bone resorption and osteoblastic bone deposition in response to pressure and tension, respectively (Nishioka et al., 2006). Transient or chronic imbalances in bone remodeling, caused by cellular over-activation or inhibition of the effector cells, osteoclasts, or osteoblasts, respectively, affect alveolar bone density. Different alveolar bone densities and bone modeling/remodeling processes influence the strain on the dental root, hence affecting the orthodontic tooth movement process and the increased occurrence of external root resorption as a

harmful secondary effect (Iglesias-Linares et al., 2016).

Overall, root resorption during orthodontic treatment is intimately associated with the biological processes that occur during the displacement of a tooth in its socket by an orthodontic load. When the periodontal ligament tissues are over-compressed by orthodontic forces, heavy functional loads are transferred directly to a relatively small area of the lamina dura. This results in hyalinized necrotic periodontal tissue areas that necessitate undermining resorption for the removal of this necrotic tissue before tooth movement can occur. It has been suggested that root resorption might be related to the reduced rate of bone resorption at the compressed necrotic areas in the periodontal ligament triggering series of fatigue-related events leading to external root resorption (Iglesias-Linares et al., 2016). Root resorption under loading stress in the apical and cervical thirds has been found to be more severe than in root regions that were not mechanically stressed (Iglesias-Linares et al., 2017).

Some studies also suggest that the direction of tooth movement plays an important role in triggering root resorption (Viecilli et al., 2008). It has been hypothesized that when an orthodontic force is applied, compressive and tensile stresses tend to concurrently separate and crush the dentinal tubules, so affecting the overlying cementum layer and causing microcracks. Cementum is generally considered as an anti-resorptive barrier because it lacks a mineral remodeling process. It remains to be determined whether the anti-resorptive properties originate from a cellular antiresorptive signaling related to local cells or a tissue component or even if they are the product of the anatomic distance from the clastic precursor and vascular supply (Iglesias-Linares et al., 2017). Consequently, although cementum shows a higher resistance to resorption than alveolar bone, the force application and the resultant root deformation may have an effect on both the cementum and the dentine (Khouw and

Goldhaber, 1970).

Histologically it has been shown that the resorption process is initiated by osteoclast-like cells referred to as odontoclasts (Dindaroğlu and Doğan, 2016). Following the application of orthodontic forces, resident periodontal ligament and bone marrow–derived circulating mononuclear hematopoietic precursor cells might be focused toward odontoclast differentiation from a semi-quiescent state to one of super-specialization, necessary to promote alveolar bone as well as root resorption (Hienz et al., 2015).

The activated odontoclasts/osteoclasts subjoin the mineral matrix, creating a sealing zone and arrange a polarized morphology with ruffled border secretors of proteases which induce mineral resorption (Georgess et al., 2014). Appropriate adhesion of the clastic cell to the mineral substrate allows activation of all the intracellular machinery necessary to degrade the mineral component (Warren et al., 2015). Specific enzymes then will be catalyzed to the ruffled border membrane, releasing them into the resorption pit and generating an acidic microenvironment (Matsumoto et al., 2014). Lastly, the resorption process ends by degrading the organic component (Teitelbaum, 2007). Initially, root resorption occurs in the margins of the necrotic periodontal ligament, but severe external root resorption may result when the process of removal of the necrotic cells penetrates through the cementum and dentine to produce permanent loss of root length (Dindaroğlu and Doğan, 2016).

Remarkably, clastic cells have been noticed to adhere around 45% more to root dentin than to bone (Rumpler et al., 2013). Data from in vitro experiments further suggest that the dentin substrate shows much greater potential than bone for inducing the genesis and maturation of new clastic cells. A possible explanation for this resorption behavior is that dentin contains more matrix proteins of non-collagenous origin when

compared with bone (Azari et al., 2011). In addition studies have shown that other compounds in the dentin might also interfere in the odontoclast/osteoclast migration (Destaing et al., 2008). The lack of regulatory osteocytes and osteocyte proteins in dentin might also be considered for the quantitative variations (Cabahug-Zuckerman et al., 2016). Furthermore, different cell types and a wide range of cytokines and molecular factors intervene in the maturation stages of odontoclast/osteoclast cell differentiation, inducing greater or less specialization, rate of proliferation, life span, and range of activity (Hayashi et al., 2012; Lee et al., 2015), thereby determining root resorption activity during orthodontic tooth movement. Thus, any cytokine level variation may have an effect not only on bone modeling/remodeling but also on the following increase in radicular stress during orthodontic tooth movement (Iglesias-Linares et al., 2017). Similarly, differences in remineralization and even root tissue formation by odontoblast-like cells may account for differences in repair capabilities or the susceptibility of the dental root to pathologic resorption by clastic cells (Iglesias-Linares et al., 2017).

Specific receptors are found on the surfaces of macrophages which are involved in the response to orthodontic loading. Activation of this receptor by products of the necrotic tissue leads to autocrine and paracrine cell stimulation with overexpression of cytokines and other inflammatory-related molecules. The released molecules all function as a chemotactic stimulus of the phagocytic cellular system (neutrophils and lymphocytes) responsible for eliminating apoptotic cells and necrotic tissue, so allowing the root to move through the bone and orthodontic tooth movement to take place (Barberà-Cremades et al., 2016).

A study described the critical effect of macrophages on the root resorption process (He et al., 2015). Two distinguished in vitro phenotypes are described: classically

activated macrophages (M1), or “killer” macrophages, and alternatively activated macrophages (M2), or “healer” macrophages (Novak and Koh, 2013).

An outstanding plasticity can be detected in the switch from M1 to M2 polarization states depending on the different conditions in the cellular microenvironment (He et al., 2015), which allows them to mediate inflammation and tissue homeostasis. In this respect, increased numbers of the M1 versus M2 cell type is likely to be associated with root resorption (increased M1:M2 ratio). The mechanism explaining this is that M1 macrophages promote inflammation by secreting proinflammatory cytokines while M2 macrophages have an inhibitory effect on inflammation mediated by interleukins (Davies et al., 2013; He et al., 2015). Under prolonged orthodontic force, root resorption lesions were found concomitant with an increase in M1-like macrophages. When the orthodontic force was removed, there was visibly decreased root resorption, with an increased M2-like macrophages and a decreased number of M1-type cells. The severity of root resorption was partly attenuated when a decrease in the ratio of M1:M2 macrophages was detected (He et al., 2015).

The biological reaction induced by orthodontic force is not limited to regional cellular recruitment. Instead, the mononuclear phagocyte system in peripheral blood and spleen reservoir monocytes noticeably decreases from days 1 to 3 and then recovers on day 7 after strain application, as shown by flow cytometry (Zeng et al., 2015). Moreover, this decrease in the systemic inflammatory monocytes correlates with an increase in regional monocytes colocalizing with the TRAP+ osteoclasts adjacent to the root surface in the “compressed” PDL (Iglesias-Linares et al., 2017).

Consequently, external root resorption associated with orthodontic force constitutes a complex phenomenon, related to multiple factors, including the overexpression of cytokines and other inflammatory-related molecules, that involve the reaction of the

dental root, the periodontal ligament, and the alveolar bone to the force-induced strain on the root. Up until now, it is not clear how all of these factors influence alveolar bone density and the concomitant effect on the duration and degree of the strain on the dental root, leading to resorption. The mixture of factors that may result in this complex trait appear to vary sample to sample and likely individual to individual, making an accurate prediction of the occurrence of external root resorption improbable (Iglesias-Linares et al., 2016).

2.5. Asthma and airway allergy

Asthma and allergic rhinitis are complex heterogenous dynamic multifactorial immunological disorders and considered as the most common chronic inflammatory allergic respiratory diseases (Bousquet et al., 2019), characterized by bronchoconstriction, hyper-sensibility of the tracheobronchial tree to several stimuli and airway inflammation demonstrated by generalized narrowing of airways. Clinically, asthma manifests itself through wheezing, coughing, chest tightness and dyspnea while allergic rhinitis manifests itself through mucus hypersecretion, edema, itching, sneezing, rhinorrhea and fatigue symptoms (Wikstén et al., 2018). These are episodic diseases in which acute exacerbations are interposed with asymptomatic periods and can be relieved spontaneously or with the use of medications (Machado et al., 2012). It is worth noting that around 85% of asthmatic patients have allergic rhinitis, while 15–38 % of allergic rhinitis patients have asthma (Wikstén et al., 2018).

2.5.1. Prevalence of asthma and airway allergy

Asthma and allergic rhinitis are major public health problems affecting over 350 million people including both children and adults worldwide (Soriano et al., 2017).

Due to the significant increase in the incidence and prevalence of allergic airway diseases during the last few decades and their socio-economic burden, they have gained attention recently worldwide in spite of the advances made in treatment (Soriano et al., 2017; Enilari and Sinha, 2019). The increased prevalence of asthma is complex and multifactorial in etiology and has been accompanied by an increase in morbidity and mortality which reflect the changes in the underlying cause of allergic airway diseases and its exacerbating factors especially in the developed countries, in which the increased urbanization of lifestyle and rapid industrialization have increased air pollution and consequently airway hyperresponsiveness secondary to exposure to environmental triggers (Machado et al., 2012). On the other hand, as per WHO's Study on Ageing and Adult Health (SAGE) documentation (Arokiasamy et al.,2017) in some under developed countries there is substantial under-diagnosis of asthma, which is a factor that might also potentially explain their lower prevalence rates compared to the developed countries (Enilari and Sinha, 2019).

A wide range in prevalence rates of asthma and allergic diseases have been documented through studies of both children and adults and have revealed low prevalence rates (2%–4%) in Asian countries (especially Vietnam, India and China) and higher rates (15%–20%) in the United Kingdom, Netherlands, Canada, Sweden, Australia, New Zealand and over 25% of the European population (Enilari and Sinha, 2019) and in 2015 asthma had the highest prevalence among the chronic respiratory diseases worldwide (Soriano et al., 2017).

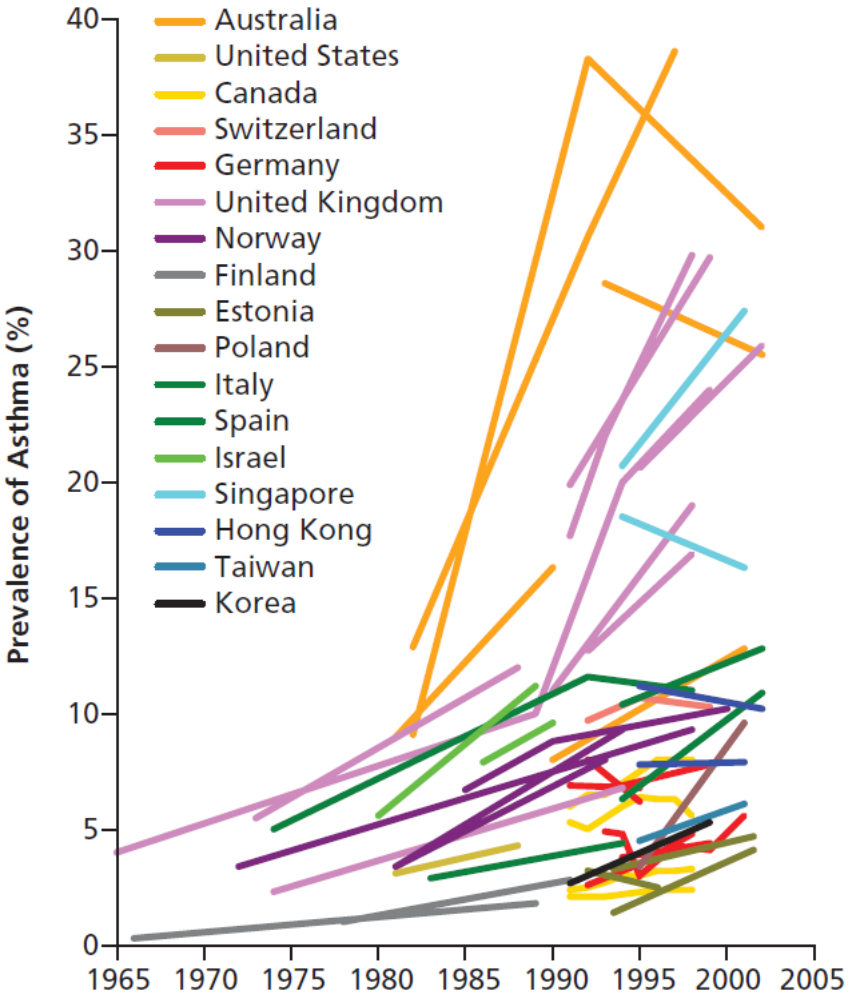

Figure 1. Changes in prevalence of diagnosed asthma (reproduced after permission by CMAJ, Appendix III) [from Subbara et al. 2009].

In general, there are gender and racial differences in asthma prevalence. Asthma is more common in boys than girls in childhood; however, this trend reverses in adulthood, when more women have asthma than men. Adults are nearly five times more likely to die from asthma than children and with regards to race, prevalence rates among different ethnic groups vary dramatically and blacks have the highest risk of hospitalization and death related to asthma (Lugogo and MacIntyre, 2008). There are many postulated causes for the increased incidence and prevalence of asthma, which may vary considerably. Much remains unknown because of the complex

interaction between the immunologic, genetic, and environmental mechanisms underlying the development of these allergic conditions (Subbarao et al., 2009).

2.5.2. Etiology of asthma and airway allergy

The etiology of asthma and other airway allergies is multi-factorial, complex and much remains to be discovered (Wikstén et al., 2018). As mentioned earlier, there is an interaction between environmental stimuli and genetic factors contributing to the development of an intermediated immune response (Machado et al., 2012). Asthma includes a range of heterogeneous phenotypes that vary in etiology, presentation and pathophysiology. The risk factors for each recognized phenotype of asthma include host, genetic and environmental factors. Even though a family history of asthma is common, it is neither sufficient nor necessary for the development of asthma (Subbarao et al., 2009). The increased heterogeneity in the genetic basis of asthma and the gene - environment interactions have made it difficult for researchers to precisely identify and quantify the environmental exposures and their timing and to replicate genetic associations (Subbarao et al., 2009; Wikstén et al., 2018).

The International Study of Asthma and Allergies in Childhood compared data from centers in China with data from Vancouver, Canada, and found significant differences in the prevalence rates between children of similar genetic ancestry living in different environments. In addition, it provided evidence for the effect of residence duration in the new environment (Wang et al., 2008). Prevalence rates for asthma among 13–14 years old children were the lowest for Chinese children who were born and studied in China, intermediate for Chinese children who had migrated during their lifetime to Canada and highest for Chinese children who had been born in Canada. Moreover, the prevalence rate for the third group was still lower than among non-Chinese children in

the same environment. So, these results suggested gene - environment interactions (Wang et al., 2008). Furthermore, environmental changes might affect asthma differently at different times of the person's life, and the relevant risk factors might change over time as well (Subbarao et al., 2009).

Environmental factors like exposure to endotoxins and infections might be protective or might act as risk factors, depending partially on the timing of exposure in infancy and childhood (Bousquet et al., 2019). Some prenatal risk factors, like maternal tobacco smoking, have been well recognized, but nutrition and diet, use of antibiotics, mode of delivery and stress might as well affect the early development of asthma and allergy. During childhood, assumed risk factors include gender (until 13-14 years of age, the prevalence and incidence of asthma are greater among boys than girls), birth weight, breastfeeding, viral respiratory tract infections in infancy, family structure and size, phenotypes of asthma, lung function, socio-economic status, antibiotics and infections, exposure to environmental tobacco smoke, exposure to animals and allergic sensitization (Bousquet et al., 2019).

During adulthood, recurrence of childhood asthma might be as common as new-onset asthma (Subbarao et al., 2009). Adult asthma might also develop due to specific drug treatments (like nonsteroidal anti-inflammatory drugs or in women, like hormone replacement therapy) or occupational exposure to sensitizing irritants or agents (like car paints, various hairdressing chemicals, commercial and domestic cleaning solutions and latex used by health care professions) which is considered the most common (Subbarao et al., 2009; Lemanske and Busse, 2010). Sensitization to house dust mites, female gender and airway hyperresponsiveness in mid and later childhood were all independently and significantly related to the likelihood of persistence of childhood asthma in to early adulthood (Subbarao et al., 2009). A better

understanding of these risk factors might finally provide better chances for the primary prevention of asthma (Wikstén et al., 2018).

Exposure to allergens, particularly during the first years of life, can determine the chronic inflammation of airways of those who are genetically susceptible to asthma development (Machado et al., 2012). Asthmatic reaction can be initiated as a result of inhalation of domestic dust, mold, spores and pollens, smoke, hair, dust mites, cockroach dust, spider mites, chemical sprays, strong odors, flour dust, chalk powder or chemical air pollutants; climate and temperature changes; emotional distress; viral infection; physical exercise; and hyperventilation (Subbarao et al., 2009; Machado et al., 2012). In contrast, the "hygiene hypothesis" suggests that increases in the prevalence of autoimmune and allergic diseases results from a decrease in the prevalence of childhood infections and improved hygiene (Lugogo and MacIntyre, 2008). Furthermore, studies have reported that children growing up in farm environment developed less asthma and other allergic diseases. This protective "farm effect" has been attributed to the contact with farm animals and their microbes. These studies suggest that airborne substances likely derived from farm animals and their microbes shape innate immunity and reduce the risk of developing asthma and other allergic diseases (Ober et al., 2017; Wikstén et al., 2018).

2.5.3. Mechanisms of asthmatic reaction

Asthma is a complex inflammatory disorder that shows heterogeneity and variability in both acute and chronic clinical expressions (Lemanske and Busse, 2010). The molecular and cellular patterns associated with the pathophysiology of airway inflammation in asthma are complex, excessive, interactive and variable for most patients but not all being early in life, as they are determined by the phases of asthma,

for example acute, persistent, severe/non-severe or under treatment (Lemanske and Busse, 2010).

Laboratory analysis of the broncho-alveolar lavage fluid from asthmatic patients shows generalized increase in the amount and cellularity of capillaries as the most commonly detected anomaly in asthma as well as eosinophilia which is the most frequent finding in the blood count results and considered as a characteristic feature of allergic inflammation (Lemanske and Busse, 2010; Machado et al., 2012). Asthmatic inflammatory reactions are characterized by increase in total cell volumes of eosinophils, polymorphonuclear cells, lymphocytes, epithelial cells, neutrophils, basophils, macrophages/monocytes and mast cells (Lemanske and Busse, 2010; Machado et al., 2012). Additionally, increased levels of leukotriene, inflammatory cytokines and prostaglandins which serve to continue inflammatory events in the airway even while using corticosteroid medications (Lemanske and Busse, 2010). Leukotrienes are proinflammatory mediators and the excessive increase in their production and activation is associated with asthma pathogenesis and contributes to all the symptoms perceived in airway allergic diseases in which they produce immediate and acute inflammatory reactions, including tissue edema, vascular congestion and bronchoconstriction (Asaad et al. 2017).

Mast cells contribute significantly to both the initiation of asthma and the release of inflammatory mediators, including leukotrienes, and inflammatory cytokines (Lemanske and Busse, 2010). In addition, lymphocytes contribute to further increase the inflammatory process by releasing inflammatory cytokines to boost inflammation by recruitment of eosinophils and regulating IgE production (Lemanske and Busse, 2010). While, eosinophils as a prominent feature of airway pathology are responsible for causing inflammation of the airway, inflammation persistence and enhancement of

airway hyperresponsiveness lead to injury to the airway and obstruction of the airflow (Lemanske and Busse, 2010; Machado et al., 2012).

The airway epithelium in asthmatic patients is both a target and a contributor of inflammatory airway changes. Histologic assessments of airways in asthmatic patients, especially those with a more severe asthma, show epithelium injury and loss of its cells (Lemanske and Busse, 2010). On the other hand, epithelial cells are an important source of inflammatory mediators and growth factors. Furthermore, smooth muscle of the airway can be a source of both inflammatory cytokines and growth factors and often show hyperplastic and hypertrophic changes in patients with severe asthma (Lemanske and Busse, 2010). Moreover, blood vessels and mucous glands are other airway cells involved in asthma histopathology. As mucous glands hypertrophy occurs and the activation of their cells leads to mucus production to occlude the airways and to become the primary cause for resistance to treatment in severe exacerbations. In addition, multiple factors produced in asthma (ie, vascular endothelial growth factor) can induce airway vessels to proliferate and as a result narrow the patient's airways (Lemanske and Busse, 2010).

2.5.4. Oral health in individuals with asthma and airway allergy

Patients with allergic respiratory disorders like asthma and allergic rhinitis are at risk of compromised oral health (Thomas et al., 2010; Widmer, 2010). Studies have shown that both dental hard tissue damage (dental caries, mild enamel developmental defects, tooth erosion) and soft tissue damage (gingivitis, calculus formation, periodontal disease) are more likely to occur for asthmatic children (Thomas et al., 2010; Widmer, 2010; Machado et al., 2012). The etiology of this increased risk of oral

health problems is associated both with the airway allergic condition itself and/or the therapeutic drugs used (Thomas et al., 2010; Widmer, 2010).

In the elderly population, resorption of the mandibular canal wall is more prevalent in individuals with asthma, and these patients are in the high-risk group for severe resorption of the residual mandibular ridge after tooth loss (Machado et al., 2012).

Allergic airway diseases are often associated with altered salivary composition and flow rates, either due to the condition itself as a result of mouth breathing (specially nocturnally, when salivary flow is already reduced) or as a side effect of the medications used and that can significantly affect the periodontal health (which is strongly dependent on adequate salivary flow) (Thomas et al., 2010; Widmer, 2010). In addition, saliva is not only crucial with regards to buffering against the decrease in intraoral pH but also provides a source of ions to re-mineralize the demineralized tooth structure (Thomas et al., 2010; Widmer, 2010).

Patients taking asthma medication might be at increased risk of tooth erosion, dental caries, periodontal diseases, and oral candidiasis (Thomas et al., 2010; Widmer, 2010). Almost all asthma medications, particularly in the inhaled and powdered forms, induce xerostomia effect and a pH of less than 5.5. Therefore, asthmatic children particularly have been found to be at risk of tooth erosion and dental caries. Additionally, children are more likely to develop fungal infection like oral candidiasis after using inhaled steroids especially if the child's salivary flow has also been reduced (Widmer, 2010). Though, some studies revealed that there is no significant difference in caries experience of asthmatic patients as compared to their non-asthmatic peers and others found that most asthma medications were above the critical pH level for enamel dissolution (Shulman et al., 2001; Dugmore and Rock, 2003). Probable explanations for differences between studies include differences in asthma

severity, different fluoride exposure, medication usage, preparation nature, timing and delivery devices (dry powder, metered dose inhalers and spacers) (Shulman et al., 2001).

2.5.5. Possible implications for orthodontics

Inflammation in the periodontium is an essential part of tissue reaction to orthodontic force during the initial period of orthodontic tooth movement (McNab et al., 1999; Machado et al., 2012). In the phase of acute inflammation, structural changes and increase in the caliber of blood vessels can be observed in the periodontal ligament tissues. Consequently, a rapid and small dental displacement occurs for 4 - 7 days soon after force application as a result of gradual compression and inflammatory changes of the periodontal ligament (Machado et al., 2012). In this process, immune cells migrate out of the capillaries in the periodontal ligament and interact with locally established cells through a large system of signal molecules (McNab et al., 1999). As mentioned earlier, external root resorption associated with orthodontic force constitutes a complex phenomenon, related to multiple factors, including the overexpression of cytokines and other inflammatory-related molecules (Iglesias-Linares et al., 2016; Morford and Hartsfield, 2016). Many of the signal molecules that mediate the inflammatory responses are produced in diseased organs (like lungs) and upregulated in airway allergy and asthma, could circulate throughout the body via blood vessels (McNab et al., 1999). These inflammatory mediators may enter the extravascular space of the periodontal ligament, particularly during orthodontic tooth movement, which causes a progressive increase in the vascularity of the periodontal ligament, dental pulp, and local alveolar bone and thus may enhance external root resorption (McNab et al., 1999). Moreover, it has been hypothesized that increased

osteo-clastogenesis during allergen-induced inflammation may be a possible pathway for increased bone and root resorption (Iglesias-Linares et al., 2017).

Davidovitch et al. (1996) hypothesized that individuals who have conditions like asthma and airway allergy that disturb the immune system might be at a high-risk level for developing severe root resorption during orthodontic treatment. Using cellular biology methods, they investigated whether inflammatory mediators generated outside the periodontal ligament influence the cellular interactions involved in root resorption, by activating and/or attracting cementoclast progenitors. The researchers induced allergic asthma in guinea pigs and applied orthodontic force against the maxillary molars. Even though root resorption was not detected on these continuously erupting and cementum-free teeth, the number of alveolar bone osteoclasts in the areas of compressed PDL increased over the controls, indicating that chemical mediators produced in the asthmatic state might influence cell populations and therefore the resorption process (Davidovitch et al., 1996).

Recently, animal studies investigated the effect of allergen sensitization on root resorption associated with orthodontic tooth movement. Machado et al. (2012) established allergic inflammatory reactions in the experimental animals, simulating those of the bronchial asthma in humans, with substantial increase in blood and bronchoalveolar total leukocyte and eosinophil counts. A more intense response after the application of orthodontic forces was observed in the sensitized animals. Moreover, the alveolar bone exhibited indirect resorption areas close to the pressure areas of the periodontium, signifying a more severe tissue response. The investigators observed increased compression in the pressure areas and increased stretching in the traction areas of the periodontal ligament from the orthodontic force application and suggested that the increased level of eosinophils circulating in the blood would

stimulate chemotactic cytokines to trigger and increase local inflammation in the periodontium to which eosinophils, polymorphonuclear leukocytes and platelets were attracted. Under such conditions, the increased vascular permeability and formation of inflammatory exudates and infiltrates may produce an acidic environment that favors the influx and persistence of clastic cells. Therefore, these findings proposed that inflammatory-like changes in the periodontium from the application of orthodontic forces could be aggravated by the presence of the allergic systemic condition (Machado et al., 2012).

Another study on allergen sensitized animals (Murata et al., 2013), found that the amounts of external apical root resorption, alveolar bone resorption and orthodontic tooth movement appeared to be associated with the systemic allergic condition. The numbers of odontoclasts/osteoclasts were increased on the pressured side during orthodontic tooth movement in the ovalbumin-sensitized rats, proposing the increased induction of odontoclastogenesis and osteoclastogenesis by the systemic allergen sensitization under the condition of orthodontic force application. These findings suggested that allergic diseases might be associated with susceptibility to external apical root resorption and might affect orthodontic tooth movement (Murata et al., 2013).

During orthodontic treatment, osteocytes release different biomolecules including prostaglandins which are considered the most significant because they stimulate both osteoblasts and osteoclasts (Iglesias-Linares et al., 2016). In addition, prostaglandins increase the levels of metalloproteinases that leads to decrease in the procollagen production (which is essential for the remodeling of bone and periodontal ligament) (Krishnan et al., 2015). As mentioned earlier, prostaglandin production is increased in

asthmatic inflammatory reactions (Lemanske and Busse, 2010). Therefore, it might increase the rate of orthodontic tooth movement as well (Knop et al., 2012).

Furthermore, increased expression of pro-inflammatory cytokines, together with RANKL (which is an essential cytokine that play an important role in bone resorption by inducing osteoclast differenciation) (Heath et al., 1985; Bertolini et al., 1986), that were detected in the periodontal tissues of teeth moved orthodontically in ovalbumin sensitized animals (which is extensively used in animal models of asthma), suggest increased amounts of external apical root resorption and rates of orthodontic tooth movement (Murata et al., 2013). Additionally, increased levels of leukotrienes B4 (LTB4), which are implicated in bone remodeling process by increasing bone resorption (Bellofiore and Martin, 1988) are found in inflammatory diseases such as asthma and play an important role in allergic inflammation (Hallstrand and Henderson, 2010).

Asthma and airway allergies are chronic diseases commonly treated with corticosteroids, which are anti-inflammatory drugs. In general the local or systemic administration of any medication might affect the orthodontic tooth movement molecular signaling pathways, which control the periodontal and dental tissue homeostasis, clastic cell regulation and changes that happen during orthodontic tooth movement (Knop et al., 2012; Kaklamanos et al., 2019; Makrygiannakis et al., 2019). Animal studies have shown that corticosteroid administration could possibly affect the bone metabolism and interfere with the rate of orthodontic tooth movement which might influence the prognosis of orthodontic treatment (Ong et al., 2000; Verna et al. 2006).

Debatable data were found regarding the effect of corticosteroid therapy on the apical root resorption and the rate of orthodontic tooth movement. Short-term treatment with

1 mg/kg oral prednisolone in rats showed conflicting results with significantly less external root resorption, indicating a suppressing role of these drugs on the clastic activities (Verna et al., 2006). On the other hand, the effect of acute or prolonged use of medication has not been investigated yet (Ong et al., 2000; Verna et al., 2006).

Ashcraft et al. (1992) treated rabbits with cortisone acetate injections with osteoporotic doses (15 mg/kg) and showed expressively more rapid orthodontic tooth movement and greater predisposition to external root resorption in the pressure areas. On the other hand, Yamane et al. (1997) stated that the rate of tooth movement was reduced in rats treated with 10 mg/kg per day of hydrocortisone, and Davidovitch et al. (1972) observed slower rate of tooth movement in cats treated with cortisone acetate (12.5 to 25 mg/day). An animal study by Geurtzen et al. (2017) showed that prednisolone affects negatively on both, osteoblasts and osteoclasts, particularly in the initial phases of osteoclastogenesis stimulated by RANKL.

These variations might be explained by the differences within the studied animal species, experiment duration, forces used to move teeth, time interval of administration and dosage, and effectiveness of the steroid used (Ong et al., 2000).

Montelukast is a medication that is used extensively as an adjunct to corticosteroids for the treatment of bronchial asthma, particularly for children, who may need orthodontic treatment. The therapeutic activity of Montelukast is achieved through antagonism of leukotriene receptors, so it could potentially decrease osteoclast activity which could lead to decreasing the rate of orthodontic tooth movement (Asaad et al., 2017).

Since severe root resorption associated with orthodontic treatment could jeopardize tooth longevity, it is important to identify possible associated factors, so that patients are informed about possible risks before commencing treatment and the clinician

modifies goals, plans and mechanics accordingly (Haugland et al., 2018). Thus, understanding the association between asthma and airway allergies and the degree of external root resorption after orthodontic treatment and considering the possible implications related to the proposed treatment could be of benefit to the clinical orthodontist. However, relevant information has not been summarized in an evidenced-based manner.

3. AIM

3.1. Aim of the systematic review

To systematically investigate and critically appraise the quality of the available evidence from human studies regarding the association of asthma and airway allergy with external root resorption related to orthodontic treatment.

3.2. Objectives of the systematic review

To retrieve data on the extent and severity of external root resorption in individuals with and without asthma or airway allergy related to orthodontic treatment.

3.3. Null hypothesis

There is no association between asthma and airway allergy with external root resorption related to orthodontic treatment.

4. MATERIALS AND METHODS

4.1 Protocol development

The present review was based on a specific protocol developed and piloted following the guidelines outlined in the PRISMA-P statement (Shamseer et al., 2015). In addition, conduct and reporting followed the Cochrane Handbook for Systematic Reviews of Interventions (Higgins and Green, 2011) and the PRISMA statement (Moher et al., 2009), respectively.

4.2. Eligibility criteria

The selection criteria for the domains of study design, participants' characteristics, intervention characteristics and principal outcome measures applied for the present review adhered to the PICOS (participants, interventions, comparisons and outcomes study designs) acronym and were as follows:

4.2.1. Types of study design

Studies eligible for inclusion had to be observational studies evaluating, in human subjects, the extent and/or the severity of external root resorption after the completion of comprehensive orthodontic treatment with fixed appliances and investigating the association with asthma or allergy. Animal studies and reviews (traditional reviews, systematic reviews, and meta-analyses) were not included in the present investigation. The type of study design was assessed using the algorithm available from SIGN (Scottish Intercollegiate Guidelines Network) available from http://www.sign.ac.uk (Appendix I) and Hulley et al. (2013).

4.2.2. Types of participants

The included studies could involve human individuals of any age and gender. Studies that included patients with clefts, syndromes or congenital anomalies of the craniofacial region were excluded.

4.2.3. Types of interventions

The included studies could involve patients who received comprehensive orthodontic treatment with fixed appliances of any type regarding technique, bracket characteristics, etc. However, studies with additional interventions such as orthognathic surgery were excluded.

4.2.4. Types of outcome measures

The studies included in the present review had to provide measurements on the extent or the severity of external root resorption (assessed using linear measurements or grading scales).

4.3. Information sources and search strategy

The principal investigator (RKA) developed detailed search strategies for each database. These were based on the strategy developed for MEDLINE, but revised appropriately for each database to take account of the differences in controlled vocabulary and syntax rules. The following electronic databases were searched (Appendix II): MEDLINE via PubMed, CENTRAL, Cochrane Database of Systematic Reviews, Scopus, Web of Science™ Core Collection, Arab World Research Source, Clinical Trials registry and ProQuest Dissertations and Theses Global database.

No restriction was placed on the language, date or status of publication. In addition, efforts were made to obtain conference proceedings and abstracts where possible and the reference lists of all eligible studies for additional records were searched.

4.4. Study selection

The principal investigator (RKA) and the thesis principal supervisor (EGK) assessed the retrieved records for inclusion independently. They were not blinded to the identity of the authors, their institution, or the results of the research. They obtained and assessed, again independently, the full report of records considered by either reviewer to meet the inclusion criteria. Disagreements were resolved by discussion or consultation with the co-supervisor (AEA). All decisions on study identification were recorded.

4.5. Data collection and data items

The same two persons (RKA and EGK) performed data extraction independently and any disagreements were again resolved by discussion or consultation with the thesis co-supervisor (AEA). Data collection forms were used to record the desired information.

a. Bibliographic details of the study.

b. Details on study design and verification of study eligibility.

c. Participant characteristics (where available number, age, gender).

d. Intervention characteristics (e.g. type of appliances, orthodontic treatment with/without extractions or with/without expansion, etc.).

e. Details on outcomes assessed and assessment procedures.

f. Additional information: a prior sample size calculation, methodology reliability assessment.

When clarifications were needed regarding the published data, or additional material was required, then attempts to contact the corresponding authors were made.

4.6. Risk of bias in individual studies

The principal investigator (RKA) and the thesis principal supervisor (EGK) assessed the risk of bias in the included studies, independently and in duplicate, during the data extraction process, using the Newcastle-Ottawa Scale (NOS) (Wells et al., 2008). Any disagreements were resolved by discussion or consultation with the thesis co-supervisor (AEA). The Newcastle-Ottawa Scale (NOS) assessment tool includes the following domains:

a. Selection

b. Comparability

c. Exposure/Outcome

4.7. Synthesis of results

Although we intended to do a meta-analysis as per the protocol, it was not possible because of study heterogeneity.

4.8. Risk of bias across studies and additional analyses

If a sufficient number of trials were identified, analyses were planned for "small-study effects" and publication bias (Higgins and Green, 2011). If deemed possible, exploratory subgroup analyses were planned according to participant and intervention characteristics. Finally, the quality of evidence was planned to be assessed based on

the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach (Guyatt et al., 2011).

5. RESULTS

5.1. Study selection

The flowchart of records through the reviewing process is shown in Figure 1. The data search took place in July 2019. Initially 434 records were identified, 27 were identified as duplicates, a further 398 were excluded on the basis of their title and abstract, three because they were animal studies (Machado et al., 2012; Murata et al., 2013; Aghilli et al., 2013) and one human study because the patients did not undergo complete orthodontic treatment (Owman-Moll and Kurol, 2000). Finally, five full-text human studies were included in the systematic review (McNab et al., 1999; Nishioka et al., 2006; Nanekrungsan et al., 2012; Malan, 2017; Pastro et al., 2018).

5.2. Study characteristics

The general characteristics of the studies included in the present systematic review, as well as sample characteristics, are presented in Tables 1 and 2. The located eligible studies were published between 1999 and 2018. Three studies had a cohort design (McNab et al., 1999; Nanekrungsan et al., 2012; Malan, 2017) and two a case-control design (Nishioka et al., 2006; Pastro et al., 2018). McNab et al. (1999), Nishiokia et al. (2006) and Malan (2017) considered the association of asthma and root resorption development following comprehensive orthodontic treatment with fixed appliances. Nishiokia et al. (2006), Nanekrungsan et al. (2012) and Pastro et al. (2018) investigated the association of allergy and root resorption development. However, in the latter studies it was not specified whether the records indicated airway allergy or other kind of allergic condition. After communicating with the respective authors, we could not obtain any further information.

Two studies used orthopantomograms for the assessment of root resorption (McNab et al., 1999; Nishioka et al., 2006), two used periapical radiographs (Nanekrungsan et al., 2012; Pastro et al., 2018) and one used CBCT (Malan, 2017). Two of the included studies used for the assessment of resorption grading scales, assigning different resorption grades to the investigated teeth (McNab et al., 1999; Pastro et al., 2018), whereas the rest measured the actual root or tooth length and used the measurements to identify an excessive resorption group (Nishioka et al., 2006), or calculated the percentage of root resorption (Nanekrungsan et al., 2012) or the pre- to post-treatment length differences (Malan, 2017). McNab et al. (1999) assessed the amount of external root resorption by using either the grading scale in all first and second premolars, mesiobuccal and distobuccal roots of the upper first molars, mesial and distal roots of the lower first molars, Nishioka et al. (2006) in all teeth with complete root formation, Nanekrungsan et al. (2012) used the maxillary central and lateral incisors, Malan (2017) used the maxillary centrals and Pastro et al. (2018), used the maxillary and mandibular centrals.

With regard to the age of the patients at the beginning of treatment great variability was observed, with the exception of McNab et al. (1999) and Pastro et al. (2018) that focused mostly on adolescents. The duration of the orthodontic treatment also varied extensively in all studies and groups and all studies included patients who had extractions as part of their treatment plan. However, Malan (2017) included patients who had expansion as well.

Other variables that were considered in the included studies were any systemic disease, medications use, type of initial malocclusion, treatment plan, duration of treatment, gender, age, ethnicity, root morphology, overjet, overbite, history of trauma, parafunctional habits (thumb sucking, nail biting, tongue thrusting, bruxism),

mouth breathing and periodontal problems. However, these parameters were not always considered as confounding factors regarding the effect of history of asthma or allergy in root resorption development. Only three studies considered and demonstrated comparability between the investigated groups. McNab et al. (1999) demonstrated comparability for gender, age, treatment duration, type of bracket edgewise, headgear use, overjet, overbite and performance of extractions or not, and controlled in the statistical analysis model for the effect of the type of appliance, whether extractions had been performed, and the length of treatment. Nishioka et al. (2006) also showed group comparability for gender, age, treatment duration, and the type of malocclusion. Pastro et al. (2018) observed that the no/mild resorption and the moderate/severe resorption groups of patients were comparable regarding gender, age at start, type of malocclusion, bruxism, onychophagy, biting habits, tongue thrusting and sucking.

All the included studies did not mention if they had performed sample size calculations. Two studies (McNab et al., 1999; Pastro et al., 2018) assessed the method error using the Kappa score, Nishioka et al. (2006) used the ANOVA, Malan (2017) used the inter-class correlation coefficient, and Nanekrungsan et al. (2012) used the Pearson's product-moment correlation.

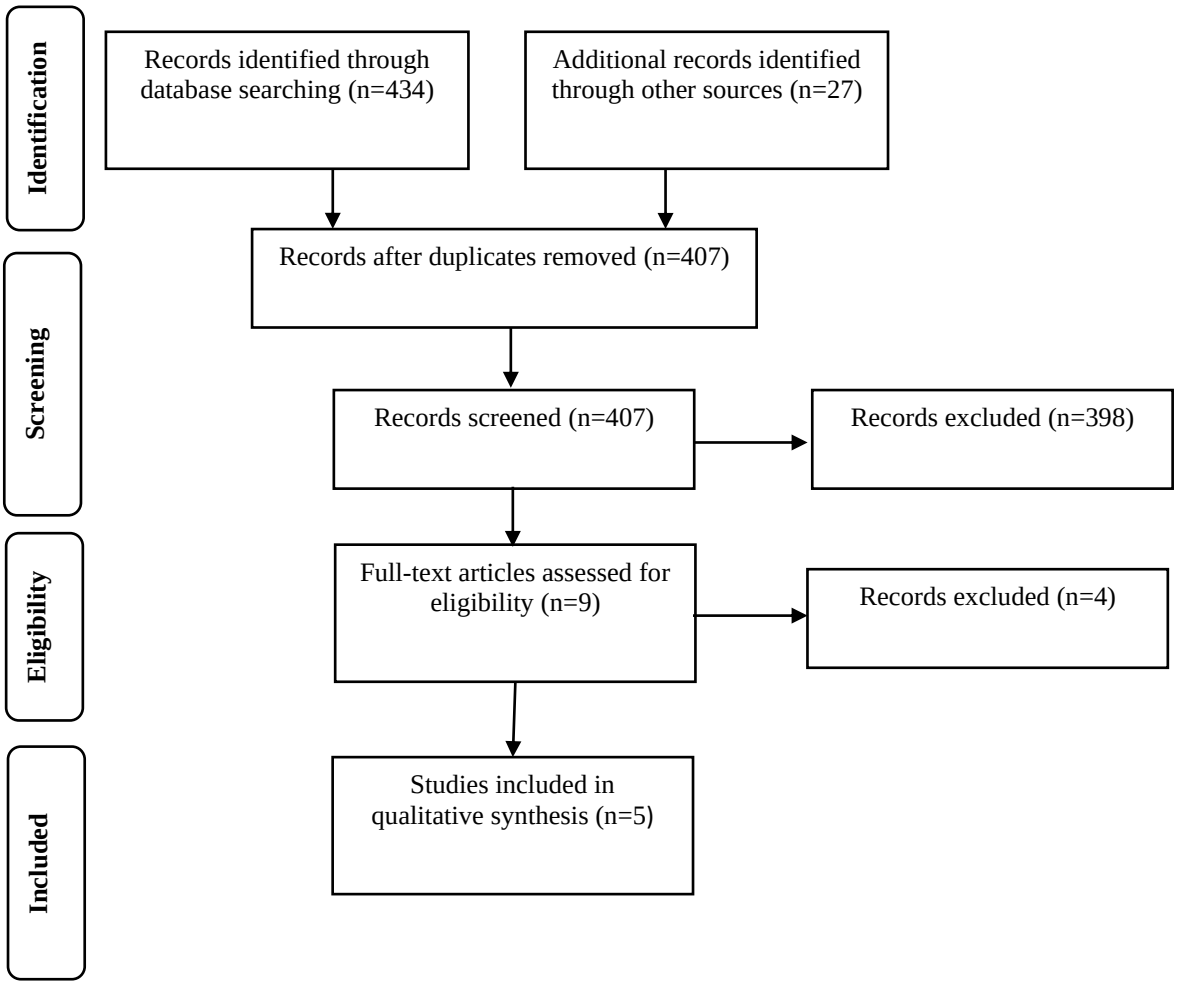

Figure 2. Flowchart of records through the reviewing process

Table 1. General characteristics of the studies included in the systematic review.

Study	Intervention characteristics	Teeth assessed and RR assessment methods	Other variables considered	Additional information
McNab et al. 1999 Double cohort study	Comprehensive orthodontic treatment with fixed appliances [with or without extractions; potential use of HG]	Pms, Mx FM(s) [MB, DB roots]; Md FM(s) [M, D roots] OPG [RR classification based a grading scale (Sharpe et al., 1987), unit of analysis the tooth]	Gender, age, Tx duration, % edgewise, % HG, OJ, OB, % non-extraction	Power calculations: NM Group comparability: Yes [gender, age, Tx duration, % edgewise, % HG, OJ, OB, % non-extraction] Method error: Kappa score
Nishioka et al. 2006 Case-control study	Comprehensive orthodontic treatment with fixed appliances [edgewise brackets; with or without extractions]	All teeth with complete root formation OPG [Root length (CEJ to apex); unit of analysis the individual] Excessive RR: shortening by at least 25% of the original length	Root morphology, extraction/non-extraction, trauma, gingivitis, systemic disease, medication use, thumb sucking, nail biting, tongue thrusting, mouth breathing	Power calculations: NM Group comparability: Yes [gender, age, Tx duration, type of malocclusion] Method error: ANOVA
Nanekrungsan et al. 2012 Cohort study	Comprehensive orthodontic treatment with fixed appliances [standard edgewise or preadjusted edgewise brackets; with or without extractions]	Mx central and lateral incisors PA [% of RR (root length from CEJ to apex); measurements corrected for enlargement; unit of analysis the tooth]	Age at the start of Tx, OJ, OB, root shape, history of trauma, extraction/non-extraction, gender, type of malocclusion and appliance, root morphology, tongue thrusting	Power calculations: NM Group comparability: NM Method error: Pearson's product-moment correlation
Malan 2017 Cohort study	Comprehensive orthodontic treatment with fixed appliances [with or without extractions or expansion]	Mx central incisors CBCT [RR: difference in pre- to post-Tx tooth length (incisal edge to apex; unit of analysis the tooth]	Age at the start of Tx, ethnicity, extraction/non-extraction, duration of Tx, gender, expansion/non-expansion	Power calculations: NM Group comparability: NM Method error: intra-class correlation coefficient
Pastro et al. 2018 Case-control study	Comprehensive orthodontic treatment [with or without extractions]	Mx and Md central incisors PA [RR classification based a grading scale (Malmgren et al., 1982), the highest degree of degree of resorption of all teeth was considered, unit of analysis the person]	Age at the start of Tx, age at the end of Tx, duration of Tx, gender, malocclusion, extraction/non-extraction, bruxism, onychophagy, biting habits, tongue thrusting, sucking, RR at pre-Tx	Power calculations: NM Group comparability: Yes [gender, age at start, type of malocclusion, bruxism, onychophagy, biting habits, tongue thrusting, sucking] Method error: Kappa score

CEJ: cementoenamel junction, DB: disto-buccal; HG: headgear; MB: mesio-buccal, Md: mandibular, Mx: maxillary, NM: not mentioned, OB: overbite, OJ: overjet, OPG: orthopantomogram, PA: periapical radiograph, Pm(s): premolar(s); RR: root resorption, Tx: treatment

Table 2. Sample characteristics in the studies included in the systematic review.

Study	Inclusion and exclusion criteria	Analyzed sample
McNab et al. 1999 Double cohort study	**Inclusion criteria:** Complete records, Tx plan and Tx history, pretreatment OPG and another OPG taken within 1 month of debanding using the same machine and a standardized technique. Asthmatic group included unmedicated and medicated asthma patients. Control group patients must be free of any known medical condition, age-matched and sex-matched to provide a minimum of 2 controls per asthmatic patient. Only teeth with complete root formation were measured. **Exclusion criteria:** Dental agenesis, invaginations and taurodontism, Apices which could not be visualized accurately. Anterior teeth. Teeth with pretreatment RR.	**141 patient**s Asthmatic group: 44; 531 apices Healthy group: 97; 1177 apices **Age at the beginning of Tx (mean ±SD):** Medicated asthmatic group: 14 ±1.2 years Unmedicated asthmatic group: 14.5 ±3.2 years Healthy group: 13.9 ±1.8 years **Tx duration (mean ±SD):** Asthmatic group: 1.8 ±0.4 years Healthy group: 1.9 ±0.5 years
Nishioka et al. 2006 Case-control study	**Inclusion criteria:** Complete records of the malocclusion, Tx plan and Tx history. Only teeth with complete root formation were measured. Control group patients matched on age, sex Tx duration and type of malocclusion **Exclusion criteria:** Teeth with apices that could not be observed accurately; teeth whose crown lengths (defined as cementoenamel junction to incisal edge) were obviously different before and after Tx because of the distortion of the image.	**120 patients** Excessive RR group: 60; 18M, 42F Control group: 160; 18M, 42 F **Age at the beginning of Tx (mean ±SD):** Excessive RR group: 16.8 ±5.9 years Control group: 17.7 ±5.9 years **Tx duration (mean ±SD):** Excessive RR group: 3.1 ±1.19 years Control group: 2.96 ±0.56 years
Nanekrungsan et al. 2012 Cohort study	**Inclusion criteria:** Complete Md and Md arches. Fixed appliance Tx. Complete records including pre- and post-treatment intra-oral PA radiographs. **Exclusion criteria:** Crown dimensions alteration during the treatment period due to tooth fracture or abrasion. Radiographs exclude: poor projection, crown or apex was not fully visible, CEJ blurred.	**181 patients** Allergic condition group: 88 teeth Without allergic condition group: 472 teeth

M: males: F: females; Tx: treatment; Md: mandibular; Mx: maxillary; Pm: premolars; OPG: orthopantomogram; PA: periapical; RR: root resorption; CEJ: cementoenamel junction

Table 2. Sample characteristics in the studies included in the systematic review. [Continued]

Study	Inclusion and exclusion criteria	Analyzed sample
Malan 2017 Cohort study	**Inclusion criteria**: complete fixed orthodontic Tx. Pre- and post-Tx CBCT scans taken from NewTom 5G **Exclusion criteria:** Missing or not fully formed maxillary central incisor. Phase 1 Tx. Mx surgical cases. Changes in incisal contour of central incisor crown.	**291 patients:** 120M, 71F **Age at the beginning of Tx (mean ±SD):** 17 ±9.5 years Asthmatic group: 66 teeth Non-asthmatic group: 516 teeth **Tx duration (mean ±SD):** 26.6 ±8.3 months
Pastro et al. 2018 Case-control study	**Inclusion criteria:** Complete records of the malocclusion, Tx plan and Tx history. Good PA radiographs of the Mx and Md incisors pre- and post-Tx, at the beginning and end of the orthodontic treatment. **Exclusion criteria:** teeth not showing normality parameters, for example, endodontic treatment and tooth reimplantation.	**600 patients:** 292M, 308F Absent or mild RR: 507 (252M, 255F), mean age 14.21 years Moderate or severe RR: 93 (40M, 53F), mean age 14.57 years **Age at the beginning of Tx (mean ±SD):** Absent or mild RR: 14.21 ±2.45 years Moderate or severe RR: 14.57 ±2.97 years **Age at the beginning of Tx (mean ±SD):** Absent or mild RR: 16.02 ±2.56 years Moderate or severe RR: 16.99 ±2.97 years **Tx duration (mean ±SD):** Absent or mild RR: 1.81 ±0.83 years Moderate or severe RR: 2.41 ±0.99 years

M: males: F: females; Tx: treatment; Md: mandibular; Mx: maxillary; Pm: premolars; OPG: orthopantomogram; PA: periapical; RR: root resorption; CEJ: cementoenamel junction

5.3. Risk of bias within studies

Table 3 presents the summary of findings regarding risk of bias assessment for the included studies. Three of them were awarded most stars for the considered categories (McNab et al., 1999; Nishioka et al., 2006; Pastro et al., 2018). In general, most issues were encountered in the comparability category, as important parameters associated with root resorption development were not considered in the analyses regarding the association of history of asthma or allergy in root resorption development. Only three studies examined and demonstrated comparability between the investigated groups (McNab et al., 1999; Nishioka et al., 2006; Pastro et al., 2018). Nanekrungsan et al. (2012) and Malan (2017) did not verify that the outcome of interest, i.e. root resorption was absent at the start of the study, consequently did not receive a star for item 4 in the selection category. The two case control studies, did not receive a star for item 4 in selection, because the controls included individuals with mild forms of root resorption. In addition, the compared groups in Pastro et al. (2018) showed different levels of pre-existing apical root resorption. All studies did not receive a star for the ascertainment of exposure, as it was based on the patient's history and not on secure records on the condition.

Table 3. Summary of the risk of bias assessment.

Study	Type	Newcastle-Ottawa scale categories		
		Selection	Comparability	Outcome/exposure
McNab et al. [1999]	Cohort	***	**	***
Nishioka et al. [2006]	Case control	***	*	**
Nanekrungsan et al. [2012]	Cohort	**		***
Malan [2017]	Cohort	**		***
Pastro et al. [2018]	Case control	***	*	**

5.4. Results of individual studies

The results of the cohort studies were contradictory. McNab et al. (1999) showed in the combined tooth analysis (after adjusting for treatment time, appliance type, and the inclusion or not of extractions in the treatment plan) that asthmatic patients had significantly more external apical root resorption of posterior teeth after treatment compared with the healthy group (p=0.0194). Similarly, Nanekrungsan et al. (2012) observed that allergic condition was a significant factor for root resorption (p=0.003). On the contrary, Malan (2017) found that root resorption was not different between asthmatics and non-asthmatic patients (p=0.954).

The results from the case-control studies were also conflicting. Although Nishiokia et al. (2006) observed that the incidence of allergy was significantly higher in the excessive root resorption group (p=0.030), the same was not shown for the incidence of asthma (p=0.063), despite the fact that external root resorption tended to be higher in latter. Finally, Pastro et al. (2018) did not demonstrate that the history of allergy was greater in the moderate or excessive resorption group compared to the group without or with only mild grade of resorption (p=0.182).

5.5. Risk of bias across studies and additional analyses

Because it was not possible to retrieve a sufficient number of trials, we were not able to conduct analyses for “small-study effects” and publication bias (Higgins and Green, 2011) nor were we able to assess the quality of evidence based on the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach (Guyatt et al., 2011).

6. DISCUSSION

6.1. Summary of evidence

Even though external apical root resorption is one of the common sequela of orthodontic treatment, noticeable amounts of resorption during a relatively short period, such as the course of orthodontic treatment, is not so common (Owman-Moll and Kurol, 2000). Nonetheless, it has been suggested that that individuals who have conditions like asthma and airway allergy that disturb the immune system might be at risk for developing severe root resorption during orthodontic treatment (Davidovitch et al., 1996). However, the information provided in the studies included in the present review was contradictory. Although, various concerns were raised during risk of bias assessment compelling the clinician to approach the relevant observations with caution, good practice would suggest that it is important to identify patients with asthma or allergy and consider the possible implications.

Only five studies were found to investigate the association of asthma and airway allergy with external root resorption after orthodontic treatment. McNab et al. (1999), Nishioka et al. (2006) and Malan (2017) considered the association of asthma and root resorption development following comprehensive orthodontic treatment with fixed appliances. Only the double cohort study of McNab et al. (1999) showed an association of asthma history (both medicated and unmedicated) with more external apical root resorption of posterior teeth, after adjusting for potential confounders. Considering this study, it is important to mention that asthmatics tended to have more teeth with minor root resorption, while more severe grades of resorption were approximately the same in healthy and asthmatic patients. The cohort study of Malan

(2017) and the case-control study of Nishioka et al. (2006) did not demonstrate any association.

Regarding the association of airway allergy and root resorption, Nishioka et al. (2006) observed that the incidence of allergy was significantly higher in the excessive root resorption group. The same was observed in a cohort study design by Nanekrungsan et al. (2012). However, in the case-control study of Pastro et al. (2018) no association between history of allergy and moderate or excessive resorption could be observed.

Owman-Moll and Kurol (2000) also investigated in a case-control design the association of allergy as a predisposing factor for root resorption development. Relevant information was obtained through patient interviews, and a differentiation was made for the self-reported cases and those verified by consultation with the physician or by on-going medication. However, in this study the intervention did not include a complete course of comprehensive orthodontic treatment with fixed appliances. After buccal movement of maxillary premolars for 1 to 7 weeks, the experimental teeth were extracted and subjected to histological analysis and measurement of the resorbed root area. Individuals with allergy showed an increased risk of root resorption, but this was not statistically significant.

The results from animal experiments regarding the allergen sensitization on external root resorption associated with orthodontic tooth movement, have suggested that allergy may increase the susceptibility to root resorption. A histomorphometric study of the periodontal ligament of Wistar rats in the initial period of orthodontic movement showed an enhanced response to mechanical stimuli in the animals sensitized nasally with ovalbumin. In the asthmatic rats the periodontal ligament was more compressed at the pressure area and more stretched in the traction area, a response that could potentially indicate increased bone turnover and

osteoclastogenesis/odontoclastogenesis (Machado et al., 2012). Murata et al. (2013) investigated in ovalbumin-sensitized Brown–Norway rats, the amounts of orthodontic tooth movement and root resorption and compared it to those measured in animals subjected to orthodontic force alone. They observed that both amount of movement and root resorption was more pronounced in the former group. Moreover, the expression levels of RANKL and proinflammatory cytokines were increased in the periodontal tissues of sensitized animals. At the same time an upregulation of leukotriene B4 (LTB4), a potent lipid mediator of allergic inflammation, and enzymes of the 5-lipoxygenase pathway, the biosynthetic pathway of leukotrienes, was observed. Moreover, low doses of aspirin suppressed root resorption in allergen-sensitized rats, as well as the expressions of RANKL, proinflammatory cytokines, and LTB4. On the contrary, Aghili et al. (2013) did not observed a statistically significant difference in root resorption development between sensitized and non-sensitized animals.

External root resorption following orthodontic tooth movement is considered to be a complicated phenomenon, associated with a multitude of parameters and inflammatory related pathways (Iglesias-Linares et al., 2016). The various implicated factors are believed to be be both biological (Brezniak and Wasserstein, 2002) and mechanical (Levander and Malmgren, 1988; Linge and Linge, 1983; Kaley and Phillips, 1991; Costopoulos and Nanda, 1996) and might not be involved in the same degree in resorption severity and extent development in all affected individuals. Thus, sometimes no single explanation can be given nor we are able to unequivocally predict individual susceptibility (Iglesias-Linares et al., 2016).

Overall, the located studies did not present analyses that accounted for the confounding effect of the various implicated factors in their investigation of the

association of history of asthma or allergy in root resorption development. Three out of the five eligible studies examined and demonstrated comparability between the investigated groups (McNab et al., 1999; Nishioka et al., 2006; Pastro et al., 2018). In these papers the potential confounding effect of the following variables was excluded: gender, age at start of treatment, treatment duration, type of edgewise bracket, headgear use, overjet, overbite and performance of extractions or not (McNab et al., 1999); gender, age, treatment duration and type of malocclusion (Nishioka et al., 2006); gender, age, type of malocclusion and various habits (Pastro et al., 2018). In the study of Nishioka et al. (2006), the case and the control groups were not comparable in terms of pre-treatment root morphology abnormality (shortened, blunt, eroded, pointed, bent or bottle shaped roots). However, this was not accounted for statistically. The same was observed in Pastro et al. (2018) study were the no/mild resorption and the moderate/severe resorption groups differed in terms of the inclusion of extractions in the treatment plan and the pre-existing apical root resorption. In the rest of the included studies a multitude of factors was investigated but not as confounding factors regarding the association of history of asthma or allergy in root resorption development.

It is noteworthy, that two out of the three located cohort studies did not control for the potential confounding effect of the pre-treatment root resorption (Nanekrungsan et al., 2012; Malan, 2017). Only McNab et al. (1999) excluded those teeth and their analysis involved directly the degree of posttreatment root resorption. The two case-control studies, included individuals with pre-existing resorption in the control group (Nishioka et al., 2006; Pastro et al., 2018). Indeed, in Pastro et al. (2018) the no/mild resorption and the moderate/severe resorption groups differed significantly.

Another potential source of confounding might stem from the way the exposure to the investigated risk factor, i.e. asthma or allergy was ascertained. The patients' medical history from their orthodontic treatment file was used without further verification, clarification or elaboration on the exact nature and severity of the condition and the associated symptoms or the medication used. Moreover, the studies that investigated the association of allergy and root resorption development (Nishiokia et al., 2006, Nanekrungsan et al., 2012; Pastro et al., 2018), did not specify whether they were referring to airway allergy or other kind of allergic condition. However, it was not possible to obtain further information from the respective authors.

The results reported in the eligible studies might have been affected by the methodology employed for the assessment of resorption. Although root resorption associated with orthodontic tooth movement constitutes a three-dimensional process, most studies investigated the existence and amount of resorption using conventional radiographs, orthopantomograms (McNab et al. 1999; Nishioka et al., 2006) and periapical radiographs (Nanekrungsan et al., 2012; Pastro et al., 2018) limiting the investigation to two dimensions. In these cases, root resorption can only be discovered on the apex, as well as the mesial and distal surfaces. Additionally, both methods are considered as inadequate tools for accurate measurements and unsuitable for the identification of the progression of the relative minor root resorption that might occur during the course of treatment with fixed orthodontic appliances (Nishioka et al., 2006). The standardized procedure of taking intra or extra-oral radiographs is technique sensitive that might cause distortion to the tooth image thus having inherent limitations in the measurement reliability especially for the panoramic radiographs predominantly in the incisor region (Pastro et al., 2018). Therefore, these expected errors associated with the two-dimensional radiographic techniques, might be

overcome by the use of cone-beam computed tomography as in the Malan (2017) study.

Only three of the included studies made actual root or tooth length measurements (Nishioka et al., 2006; Nanekrungsan et al., 2012, Malan 2017), whereas the rest assigned a score based on ordinal grading scales, a fact that could potentially have influenced the precision of the results. Moreover, all studies assessed multiple teeth. However, only McNab et al. (1999) analysed the sample with an overall model that acknowledged that repeated observations came from multiple teeth per subject. Furthermore, although Pastro et al. (2018) graded root resorption in the maxillary and mandibular incisors, only the highest degree of resorption of all teeth was considered, an approach that dealt with the problem of repeated observations, but at the same time obscuring the extent and the severity of root resorption in the rest of the incisors and potentially ignoring important information. In the rest of the located studies relevant statistical adjustments were not employed or considered.

Despite the shortcomings of the included studies, compelling the clinician to approach the relevant observations with caution, and more data become available, good practice would suggest that it is important to identify patients with asthma or airway allergy and consider the possible implications. In these cases, application of lower forces and more frequent appointments and radiographic follow-up might be warranted, as well as to paying attention to the other factors that have been associated with root resorption development (Sondeijker et al., 2019). Such mechanical or treatment related factors include tooth movement into the labial or cortical bone (Malmgren et al., 1994), long treatment duration and increased magnitude of force (Kvam,1967; Harry and Sims, 1982; Vardimon et al., 1991; Eross et al., 2015), the amount of apical displacement (Topkara et al., 2012), the inclusion of extractions in the treatment plan

(Nishioka, 2006; Pastro, 2018) and the use of inter-maxillary elastics (Linge and Linge, 1983). Moreover, biological or patient related factors should be considered. Some studies have reported that root resorption associated with orthodontic treatment is more prevalent in older individuals (Mavragani et al., 2000; Sameshima and Asgarifar, 2001; Nanekrungsan et al., 2012), although others have not observed similar associations (McNab et al., 1999; Malan 2017; Nishioka et al., 2006; Pastro et al., 2018). Dental anomalies (ectopia, agenesis, taurodontism) (Kjaer, 1995; Lee et al., 1999), teeth with pipette-shaped, blunt, abrupt deflection or narrow roots (Levander and Malmgen, 1988; Kjær, 1995; Mirabella and Årtun, 1995a; Lee et al., 1999), individuals with parafunctional oral habits (Odenrick et al., 1985; Linge and Linge, 1991), type of malocclusion (Motokawa et al., 2013), traumatized teeth (Andreasen, 1988; Malmegren et al., 1982), as well as the effect of the medication that individuals use for their medical condition warrant our attention (Verna et al., 2006).

6.2. Strengths and limitations

The strengths of the present review include using a methodology following well-established guidelines. To our knowledge, there has been no other systematic review conducted on the association between asthma and other allergic conditions with root resorption development in patients having undergone orthodontic treatment. Moreover, the search strategy employed in the present review was both exhaustive, covering electronic, manual, and gray literature material up to July 2019, and comprehensive including every available study, irrespective of language, date and status of publication. Every effort to decrease bias in the methodology employed was made. Screening, verification of eligibility, abstraction of information, assessment of risk of bias and of the quality of evidence were all performed in duplicate, and any

disagreement was resolved by discussion or consultation until a final consensus was achieved. There are also some limitations to the present review, arising mainly from the nature and the characteristics of the included studies and the data retrieved during the review process, which have been already discussed.

6.3. Recommendations for future research

Although pronounced root resorption over a relatively short period, such as the course of orthodontic treatment, is not to be expected (Owman-Moll and Kurol, 2000), the data included in the present review did not unequivocally rule out any association between asthma or airway allergy and external apical root resorption development following comprehensive orthodontic treatment. In order to investigate the phenomenon more comprehensively and considering the prevalence of asthma or airway allergy, further research is warranted. Since it is not expected to have randomized studies in order to investigate this subject, it is sensible to suggest conducting well-controlled non-randomized studies that are comparable to well-performed randomized studies (Sterne et al., 2016). Particular importance should be placed on possible ways to control possible confounding factors as outlined previously, as well as bias in the measurement of outcomes. In this respect, the use of the use of cone-beam computed tomography is advisable (De Grauwe et al., 2019; Samandara et al., 2019). Moreover, stable and easily located reference points should be considered. For example, the cementoenamel junction, although anatomically is stable, it is harder to replicate its exact location in comparison to the incisal edge (Malan, 2017).

7. CONCLUSIONS

The information regarding the association of asthma and airway allergy with root resorption following orthodontic treatment is contradictory and further research is warranted. However, until more data become available good practice would suggest that it is important to identify patients with asthma or allergy and consider the possible implications.

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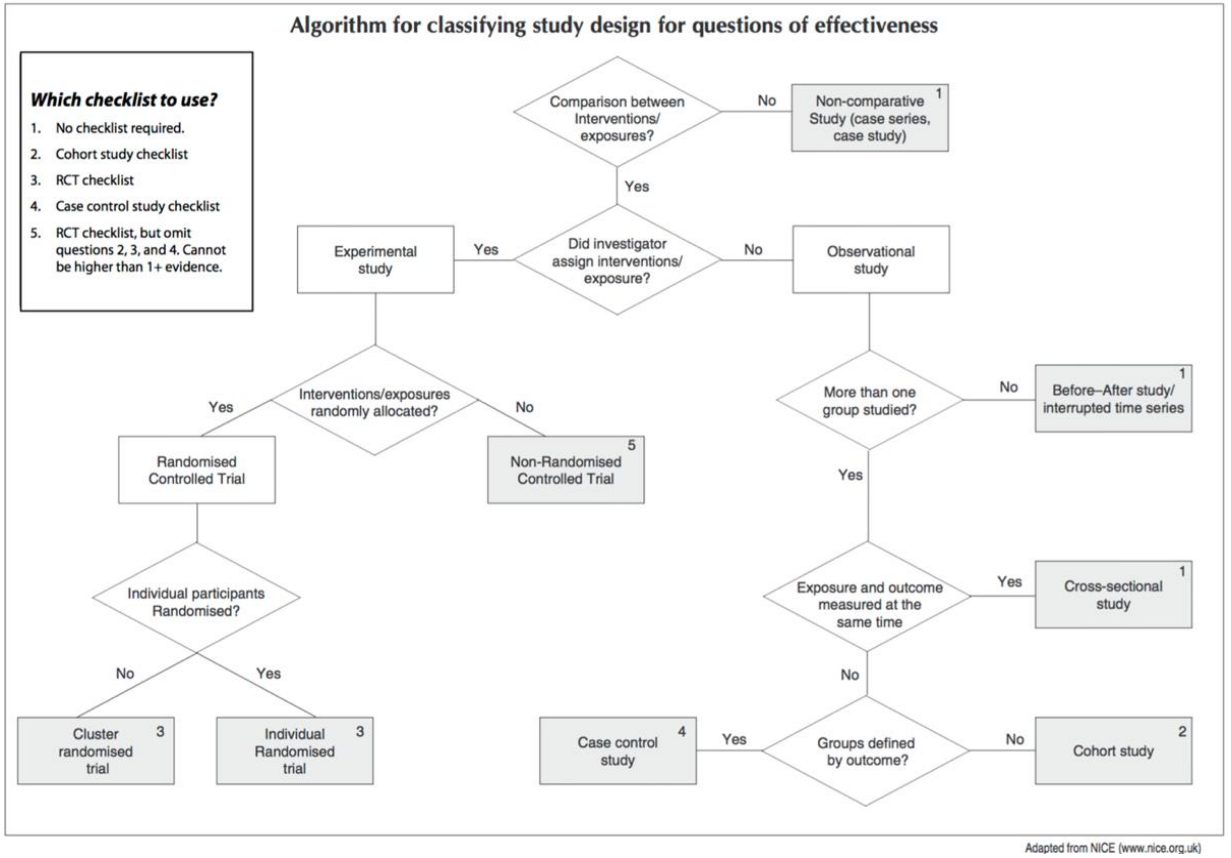
9. APPENDICES

Appendix I. Scottish Intercollegiate Guidelines Network (SIGN) algorithm for classifying study design for questions of effectiveness



Appendix II. Strategy for database search.

Database [2019 07 09]	Search strategy	Hits
PubMed	(orthodon* OR “orthodontic force” OR “mechanical force”) AND ("tooth movement" OR “orthodontic movement” OR “orthodontic anchorage” OR “root resorption”) AND (allergy OR allergic* OR sensitiv* OR hypersensitiv* OR ovalbumin OR OVA OR “Dust Mite” OR HDM OR ascaris OR aspergill* OR “cotton dust” OR latex OR DRA OR cockroach OR asthma* OR airway)	**203**
Cochrane Central Register of Controlled Trials	(orthodon* OR “orthodontic force” OR “mechanical force”) AND ("tooth movement" OR “orthodontic movement” OR “orthodontic anchorage” OR “root resorption”) AND (allergy OR allergic* OR sensitiv* OR hypersensitiv* OR ovalbumin OR OVA OR “Dust Mite” OR HDM OR ascaris OR aspergill* OR “cotton dust” OR latex OR DRA OR cockroach OR asthma* OR airway) in Title, Abstract, Keywords in Trials - (Word variations have been searched)	**11**
Cochrane Database of Systematic Reviews	(orthodon* OR “orthodontic force” OR “mechanical force”) AND ("tooth movement" OR “orthodontic movement” OR “orthodontic anchorage” OR “root resorption”) AND (allergy OR allergic* OR sensitiv* OR hypersensitiv* OR ovalbumin OR OVA OR “Dust Mite” OR HDM OR ascaris OR aspergill* OR “cotton dust” OR latex OR DRA OR cockroach OR asthma* OR airway) in Title, Abstract, Keywords in Trials - (Word variations have been searched)	**0**
Scopus	TITLE-ABS ((orthodon* OR “orthodontic force” OR “mechanical force”) AND ("tooth movement" OR “orthodontic movement” OR “orthodontic anchorage” OR “root resorption”) AND (allergy OR allergic* OR sensitiv* OR hypersensitiv* OR ovalbumin OR OVA OR “Dust Mite” OR HDM OR ascaris OR aspergill* OR “cotton dust” OR latex OR DRA OR cockroach OR asthma* OR airway))	**236**
Web of Science™	TOPIC: ((orthodon* OR “orthodontic force” OR “mechanical force”) AND ("tooth movement" OR “orthodontic movement” OR “orthodontic anchorage” OR “root resorption”) AND (allerg* OR sensitiv* OR hypersensitiv* OR ovalbumin OR OVA OR “Dust Mite” OR HDM OR ascaris OR aspergill* OR “cotton dust” OR latex OR DRA OR cockroach OR asthma* OR airway)) Timespan: All years. Databases: WOS, KJD, RSCI, SCIELO, ZOOREC. Search language=Auto	**243**
Arab World Research Source	TI tooth movement AND AB tooth movement	**3**
ClinicalTrials.gov	(orthodontic OR orthodontics) AND (tooth movement)	**37**
ProQuest Dissertations and Theses Global	ti((orthodon* OR “orthodontic force” OR “mechanical force”) AND ("tooth movement" OR “orthodontic movement” OR “orthodontic anchorage” OR “root resorption”) AND (allergy OR allergic* OR sensitiv* OR hypersensitiv* OR ovalbumin OR OVA OR “Dust Mite” OR HDM OR ascaris OR aspergill* OR “cotton dust” OR latex OR DRA OR cockroach OR asthma* OR airway)) OR ab((orthodon* OR “orthodontic force” OR “mechanical force”) AND ("tooth movement" OR “orthodontic movement” OR “orthodontic anchorage” OR “root resorption”) AND (allergy OR allergic* OR sensitiv* OR hypersensitiv* OR ovalbumin OR OVA OR “Dust Mite” OR HDM OR ascaris OR aspergill* OR “cotton dust” OR latex OR DRA OR cockroach OR asthma* OR airway)) [Full text]	**7**

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