EFFECT OF OVARIECTOMY-INDUCED MENOPAUSE ON THE RATE OF ORTHODONTIC TOOTH MOVEMENT: A SYSTEMATIC REVIEW OF ANIMAL STUDIES

Ayesha Omar Hussain Abdulla Mohammed
BDS, University of Sharjah, 2013

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
2019

ABSTRACT

Effect of ovariectomy-induced menopause on the rate of orthodontic tooth movement: a systematic review of animal studies

Ayesha Omar Mohammed, BDS

Supervisor: Associate Professor Eleftherios G. Kaklamanos

Background: The menopause may theoretically affect the biochemical events leading to orthodontic tooth movement.

Aim: To systematically investigate and appraise the quality of the available evidence from animal studies regarding the effect of experimentally induced menopause on the rate of orthodontic tooth movement.

Materials and Methods: Search without restriction for published and unpublished literature and hand searching took place. Controlled studies investigating the effect of ovariectomy-induced menopause on the rate of orthodontic tooth movement were reviewed. Following study retrieval and selection, relevant data was extracted and the risk of bias was assessed using the SYRCLE's Risk of Bias Tool.

Results: From the initially identified records, finally, 11 studies met the inclusion criteria. The majority of the retrieved studies were found to be of an unclear risk of bias. The rate of orthodontic tooth movement in ovariectomized animals was greater than in the control group. This difference between the two groups gradually widened as the duration of force application increased.

Conclusion: Ovariectomy-induced menopause may affect the rate of orthodontic tooth movement. Although the overall quality of evidence only provides the clinician with a

cautious perspective on the strength of the relevant recommendations, the orthodontist should be capable of identifying such patients and consider the possible implications.

DEDICATION

This dissertation is dedicated:

To my beloved Mother who has been my source of strength and support every day of my life, I could never have done this without your faith and constant encouragement and prayers. Thank you for being in my life, believing in me and teach to believe in myself and dreams.

To my Great Father Colonel Omar Mohammed, who loved, believed, encouraged and prayed for me to be a better person every day, without the inspiration, drive, and support that you have given me, I might not be the person I am today.

To the one who stole my heart the moment he was born, my incredible son Abdulaziz Almashghouni; 3 years ago I promised to make you proud and finish this Master program and dissertation. Today I'm writing these words to thank you for being in my life, without your smiles, hugs and kisses it would have been very difficult to accomplish any goal in my life.

To my husband Majid Almashghouni, I have always had you supporting me in all the good and bad times. Thank you for making me believe that I can do anything and everything in life

To my lovely young sister, brother, family members and friends who shared their words of advice everyday with me, thank you all for your support and continuing prayers.

To my One and Only Great sister Dr. Moaza Omar Mohammed who shared with me the journey of my life, to you my role model I would like to extend my thanks and great appreciation. Thank you for being my sister, my friend and colleague. No amount of thank you words can describe how thankful I am to you, without you I would have not been able to accomplish this program successfully.

To my Supervisor Dr. Eleftherios G. Kaklamanos, Professor Athanasios E. Athanasiou and all the Professors for the endless encouragement, motivation and support throughout my program.

And above all, to Allah.

DECLARATION

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

Name: Ayesha Omar Hussain Abdulla Mohammed

Signature:

ACKNOWLEDGMENTS

My special thanks and appreciation to Associate Professor in Orthodontics Eleftherios G. Kaklamanos for believing in me and for his steadfast support and hard work for the completion of this dissertation. Your constant motivation and guidance made me improve significantly during my residency.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1. INTRODUCTION

In recent years, the numbers of older adult individuals seeking orthodontic treatment has risen significantly as a result of the increased awareness of the benefits associated with providing a stable, acceptable function, as well as having a pleasant appearance (Tanaka et al., 2012; Yamashiro and Takano-Yamamoto, 2001). As orthodontic tooth movement is achieved by alternating processes of bone resorption and formation, the rate of movement is determined by several factors, including the quality of alveolar bone and surrounding tissues (Proffit et al., 2019). In post-menopausal women, lack of estrogens will lead to hormonal imbalances increasing bone turn-over (Tanaka et al., 2002; Hsieh et al., 1995). When bone resorption rate exceeds bone deposition, the osteoporosis occurs. The alveolar processes are sites commonly affected by osteoporosis (Dai et al., 2014; Tanaka et al., 2002).

Understanding the impact of menopause on orthodontic tooth movement 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. The aim of the present study was to systematically investigate and critically appraise the quality of evidence regarding the effect of experimentally induced menopause on the rate of orthodontic tooth movement.

2. REVIEW OF THE LITERATURE

Women in their life pass through different stages including puberty, menstruation, pregnancy and menopause (Suri and Suri, 2014; Morabia et al., 1998). Menopause is the permanent cessation of menses for 1 year in healthy individuals aged 45-65 years, while post-menopause is defined as the period after the last menstrual period (Kase, 2009; Speroff et al., 1999).

Menopause can be divided into natural menopause, surgical menopause, radiation-induced and chemotherapy-induced menopause (Nelson, 2008). Natural menopause is cessation of menses for 1 year without a known cause such as pregnancy while surgical menopause occurs by removing the uterus with one ovary or removing both ovaries with or without uterus removal. Both types of surgery will result in cessation of menses, but only the later will cause severe reduction in sex hormones levels (Sonja, 1996). Women undergoing chemotherapy or radiation will also demonstrate severe menopausal symptoms as a result of ovarian inadequacy (Santen et al., 2017).

With ageing, the natural death of ovarian cells will cause a noticeable reduction in ovarian estrogen (Kase, 2009). The menopausal period is usually divided into 3 different phases: peri-menopause, menopause and post-menopause (Kase, 2009).

Peri-menopause is the stage of approximately 2-8 years prior to menopause characterized by irregular periods with increased frequency of amenorrhea and the periods becoming irregular until they stop completely (Kase, 2009; Sonja, 1996). This stage, at which an increased reactivation of ovarian follicles is observed before complete cessation, is diagnosed by when the number of follicles reaches around 25000, together with a reduction in Inhibin B levels and a marked increase in Follicular-Stimulating Hormone (Prior, 1998). On the contrary, the Luteinizing Hormone in this phase remains stable and unchanged (Santoro et al., 2011; Hee et al., 1993; Faddy et

al., 1992; MacNaughton et al., 1992). Moreover, earlier in this phase, the increased Follicle Stimulating Hormone levels will result in a temporary activation of small ovarian follicles causing a rise in the circulating estradiol levels (Kase, 2009). Menopause is the final year of the menstrual period, while post-menopause is defined as the period after the last menstrual period and is further divided into the early post-menopause, when estrogen levels are rapidly decreasing, and the late post-menopause, when a prolonged decrease in estrogen levels is observed (Society, 2010; Kase, 2009; Speroff et al., 1999). The term climacterium has also been used to describe the entire midlife period including peri-menopausal, menopausal and post-menopausal periods' symptoms. However, the World Health Organization has abandoned this term to avoid confusion (World Health Organization, 1996).

The Stages of Reproductive Aging Workshop developed a model to divide the stages of women's reproductive ageing into reproductive, menopausal transition and post-menopause stages. The reproductive stage features a normal and regular menstrual cycle; the menopausal transition stage shows a rise in Follicle Stimulating Hormone level along with fluctuating menstrual cycles; and the post-menopausal stage starts from the last menstrual period and lasts till the end of life (Soules et al., 2001).

Menopausal associated changes commonly start from mid to late 40's and can continue for several years, with the final menstrual cycle occurring between 40 and 58 years old. Cessation of menses before the age of 40 is known as premature menopause. Several studies have suggested that low socioeconomics and smoking are associated with premature menopause (Gold et al., 2001). Other factors affecting the age at which the last period can be observed, include body-mass index, ethnicity, use of contraceptive medication and the age at menarche (Melby et al., 2005).

2.1. Consequences of menopause

The menopausal period is a point in women's lives when they pass through multiple changes in their body and life due to alterations in their biological and endocrine functions as a result of reduction in the sex hormones levels (Brace et al., 1997; Matthews, 1992).

The main consequences of menopause are due to the decrease of estrogens circulating in the female body. Estrogens are important to maintain the health of bones, as well as growth and function of multiple organs and tissues. Estrogen deficiency has an impact not only on the reproductive system but also on the other organs and systems in the body and women suffering from it can end up with multiple menopause associated problems including osteoporosis (Brzozowski et al., 1997; Turner et al., 1994). Case reports from males with estrogen receptor mutations have also shown abnormal bone density confirming that estrogens play an important role in maintaining bone density in both men and women (Smith et al., 1994).

Estradiol is the most important estrogen hormone, produced in the ovaries and responsible for the reproductive and sexual function (Gruber et al., 2002). In a normal non-pregnant woman, the most dominant estrogens are estrone and estradiol while in the pregnant women the main estrogen is estriol. Estrogens circulating in the blood will diffuse to cells and can be retained in the nuclei. Once estrogens bond to estrogen receptors, the receptor will go in a series of changes allowing it to modulate the expression of target genes (Marino et al., 2006; Ray et al., 2002; Jensen et al., 1972).

Estrogen receptors (ER) are nuclear hormone receptors. Two receptors are known, ERα and ERβ. In 1985, ERα was cloned for the first time and classified as a member of the nuclear receptor family and was called the 'Jensen' receptor. Later the second receptor was discovered and the two receptors were named as ERα and ERβ (Kuiper et al., 1996;

Greene et al., 1986). Both estrogen receptors are widely expressed in different tissue types; ERα is the most common in endometrium and mammary glands, while ERβ receptors are very plentiful in tissues that were previously classified as estrogen insensitive, such as colon and parenchyma of the lungs (Thompson et al., 2001).

2.1.1. Menopause associated systemic changes

At the beginning of the menopausal transition, hormonal levels start to fluctuate and become unstable leading to the gradual appearance of several symptoms (Santoro et al., 1996). The first symptom is usually a change in the menstrual period with lighter or heavier periods together with irregularity of occurrence (Ballinger et al., 1987). Vasomotor symptoms including hot flushes and night sweats will appear as red areas over the head, face and chest associated with a warm feeling mainly located over the chest area and accompanied with anxiety, perspiration and palpitations. Multiple triggers are known to aggravate this condition including stress, hot climate and food. Hot flushes show a great variability between women in intensity, duration and frequency and this variation has led large numbers of patients to seek medical care to treat them as they may interfere with sleep or daily activities (Santoro et al., 1996).

The theories behind the vasomotor symptoms are still not clear and fully understood. One theory is that dropping of estrogen levels during menopause will cause endorphins level to decline in the hypothalamus. Thus, both serotonin and norepinephrine neurotransmitters levels increase, which in turn lowers the set point of the thermoregulatory nucleus and causes inappropriate sweat loss (Freedman et al., 1995; 1999; Casper et al., 1985).

Emotional disturbances at this stage are secondary problems which can be aggravated by lack of sleep and hot flushes, although hot flushes are considered insufficient to

awaken a woman but enough to affect the quality of sleep (Joffe et al., 2013; 2016). Other psychological changes that can exert a deleterious effect on the patient are very common at this period. Symptoms such as irritability, mood swings, anxiety and panic attacks, poor memory and concentration, irritability and insomnia can be experienced.

In general, differences in the incidence of cardiovascular disease appear to be more clinically significant 10 years later in women than in men and menopause was found to be one of the contributing factors (Pepine et al., 2006). Coronary artery disease has been found to be the leading cause of death in post-menopausal women (Roger et al., 1998; Kannel, 1995).

Genitourinary symptoms including urethritis, urinary incontinence, dysuria, urinary frequency and recurrent urinary tract infections can be a result of mucosal thinning of the bladder and the urethra (Raz, 1993). Vaginal dryness and itching will cause sexual disturbances as estrogen levels drop and the mucosa is thinning (Biglia et al., 2003).

2.1.2. Menopause associated oral changes

There are a number of physical manifestations associated with menopause, some of which are manifested in the oral cavity. Periodontal tissues are very sensitive to hormonal imbalances during the menopausal transition phase which will affect the body's ability to fight back infections and maintain a healthy oral environment (Dutt et al., 2013). The effect witnessed in the oral cavity is very similar to that seen in the vagina due to their histological similarity. Estrogen receptors have also been detected in the gingiva, the oral mucosa and the salivary glands (Marrioti, 1994; Välimaa et al., 2004; Thompson et al., 2001; Leimola-Virtanen et al., 2000; 1997).

Estrogen receptors can be found in the periodontal fibroblasts and osteoblasts. Changes in sex hormones during the different phases of women's reproductive life will cause a

variable response in these receptors. As a result of low estrogen levels, impairment of tissues health will occur, as well as changes in inflammatory mediators, growth and differentiation of the fibroblasts and vascular permeability (Mascarenhas et al., 2003; Amar et al., 1994). Post-menopausal women are more commonly presented with periodontal problems that are more severe than those at younger ages (Yalcin et al., 2006).

Burning mouth syndrome, taste alterations and atrophic gingivitis can be seen during menopause as a result of atrophy of the oral mucosa (Friedlander, 2002; Frutos et al., 2002). Disorders such as lichen planus, pemphigus vulgaris and Sjögren's syndrome have been also documented as mucosal changes (Agha-Hosseini et al., 2009; Friedlander, 2002).

Non-medication related xerostomia has been found to be higher in post-menopausal women as a result of reduction in both stimulated and unstimulated sublingual and submandibular gland secretion (Friedlander, 2002). Moreover, the composition of saliva is also affected by the reduction in hormonal levels and the sympathetic activation which increases the concentrations of IgA and salivary proteins (Aryeh et al., 1996). As a secondary effect, women may suffer from increase in caries activity, periodontal problems, an unpleasant metallic taste in the mouth, glossodynia, oral candidiasis, difficulty in eating and swallowing, in addition to lack of stability of removable prosthesis if present (Friedlander, 2002).

Trigeminal neuralgia occurs due to a pressure on any division of the trigeminal nerve and it is one of the conditions reported during menopause (Friedlander, 2002). Electrical-like shock pain in the lower and the middle part of the face are the main symptoms frequently reported by patients and have been found to increase in women with long-term estrogen deficiency (Raina et al., 2012; Agha-Hosseini et al., 2009;

Friedlander, 2002; Frutos et al., 2002). Women suffering from long-term estrogen deficiency can also be at a high risk of developing other neurological diseases, such as Alzheimer's disease (Friedlander, 2002).

2.2. Hormonal replacement therapy

Postmenopausal hormone administration has been used to resolve and eliminate symptoms associated with gradual reduction of estrogens. Different methods can be used to deliver those hormones to women including oral, cream or gel, patches and intrauterine devices. In the 20th century Ovarin was developed. Ovarin was extracted from cow ovaries to treat post-menopausal symptoms and remained in use until pills derived from human pregnancy urine were developed. These products were later replaced by products developed from the urine of pregnant mares, like Premarin (Stefanick, 2005).

Estrogen-only therapy or estrogen combined with progesterone (or the synthetic form progestin) can be used as a line of treatment depending on the woman's medical history when the treatment is prescribed. Estrogen-only therapy is prescribed to women who have undergone a hysterectomy and can be used either transdermally or orally (Kuhl, 2005). However, it is not used for women with an intact uterus because it is associated with an increased risk of cancer (Furness et al., 2012). Non hysterectomized women receive combined treatment of both estrogen and progesterone, as progesterone is used to prevent hyperplasia of the uterus lining that may lead to uterine neoplasia (Martin et al., 2008).

Numerous studies have been conducted worldwide to justify the use of hormonal therapy, not only to treat symptoms such as hot flushes but also to protect women from other pathological conditions including osteoporosis and cardiovascular diseases

(Grodstein et al., 1995). The results of these studies have shown that the effectiveness of hormonal therapy can be affected by several factors including age, formulation, dosage, associated diseases and mode of administration (Harman, 2006).

Moreover, several studies have highlighted the possible elevated risk of breast cancer associated with the increased levels exogenous estrogen (Lee et al., 2005). Hormone replacement therapy associated with such risks received increased publicity when the results from large population studies focusing on the prevention of cardiovascular diseases, such as the Heart and Estrogen/progestin Replacement StudyI and II (post-menopausal women with an average age of 66.7 years), the Million Women Study (conducted in the UK to a group of women with an age range between 50-64 years) and the Women's Health Initiative study (post-menopausal women with age range between 50-79 years) were published. All three epidemiological studies did not guarantee the prevention of cardiovascular disease after the long-term use of hormonal replacement therapy but recommended the use of those hormones for the treatment of severe menopausal symptoms for a short period duration (European Medicines Agency, 2005; Ballard, 2002; Hulley et al., 1998). A randomized controlled trial conducted in Denmark from 1990 to 1993, was the first study to highlight the appropriate timing and the long-term effect of hormonal replacement therapy on cardiovascular diseases. This study showed that after 10 years of using hormonal replacement therapy women would have significant reduction in cardiovascular related diseases and mortality rate (Schierbeck et al., 2012). A short-term use of hormonal therapy with the lowest effective dose would be sufficient to reduce vasomotor symptoms. However, they must be evaluated annually to confirm the need to those hormones (UK public assessment report, 2007)

Several studies were conducted to explore the benefit of hormone replacement therapy on the reduction of oral symptoms associated with menopause. Estrogen therapy has been shown to increase salivary flow, alter the composition of saliva and improve oral symptoms (Eliasson et al., 2003). On the periodontium, hormonal therapy was shown to result in increased retention of teeth by making the periodontium stronger but showed no effect on increasing bone height or reducing its porosity (Taguchi et al., 2004). In contrast, other investigators demonstrated no significant effects (Marcos et al., 2005).

2.3. Menopause related osteoporosis

Menopause related osteoporosis is defined by the World Health Organization as "a progressive systemic skeletal disease characterized by low bone mass and micro architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" (World Health Organization, 1994). According to the World Health Organization, it is diagnosed when bone mineral density is at least 2.5 standard deviations lower than the average value for healthy young women (World Health Organization, 2007). It is a disease that can present with only low bone density until a fracture occurs. The most common sites of fractures include the hips, the spine, the proximal humerus and the forearm (Malhotra et al., 2008; World Health Organization, 2007).

Osteoporosis can be classified into localized and generalized, as well as primary and secondary. Post-menopausal osteoporosis is recognized as secondary to the reduction of estrogen levels (Riggs et al., 1982).

2.3.1. Pathophysiology

The human body involves two types of osseous tissue; cortical bone and trabecular bone that presents with a distinct honeycomb appearance filled with bone marrow and fat cells. Bone formation and resorption processes are four to eight times faster in trabecular bone than cortical bone. Women develop almost all their bone mass in the hips and the vertebrae by late adolescence. After that period there is slight increase in the skeletal bone mass which stops around 30 years of age. Once peak bone mass is determined, remodeling is maintained by the interplay between RANKL (Receptor Activator of Nuclear Factor-Kappa B Ligand), RANK (Receptor Activator of Nuclear Factor-Kappa B) and OPG (Osteoprotegerin). Osteoclasts contain RANK that is responsible of increasing its activity, osteoblasts contain RANK Ligand (RANKL) which in turn, proceeds to bind to RANK receptors in the osteoclasts. OPG is formed by osteoblasts and binds to RANK to prevent it from binding with RANKL, thus the resorption process is mainly controlled by the interaction between RANK and OPG (Sandy et al., 1993).

After the age of 30 years there a decline in the bone mass density by 0.7% per year (Matkovic et al., 1994; Theintz et al., 1992). Following the menopause, the total bone mass loss accounts to 1-1.15% per year (Ettinger, 1988; Lindsay, 1986).

Overall, estrogens are responsible for creating a balance between osteoblastic and osteoclastic activity; when there is absence of estrogens resorption will exceed formation. Estrogen receptors ERα and ERβ are expressed in osteoblasts. Estrogen is also known to decrease the function of osteoclasts and increase their apoptosis, thus protecting pre-menopausal women from bone loss (Bord et al., 2001; Manolagas, 2000). In the post-menopause phase, the fluctuation of hormones will increase RANKL causing an increase in the osteoclastic activity and a shift towards resorption of the bone

and osteoporosis (Khanna et al., 2017). The greatest bone loss is seen in cancellous bone which is found in the vertebra and metaphyses of the long bones, thus accounting for the high fracture rate at these sites (Lindsay, 1991). Jeffcoat and co-workers also highlighted the correlation between systemic osteoporosis and alveolar bone loss (Jeffcoat, 2005).

Moreover, cytokines such as IL-1, IL-6 and Insulin-like Growth Factors I and II which are responsible for bone resorption are modulated by estrogens. Estrogens also increase vitamin D receptors in the osteoblasts thus affecting vitamin D activity in bone. However, little evidence about the relation between estrogens and its effect on the bone by modulating calcium metabolism has been found (Liel et al., 1999; Pacifici, 1998; Prince, 1994; Turner et al., 1994). Estrogens can also inhibit bone turnover by promoting collagen synthesis (Clarke et al., 2010).

There are also other factors which can predispose women to post-menopausal osteoporosis by lowering the peak bone mass and increasing age-related bone deficiency. These factors include endocrine disorders, genetic and life style associated changes such as alcohol abuse, smoking, reduced calcium intake in the diet and vitamin D deficiency (Ismal, 1997).

2.4. Can menopause related osteoporosis affect orthodontic tooth movement?

Tooth movement is achieved by alternating processes of bone resorption and formation in response to pressure and tension, respectively. The rate of orthodontic tooth movement is determined by several factors, including the amount of applied force and the quality of alveolar bone and surrounding tissues (Proffit et al., 2019). In the post-menopause, lack of estrogens will lead to hormonal imbalance increasing bone turn-over (Tanaka et al. 2002; Hsieh et al. 1995) During this period, the mandible has been

shown to exhibit structural changes with bone appearing more aged, rough with uneven walls and reduced number of cells in the lacunae, in addition to the presence of fat cells between the marrow tissue (von Wowern et al., 1994). Comparison of the bone mineral density of the mandible to other different areas in the body (lumbar and femoral) with the use of DEXA test, showed a significant correlation between those sites. Consequently, alveolar bone is affected similarly by osteoporosis to elsewhere in the body, possibly affecting the cascade of phenomena associated with orthodontic tooth movement (Horner et al. 1996).

Tooth movement is a process that is affected by multiple factors including age, resulting in a delayed initial tissue reaction to orthodontic forces in adults (Melsen, 2012). Age associated changes involve reduction in the proliferative activities of the fibroblast-like cells(Kyomen and Tanne, 1997). Moreover, vascularity is affected by ageing phenomena, thus decreasing the amount of the progenitor cells for bone formation (Norton, 1988). Overall, the duration of orthodontic treatment was found to increase in adult patients as a result of reduced bone density and alteration in cellular reaction to those forces, Orthodontists need to use low forces and alter the mechanism used to induce tooth movement (Melsen, 2012).

Orthodontic treatment is not only used nowadays to correct the alignment of teeth and fix skeletal problems in adolescent patients but also used as a method in a multidisciplinary approach to aid in providing a stable, acceptable function as well as having a pleasant appearance in adults patients. With age, bone physiology is affected by multiple medical and systemic conditions including menopause which alter bone physiology directly and indirectly (Proffit et al., 2019).

Understanding the impact of menopause on orthodontic tooth movement 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 appraise the quality of the available evidence from animal studies regarding the effect of experimentally induced menopause on the rate of orthodontic tooth movement.

3.2. Objectives of the systematic review

To retrieve information on the effect of ovariectomy, i.e. experimentally induced menopause, on the rate of tooth movement in animals undergoing orthodontic tooth movement.

3.3. Null hypothesis

There is no difference in the rate of tooth movement between ovariectomized and control group animals.

4. MATERIALS AND METHODS

4.1. Protocol development and registration

The present review was based on specific protocol developed and piloted following the guidelines outlined in the PRISMA-P statement (Shamseer et al., 2015) and registered in PROSPERO (CRD42018118003; Appendix I). In addition, conduct and reposting 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 applying to the present review were followed:

4.2.1. Types of study design

Studies included were prospective controlled studies evaluating the rate of tooth movement in ovariectomized animals (i.e. animals with experimentally induced menopause) undergoing any kind of active orthodontic tooth movement. Human studies, ex vivo, in vitro, in silico, non-comparative studies (case reports and case series) and reviews (traditional reviews, systematic reviews and meta-analyses) were excluded from 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 II).

4.2.2. Types of participants

The included studies involved bilateral ovariectomized female animals (experimentally induced-menopause) undergoing orthodontic tooth movement. Studies on subjects undergoing any kind of orthodontic tooth movement in conjunction with other interventions such as tooth extraction etc., on subjects after the cessation of active orthodontic tooth movement or on subjects with other co-morbidities were excluded.

4.2.3. Types of interventions

The included studies involved ovariectomized female animals (experimentally induced-menopause) compared to healthy, naive female animals.

4.2.4. Types of outcome measures

The studies had to report the rate of orthodontic tooth movement (i.e. mean values of the amount of tooth movement during a specific period of time together with appropriate data on dispersion like standard deviation, standard error, etc.).

4.3. Information sources and search strategy

The principal investigator 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 III): MEDLINE via PubMed, CENTRAL, Cochrane Systematic Reviews, Scopus, Web of Science ™ Core Collection, Arab World Research Source, Clinical Trials registry and ProQuest Dissertations & Theses Global database.

There were no restrictions 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 the eligible studies for additional records were searched.

4.4. Study selection

The main investigator (AOM) and the thesis 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. The full-text of the records considered by either reviewer to meet the inclusion criteria, were obtained and assessed, again independently, while disagreements were settled by discussion.

4.5. Data collection and data items

The main investigator and the thesis supervisor performed data extraction independently and any disagreements were again resolved by discussion Data collection forms were used to record the desired information.

a. Bibliographic details of the study
b. Details on the study design and verification of the study eligibility.
c. Subject characteristics (where available number, age, weight)
d. Tooth movement model.
e. Details on outcomes characteristics and results.
f. Additional information: a prior sample size calculation, reliability assessment.

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

4.6. Risk of bias in individual studies

The main investigator and the thesis supervisor assessed the risk of bias in the included studies, independently and in duplicate, during the data extraction process, using the SYRCLE's risk of bias tool (Hooijmans et al., 2014). Any disagreements were resolved by discussion. The SYRCLE's risk tool assessment tool includes the following domains:

1: Was the allocation sequence adequately generated and applied?

2: Were the groups similar at baseline or were they adjusted for confounders in the analysis?

3: Was the allocation adequately concealed?

4: Were the animals randomly housed during the experiment?

5: Were the caregivers and investigators blinded to the intervention that each animal received?

6: Were animals selected at random for outcome assessment?

7: Was the outcome assessor blinded?

8: Were incomplete outcome data adequately addressed?

9: Are reports of the study free of selective outcome reporting?

10: Was the study apparently free of other problems that could result in high risk of bias?

After entering in the data extraction form the information reported in each study, every domain would receive a judgment of low, high, or unclear risk of bias (Hooijmans et al., 2014). The risk of bias within a study was assessed in summary according to Higgins and Green (2011).

4.7. Summary measures and synthesis of results

The random effects method for meta-analysis was to be used to combine the rate of orthodontic tooth movement data at the longest point of observation from each study in appropriate statistical forms (Weighted Mean Difference (WMD) together with measures of dispersion) (Der Simonian and Laird, 1986, Borenstein et al., 2009), since they were expected to differ across the studies due to clinical diversity in terms of participants and intervention characteristics.

To identify the presence and the extent of between-study heterogeneity, the overlap of 95% CI for the results of individual studies was to be inspected graphically, and Cochrane's test for homogeneity and the I^2 statistics were to be calculated (Higgins and Green, 2011). The results of the I^2 statistic were to be interpreted as follows (Higgins and Green, 2011):

- I^2 from 0% to 40%: heterogeneity might not be important;
- I^2 from 30% to 60%: may represent moderate heterogeneity;
- I^2 from 50% to 90%: may represent substantial heterogeneity;
- I^2 from 70% to 100%: considerable heterogeneity.

All analyses were to be carried out with Comprehensive Meta-Analysis software version 3 (©2014 Biostat Inc., New Jersey, USA). Significance (a) was set at 0.05, except for 0.10 used for the heterogeneity tests (Ioannidis, 2008).

4.8. 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, subgroup analyses and meta-regression were planned.

5. RESULTS

5.1. Study selection

The flowchart of records through the reviewing process is demonstrated in Figure 1. The data search took place until March, 2018. Initially 1476 records were identified through data base screening and 2 through hand searching. Two hundred ninety were identified as duplicates and further 1166 were excluded on the basis of their title and abstract. Subsequently, 22 full-text records were assessed for eligibility and 11 records were excluded for the following reasons: five records for being irrelevant to the scope of the present investigation and six records for not including information in appropriate statistical forms (the corresponding authors were contacted but no reply was received) (Dai et al., 2017; Mackie et al., 2016; Xu et al., 2013; Tan et al., 2008; Tan et al., 2006; Yamashiro & Takano-Yamamoto, 2001). Finally, 11 full text reports were included in the meta-analysis (Jin et al., 2000; Arslan et al., 2007; Salazar et al., 2011; Sirisoontorn et al., 2011; 2012; Celebi et al., 2013; Hashimoto et al., 2013; Salazar et al., 2015; Seifi et al., 2015; Dahhas et al., 2015; Tsolakis 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 Table 1.

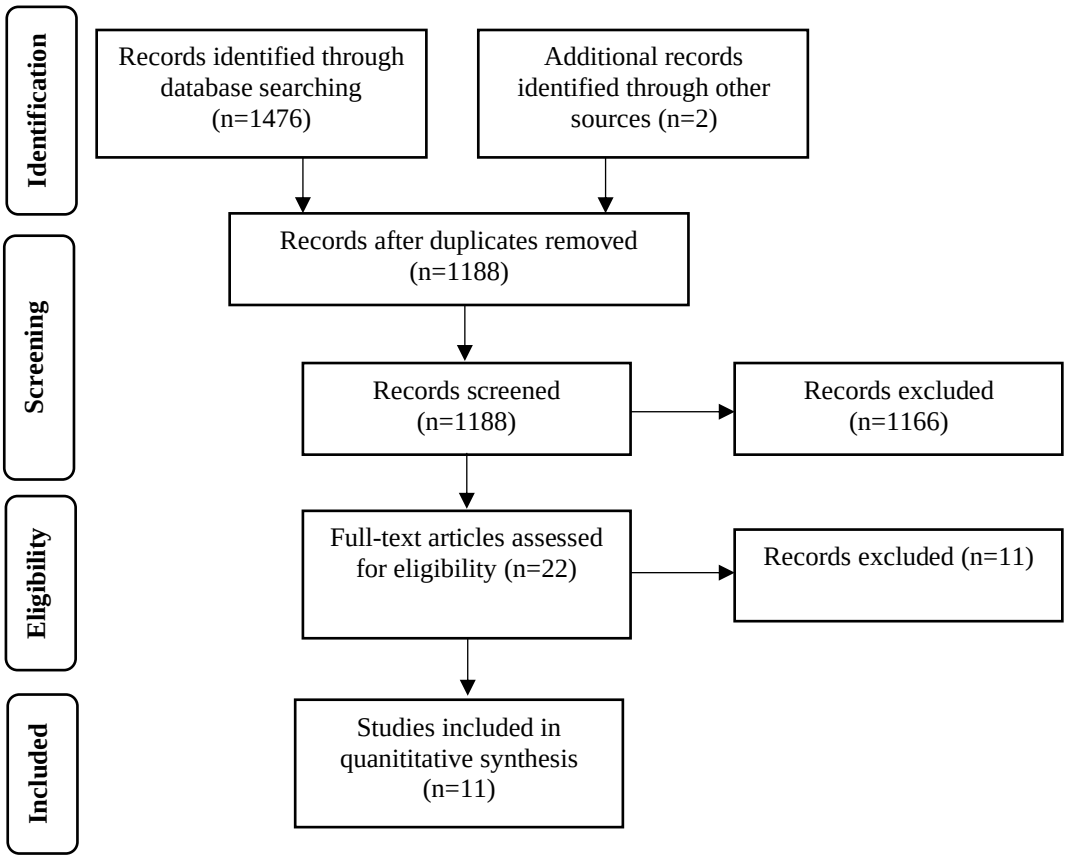


Figure 1. Flowchart of records through the reviewing process

The retrieved studies had all been published between 2000 and 2018 and investigated the effect of ovariectomy on the rate of orthodontic tooth movement in experimental animals, usually rats. Orthodontic tooth movement was usually induced by the use a nickel titanium coil spring between the incisors and the molars. An expansion spring was used in one study to apply an expansion force between maxillary central incisors (Arslan et al., 2007), while another used a coil spring anchored with miniscrews to retract the canines (Celebi et al., 2013). The force exerted by the appliance ranged between 10 to 80 g and the duration of force application ranged from 0.5 to 14 weeks. Different methods were used to determine the changes in tooth position and the rate of orthodontic tooth movement including digital caliper measurements, directly or on casts (Arslan et al., 2007; Celebi et al., 2013; Seifi et al., 2015) , measurements on micro-CT images (Dahhas et al., 2015; Hashimoto et al., 2013; Sirisoontorn et al., 2011; 2012;) or special dorsoventral radiographs (Tsolakis et al., 2018), and measurements on histological sections, directly (Salazar et al., 2011; Jin et al., 2000) or on digital images (Salazar et al., 2015). Most studies did not report method of error calculation.

Table 1. Characteristics of the included studies.

Study	Subjects & tooth movement model	Group characteristics	Measurement methodology
Arslan et al. 2007	Sprague-Dawley rats; 90(± 10) d; 200-250g SS expansion spring between Mx CIs [10g] **Force application:** 18d	**EG:** 20 **CG:** 22 **Sample size calculation:** nm	**Digital caliper:** Direct measurements at a distance 2mm from the gum. **Method error assessment:** Yes
Celebi et al. 2013	Cats; 2-4 yrs; NiTi CCS from mini implants to Mx C [80g] **Force application:** 12d	**EG:** 6 **CG$_1$:** 6; Estrous group **CG$_2$:** 6; Anestrous group **Sample size calculation:** nm	**Digital caliper:** Measurements on plaster models from silicone impressions. **Method error assessment:** nm
Dahhas et al. 2015	Wistar rats; 4 w; 120g NiTi CCS from Mx CIs to left FM [50g] **Force application:** 4w	**EG:** 8 **CG:** 8 **Sample size calculation:** nm	**Micro-CT images:** Distance from the distal contact point of the left Mx FM to the mesial contact point of the left Mx SM **Method error assessment:** nm
Hashimoto et al. 2013	Wistar rats; 10 w; 170-180g NiTi CCS from Mx Cis to left FM [25g] **Force application:** 14 w	**EG:** 7 **PG:** 7 **Sample size calculation:** nm	**Micro-CT images:** Distance from the distal contact point of the left Mx FM to the mesial contact point of the left Mx SM **Method error assessment:** nm
Salazar et al. 2011	Wistar rats; 8 w; 170-180g NiTi CCS from Mx Cis to left FM [40cN] **Force application:** 1w	**EG:** 8 **PG:** 8 **Sample size calculation:** nm	**Ruler coupled with optical microscope:** Distance between FM and SM from each cervical enamel edge **Method error assessment:** nm
Salazar et al. 2015	Wistar rats; 8 w; 215g NiTi CCS from Mx CsI to right FM [50cN] **Force application:** 5 or 7 d	**EG:** 6 force for 5d and 6 force for 7d **PG:** 6 force for 5d and 6 force for 7d **Sample size calculation:** nm	**Digital images of histological cuts:** Smallest distance between the distal surface of the FM and mesial surface of SM **Method error assessment:** nm
Seifi et al. 2015	Wistar rats; 60 days NiTi CCS from Mx CIs to right FM [60g] **Force application:** 3w	**EG:** 10 **PG:** 10 **Sample size calculation:** nm	**Digital caliper:** Direct measurements the distal surface of the FM and mesial surface of SM **Method error assessment:** nm
Sirisoontorn et al. 2011	Wistar rats; 10 w; 170-190g NiTi CCS from Mx CIs to FM [25g] **Force application:** 4w	**EG:** 5 **PG:** 5 **Sample size calculation:** nm	**Micro-CT images:** Distance from the distal contact point of the left Mx FM to the mesial contact point of the left Mx SM **Method error assessment:** nm
Sirisoontorn et al. 2012	Wistar rats; 10w; 170-180g NiTi CCS from Mx CIs to FM [25g] **Force application:** 4w	**EG:** 5 **PG:** 5 **Sample size calculation:** nm	**Micro-CT images:** Distance from the distal contact point of the left Mx FM to the mesial contact point of the left Mx SM **Method error assessment:** nm
Tsolakis et al. 2018	Wistar rats; 6 months; 255g NiTi CCS from Mx right CI to FM [60g] **Force application:** 2w	**EG:** 12 **CG:** 12 **Sample size calculation:** nm	**Special dorsoventral radiographs:** Difference in the distance between a mesial occlusal point on FM and distal occlusal point on third molar between side under tooth movement and non-movement side **Method error assessment:** Yes
Jin et al. 2000	Sprague-Dawley rats; 12w; 185± 5g NiTi CCS from Mx CIs to FM [30g] **Force application:** up to 60d [weekly reactivation]	**EG:** 5 force for 30d and 5 force for 60d **CG:** 5 force for 30d and 5 force for 60d **Sample size calculation:** nm	**Ruler coupled with optical microscope:** Distance between FM and SM from each cervical enamel edge **Method error assessment:** nm

CCS: closed coil spring; CG: Control group of healthy naive animals; CI: central incisor(s); d: days; EG: Ovariectomy group, FM: first molars; Mx: Maxillary; PG: Placebo group receiving sham operation SM: Second molar; SS: Stainless steel; w: week(s)

5.3. Risk of bias within studies

Table 2 presents the summary of findings regarding risk of bias assessment. Most included studies exhibited an unclear risk of bias, while few showed an overall high risk (Tsolakis et al., 2018; Salazar et al., 2011; 2015).

In regards to allocation sequence generation, application and concealment, most studies were assessed to be at unclear risk of bias, while few showed a high risk (Tsolakis et al., 2018; Salazar et al., 2011; 2015). The risk of bias for the domain of baseline similarity was assessed to be low for most studies, with the exception of Celebi et al. (2013) that included the study of estrous and anestrous cats. Regarding the selective outcome reporting domain, the risk of bias was assessed to be low and for the rest the examined domains unclear.

Table 2. Summary of risk of bias assessment.

	Signalling questions										
Study	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Summary**
Arslan et al., 2007	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Celebi et al., 2013	Unclear	High	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Dahhas et al., 2015	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Hashimoto et al., 2013	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Salazar et al., 2011	High	Low	High	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
Salazar et al, 2015	High	Low	High	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
Seifi et al., 2015	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Sirisoontorn et al., 2011	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Sirisoontorn et al., 2012	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Tsolakis et al., 2018	High	Low	High	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	High
Jin et al., 2000	Unclear	Low	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear

1: Was the allocation sequence adequately generated and applied?; 2: Were the groups similar at baseline or were they adjusted for confounders in the analysis?; 3: Was the allocation adequately concealed?; 4: Were the animals randomly housed during the experiment?; 5: Were the caregivers and investigators blinded to the intervention that each animal received?; 6: Were animals selected at random for outcome assessment?; 7: Was the outcome assessor blinded?; 8: Were incomplete outcome data adequately addressed?; 9: Are reports of the study free of selective outcome reporting?; 10: Was the study apparently free of other problems that could result in high risk of bias?

5.4. Synthesis of results

Quantitative synthesis of the results of the included studies is shown in Figure 2. Overall, the rate of orthodontic tooth movement was found to increase in ovariectomized animals compared to control or sham operated experimental groups (Mean Difference: 0.125 mm; 95% Confidence Interval: 0.06-0.19; I^2: 95%).

5.5. Additional analyses

It was not possible to conduct analyses for "small-study effects" and publication bias, as well as subgroup analyses.

Meta-regression showed that the difference in the rate of orthodontic tooth movement between ovariectomized animals and control or sham operated experimental groups increased as the duration of force application increased (Figures 3 and 4).

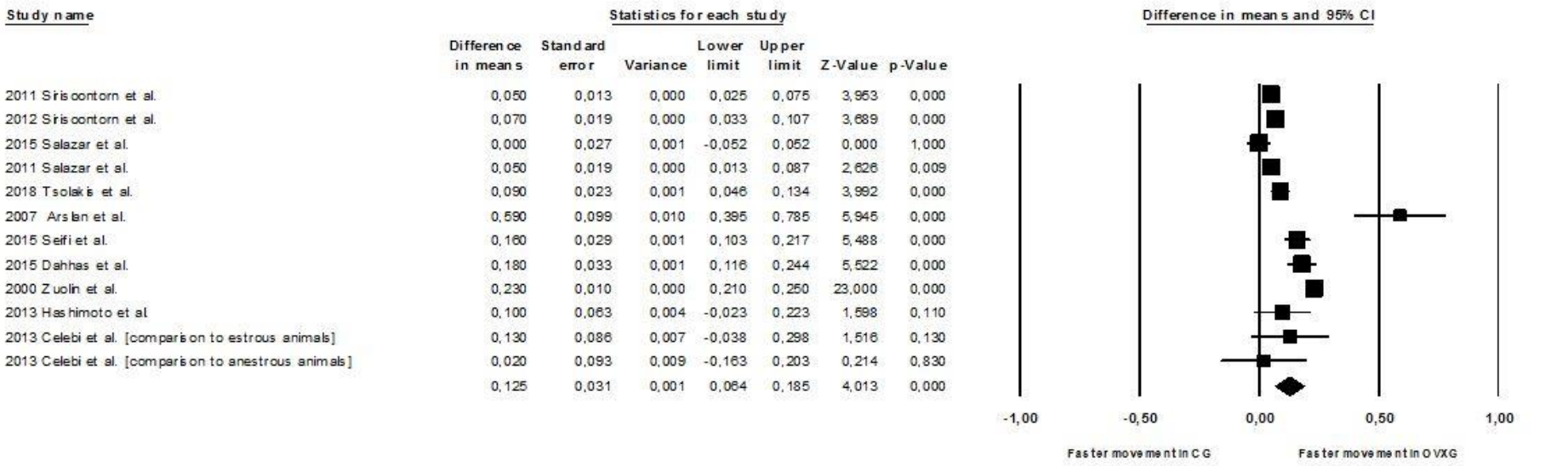


Figure 2. Quantitative synthesis of the results of the included studies.

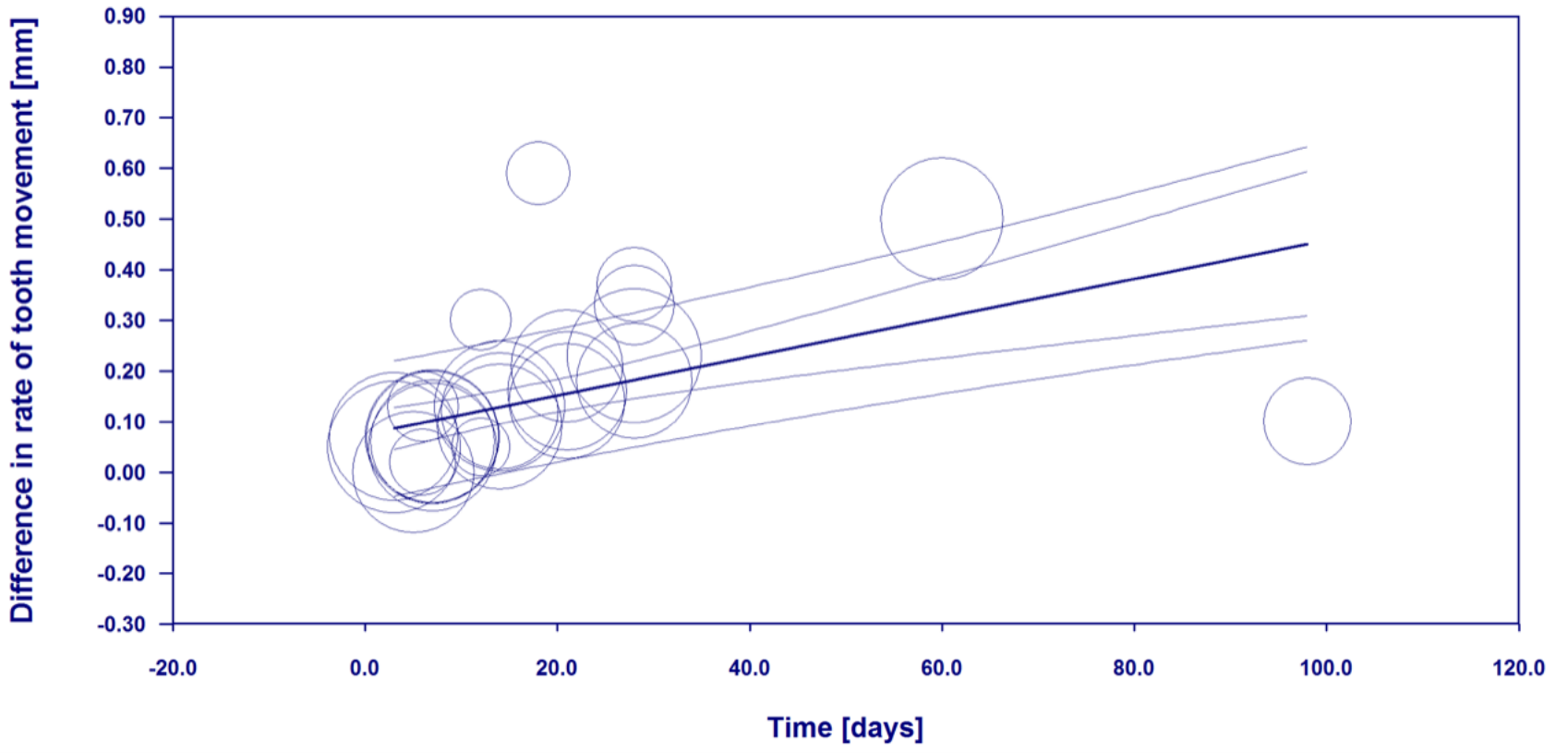


Figure 3. Meta-regression

Main results for Model 1, Random effects (MM), Z-Distribution, Difference in means

Covariate	Coefficient	Standard Error	95% Lower	95% Upper	Z-value	2-sided P-value
Intercept	0.0747	0.0184	0.0387	0.1108	4.07	0.0000
Time	0.0038	0.0007	0.0025	0.0052	5.42	0.0000

Statistics for Model 1

Test of the model: Simultaneous test that all coefficients (excluding intercept) are zero
Q = 29.40, df = 1, p = 0.0000
Goodness of fit: Test that unexplained variance is zero
Tau^2 = 0.0027, Tau = 0.0520, I^2 = 84.27%, Q = 139.84, df = 22, p = 0.0000

Comparison of Model 1 with the null model

Total between-study variance (intercept only)
Tau^2 = 0.0102, Tau = 0.1011, I^2 = 95.47%, Q = 507.85, df = 23, p = 0.0000
Proportion of total between-study variance explained by Model 1
R^2 analog = 0.73

Figure 4. Meta-regression model.

6. DISCUSSION

6.1. Summary of available evidence

Age-related menopause affects bone physiology with possible to repercussions on orthodontic tooth movement (Proffit et al., 2019; Khanna et al., 2017). Based on the information from the controlled studies retrieved in the present review, the menopause is associated with a small but statistically significant acceleratory effect on the rate of orthodontic tooth movement compared to the control group that seems to become more evident over time. Although the risk of bias was assessed to be unclear for the majority of studies, clinicians should not ignore the fact that patients in menopause may exhibit alterations in the physiological bone remodeling required for orthodontic tooth movement, as well as the possible implications.

Overall, the rate of orthodontic tooth movement was found to increase in ovariectomized animals compared to control or sham operated experimental groups. This difference can been attributed to the increase in bone turnover due to the alterations in RANK/ RANKL/OPG system that is important in maintaining regulatory control of the osteoclastogenesis in both tension and pressure sides (Tyrovola et al., 2008). In addition, as already mentioned, lack of estrogens will increase osteoclastogenesis and bone resorption, as well as affect negatively trabecular bone volume and the number of trabeculae in the alveolar bone, resulting in faster tooth movement (Khanna et al., 2017; Jeffcoat, 2005; Tanaka et al., 2002; Horowitz, 1993).

Regarding bone deposition, the negative effects of the lack of estrogens on the quality of newly formed bone have been also reported (Kubo et al., 1999; Cesnjaj et al.,1991; Wronski et al., 1989). Estrogen deficiency might affect the production of important proteins, such as osteogenin and bone morphogenic proteins, causing a disruption of bone matrix formation and affecting the early stages of bone formation (Cesnjaj et

al.,1991; Wronski et al., 1989). Histomorphometric data have also shown a reduction in osteoblast counts and further negative effects on the later stages of bone formation (Arslan et al., 2007; Kubo et al., 1999).

Based on the meta-regression analysis, the statistically significant acceleratory effect on the rate of orthodontic tooth movement became more evident over time. Tooth movement in rats can be summarized in 3 phases: instantaneous tooth movement (first phase), delayed tooth movement (second phase) and linear phase of tooth movement (third phase) (Bridges et al., 1988). The difference on the rate of orthodontic tooth movement has been reported to be minimal on day 1 and is thought to occur due to the initial compression within periodontal ligament space after force application. From day 1 until day 7, tooth movement was found to gradually increase, and exhibited steep increase afterwards (Sirisoontorn et al., 2011). Other investigators have also confirmed that ovariectomy increases the rate of tooth movement significantly during the linear phase (Yamashiro & Takano-Yamamoto, 2001). In general, the action of resorption is faster than deposition and usually requires at least 3 months to rebuild bone that was resorbed in 2-3 weeks. Thus, even when increased resorption does not coincide with impairment in bone formation, still bone loss will occur due to the difference in the rate of action between these two processes (Harada and Rodan, 2003). The studies retrieved in the present review lasted up to 2 months. Since orthodontic treatment involves a significantly longer time period, the possible implications of the gradual increase in the difference of the rate of tooth movement between the two groups cannot be overlooked. Even from this small set of animal data, clinicians might get an insight into the relevant clinical considerations related to treatment of patients in menopause. It is possible that the estimation of the duration of active treatment should be modified and appointments might need to be more frequent in order to check and control the progress. Also, in

terms of mechanotherapy, patients might present increased needs for anchorage preparation because of the altered bone turnover. Following active correction of tooth position, menopause might negatively affect the stability and maintenance of the corrections. From a clinical point of view, clinicians might encounter greater difficulty in planning retention in estrogen deficiency patients, as post-treatment changes might occur more commonly.

6.2. Strengths and limitations of the present review

The strengths of the present review include the use of a well-established methodology. The strategy employed for data retrieval from electronic and manual sources was exhaustive and comprehensive, without pre-set limitations regarding language, date and status of publication. Moreover, the processes of screening, verification of eligibility, abstraction of information, assessment of risk of bias and the quality of evidence were performed in duplicate so as to diminish all possible biases. Disagreements were resolved by discussion.

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. Animals involved in similar studies must be of a certain age to be able to stimulate the results of post-menopausal osteoporosis. It has been suggested that rats should not be younger than 6 months as they reach skeletal maturation after sexual and the peak bone mass is achieved by 9 months of age (Jee and Yao, 2001). Only the study by Tsolakis and co-workers (2018) employed 6-months-old rats, while in the remaining, the age range of the animal subjects ranged between 1 and 3 months. Rats continue to grow at the age of 3 months and it might possible that the ovariectomy effect in them is confounded by the skeletal growth effect (Jee and Yao, 2001).

Furthermore, after the surgical removal of the ovaries, bone loss starts at the earliest in two weeks, reaches 50% approximately after 4 to 8 weeks and stabilizes within 12 weeks (Wronski et al., 1989). Studies included in this review began orthodontic tooth movement from 4 to 12 weeks post ovariectomy. However, less than half of the retrieved studies confirmed the expected ovariectomy associated changes by various methods, including histological examination of tibia sections (Tsolakis et al., 2018; Hashimoto et al., 2013), observing atrophy of the uterine horns (Arslan et al., 2007), obtaining blood samples to measure estrogen and progesterone levels (Seifi et al., 2015) and measuring bone mineral density of the diaphysis of the femur bone (Salazar et al., 2015). In addition, in the majority of studies, the control groups involved animals possibly in various stages of the estrous cycle. Responses to orthodontic force application might vary depending on the specific phase of the menstrual cycle (Chiu et al., 1999; Zittermann et al., 2000; Haruyama et al., 2002).

Moreover, one should not forget that the currently available information is not only indirectly related to humans because the data originate from animal studies, but also involves a surgical procedure to produce a result similar to a condition that naturally occurs in humans. Finally, the lack of power sample calculations increases the uncertainty about the precision of the observed estimates, as well as, the clinical significance of the results, in seeking to extrapolate the retrieved animal information to everyday clinical scenarios in humans.

6.3. Recommendations for future research

Since, the number of adult female patients seeking orthodontic treatment appears to be on the rise, further well-designed experimental studies to investigate the phenomena more comprehensively and understand the effect of hormonal changes associated with

menopause could be useful for the clinician. It is highly desirable that study designs become standardized (Kilkenny et al., 2012) and possible sources of risk of bias receive the appropriate attention (Hooijmans et al., 2014). Moreover, future investigation should simulate, as closely as it is feasible, scenarios in clinical practice in humans in terms of magnitude of force as well as the characteristics of the employed method of force delivery.

7. CONCLUSIONS

Ovariectomy-induced menopause may affect the rate of orthodontic tooth movement. Although the overall quality of evidence provides the clinician with a cautious perspective on the strength of the relevant recommendations, the orthodontist should be capable of identifying such patients and consider the possible implications.

8. REFERENCES

Agha-Hosseini F, Mirzaii-Dizgah I, Mansourian A, Khayamzadeh M. Relationship of stimulated saliva 17β-estradiol and oral dryness feeling in menopause. Maturitas 2009;62:197–199.

Amar S, Chung KM. Influence of hormonal variation on the periodontium in women. Periodontol 2000 1994;6:79–87.

Arslan SG, Arslan H, Ketani A, Hamamci O. Effects of estrogen deficiency on tooth movement after force application: An experimental study in ovariectomized rats. Acta Odontol Scand 2007;65:319–323.

Ballard K. Understanding risk: women's perceived risk of menopause-related disease and the value they place on preventive hormone replacement therapy. Fam Pract 2002;19:591–595.

Ballinger CB, Browning MCK, Smith AHW. Hormone profiles and psychological symptoms in peri-menopausal women. Maturitas 1987;9:235–251.

Baltimore: Lippincott, Williams & Wilkins,1999.

Ben Aryeh H, Gottlieb I, Ish-Shalom S, David A, Szargel H, Laufer D. Oral complaints related to menopause. Maturitas 1996;24:185–189.

Biglia N, Cozzarella M, Cacciari F, Ponzone R, Roagna R, Maggiorotto F, Sismondi P. Menopause after breast cancer: A survey on breast cancer survivors. Maturitas 2003;45:29–38.

Bord S, Horner A, Beavan SCJ. Estrogen receptor alfa and beta are differentially expressed in developing human bone. J Clin Endocrinol Metab 2001;86:2309–2314.

Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. Introduction to Meta-Analysis. Chichester: Wiley, 2009.

Brace M, McCauley E. Oestrogens and psychological well-being. Ann Med 1997;29:283–290.

Bridges T, King G, Mohammed A. The effect of age on tooth movement and mineral density in the alveolar tissues of the rat. Am J Orthod Dentofacial Orthop 1988;93:245–250.

Brzozowski AM, Pike ACW, Dauter Z, Hubbard RE, Bonn T, Engström O, Carlquist M. Molecular basis of agonism and antagonism in the oestrogen receptor. Nature 1997;389:753–758.

Casper RF, Yen SSC. Neuroendocrinology of menopausal flushes: an hypothesis of flush mechanism. Clin Endocrinol 1985;22:293-312.

Celebi AA, Demirer S, Catalbas B, Arikan S. Effect of ovarian activity on orthodontic tooth movement and gingival crevicular fluid levels of interleukin-1β and prostaglandin E2 in cats. Angle Orthod 2013;83:70–75.

Cesnjaj M, Stavljenic A, Vukicevic S. Decreased osteoinductive potential of bone matrix from ovariectomized rats. Acta Orthop Scand 1991;62:471–475.

Chiu KM, Ju J, Mayes D, Bacchetti P, Weitz S, Arnaud CD. Changes in bone resorption during the menstrual cycle. J Bone Miner Res 1999;14:609–615.

Clarke BL, Khosla S. Physiology of bone loss. Radiol Clin North Am 2010;84:483–495.

Dahhas FY, El-Bialy T, Afify AR, Hassan AH. Effects of low-intensity pulsed ultrasound on orthodontic tooth movement and orthodontically induced inflammatory root resorption in ovariectomized osteoporotic rats. Ultrasound Med Biol 2015;42:1–7.

Dai Q, Zhou S, Zhang P, Ma X, Ha N, Yang X, Yu Z, Fang B, Jiang L. Force-induced increased osteogenesis enables accelerated orthodontic tooth movement in ovariectomized rats. Sci Rep 2017;7:1–8.

Dai QG, Zhang P, Wu YQ, Ma XH, Pang J, Jiang LY, Fang B. Ovariectomy induces osteoporosis in the maxillary alveolar bone: an in vivo micro-CT and histomorphometric analysis in rats. Oral Dis 2014;20:514–520.

Der Simonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88

Dutt P, Chaudhary S, Kumar P. Oral health and menopause: A comprehensive review on current knowledge and associated dental management. Ann Med Health Sci Res 2013;3:320-323.

Eliasson L, Carlén A, Laine M, Birkhed D. Minor gland and whole saliva in postmenopausal women using a low potency oestrogen (oestriol). Arch Oral Biol 2003;48:511–517.

Ettinger B. Prevention of osteoporosis: treatment of estradiol deficiency. Obstet Gynecol 1988;72:12S-17S.

European Medicines Agency. Guideline on Clinical Investigation of Medicinal Products for Hormone Replacement Therapy of Oestrogen Deficiency Symptoms in Postmenopausal Women. 2005.

Faddy MJ, Gosden RG, Gougeon A, Richardson SJ, Nelson JF. Accelerated disappearance of ovarian follicles in mid-life: Implications for forecasting menopause. Hum Reprod 1992;7:1342–1346.

Freedman RR, Krell W. Reduced thermoregulatory null zone in postmenopausal women with hot flashes. Am J Obst Gyn 1999;181:66–70.

Freedman RR, Norton D, Woodward SCG. Core body temperature and circadian rhythm of hot flashes in menopausal women. J Clin Endocrinol Metab 1995;80:2354–2358.

Friedlander AH. The physiology, medical management and oral implications of menopause. J Am Dent Assoc 2002;133:73–81.

Frutos R, Rodríguez S, Miralles L, Machuca G. Oral manifestations and dental treatment in menopause. Med Oral 2002;7:26–35.

Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia Cochrane Database Syst Rev 2012;15:CD000402.

Gold EB, Bromberger J, Crawford S, Samuels S, Greendale GA, Harlow SD. Factors associated with age at natural menopause in a multiethnic sample of midlife women. Am J Epidemiol 2001;153:865–874.

Greene GL, Gilna P, Waterfield M, Baker A, Hort Y, Shine J. Sequence and expression of human estrogen receptor complementary DNA. Science 1986;7:1150–1154.

Grodstein F, Stampfer M. The epidemiology of coronary heart disease and estrogen replacement in postmenopausal women. Prog Cardiovasc Dis 1995;38:199–210.

Gruber CJ, Tschugguel W, Schneeberger C, Huber JC. Production and actions of estrogens. N Engl J Med 2002;346:340–352.

Harada S, Rodan G. Control of osteoblast function and regulation of bone mass. Nature 2003;423:349-355.

Harman SM. Estrogen replacement in menopausal women: Recent and current prospective studies, the WHI and the KEEPS. Gend Med 2006;3:254–269.

Haruyama N, Igarashi K, Saeki S, Otsuka-Isoya M, Shinoda H, Mitani H. Estrous-cycle-dependent variation in orthodontic tooth movement. J Dent Res 2002;81:406–410.

Hashimoto M, Hotokezaka H, Sirisoontorn I, Nakano T, Arita, K, Tanaka M, Yoshida N. The effect of bone morphometric changes on orthodontic tooth movement in an osteoporotic animal model. Angle Orthod 2013;83:766–773.

Hee J, Macnaughton J, Bangah M, Burger HG. Perimenopausal patterns of gonadotropins, immunoreactive inhibin, estradiol and progesterone. Maturitas 1993;18:9–20.

Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org (31 October, 2016, date last accessed).

Hooijmans CR, Rovers MM, de Vries RB, Leenaars M, Ritskes- Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol 2014;14:43.

Horner K, Devlin H, Alsop CW, Hodgkinson IM, Adams JE. Mandibular bone mineral density as a predictor of osteoporosis. Br J Radiol 1996;69:1019-1025.

Horowitz MC. Cytokines and estrogen in bone: antiosteoporotic effects. Science 1993;260:626-627.

Hsieh YD, Devlin H, McCord F. The effect of ovariectomy on the healing tooth socket of the rat. Arch Oral Biol 1995;40:529-531.

Hulley S, Grady D, Bush T, Furberg C, Herrington S, Riggs B, Vittinghoff E. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1998;280:605–613.

Ioannidis JP. Interpretation of tests of heterogeneity and bias in meta-analysis. J Eval Clin Pract 2008;14:951-957.

Ismal NM. Postmenopausal osteoporosis: epidemiology, pathophysiology and treatment. Malays J Pathol 1997;19:21–25.

Jee WSS, Yao W. Overview: animal models of osteopenia and osteoporosis. J Musculoskelet J Musculoskelet Neuronal Interact 2001;1:193-207.

Jeffcoat M. The association between osteoporosis and oral bone loss. J Periodontol 2005;76:2125–2132.

Jensen EV, Jacobson HI, Smith S, Jungblut PW, De Sombre ER. The use of estrogen antagonists in hormone receptor studies. Gynecol Invest 1972;3:108–123.

Jin Z, Ding Y, Li X. Effects of estrogen on experimental tooth movement in osteoporosis rats. Zhonghua Kou Qiang Yi Xue Za Zhi. 2000;35:55–57.

Joffe H, Crawford S, Economou N, Kim S, Regan S, Hall JE, White D. A gonadotropin-releasing hormone agonist model demonstrates that nocturnal hot flashes interrupt objective sleep. Sleep 2013;36:1977–1985.

Joffe H, Crawford SL, Freeman MP, White DP, Bianchi MT, Kim S, Economou N, Camuso J, Hall JE, Cohen LS. Independent contributions of nocturnal hot flashes and sleep disturbance to depression in estrogendeprived women. J Clin Endocrinol Metab 2016;101:3847–3855.

Kannel WB, Wilson PW. Risk factors that attenuate the female coronary disease advantage. Arch Intern Med 1995;155:57–61.

Kase NG. Impact of hormone therapy for women aged 35 to 65 years, from contraception to hormone replacement. Gend Med 2009;6 (Suppl 1):37-59.

Khanna V, Gupta P, Khanna R, Khanna HC. Postmenopausal osteoporosis. J Cas Stud 2017;1:281–283.

Kilkenny C, Browne WJ, Cuthill IC, Emerson M., Altman DG. Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. Osteoarthr Cartilage 2012;20:256–260.

Kubo T, Shiga T, Hashimoto J, Yoshioka M, Honjo H, Urabe M, Kitajima I, Semba I, Hirasawa Y. Osteoporosis influences the late period of fracture healing in a rat model prepared by ovariectomy and low calcium diet. J Steroid Biochem Mol Biol 1999;68:197-202.

Kuhl H. Pharmacology of estrogens and progestogens: Influence of different routes of administration. Climacteric 2005;8:3–63.

Kuiper GG, Enmark E, Pelto-Huikko M, Nilsson S, Gustafsson JA. Cloning of a novel receptor expressed in rat prostate and ovary. Proc Natl Acad Sci USA 1996;93:5925–5930.

Kyomen S. & Tanne K. 1997. Influences of aging changes in proliferative rate of PDL cells during experimental tooth movement in rats. *Angle Orthodontist*, 67**,** 67-72.

Lee SA, Ross RK, Pike MC. An overview of menopausal oestrogen-progestin hormone therapy and breast cancer risk. Br J Cancer 2005;92:2049–2058.

Leimola-Virtanen R, Salo T, Toikkanen S, Pulkkinen J, Syrjänen S. Expression of estrogen receptor (ER) in oral mucosa and salivary glands. Maturitas 2000;36:131–137.

Leimola-Virtanen R, Pennanen R, Syrjänen K, Syrjänen S. Estrogen response in buccal mucosa: A cytological and immunohistological assay. Maturitas 1997;27:41-5.

Liel Y, Shany S, Smirnoff P, Schwartz B. Estrogen increases 1,25-dihydroxyvitamin D receptors expression bioresponse in the rat duodenal mucosa. Endocrinol 1999;14:280–285.

Lindsay R. Oestrogens, bone mass and osteoporotic fracture. Am J Med 1991;91:10s–13s.

Lindsay R. Prevention and treatment of osteoporosis. Lancet 1986;801–805.

Mackie M, Momeni Danaei S, Habibagahi S, Tanide N, Dehghani Najvani A., Montazeri M. Effect of ovariectomy on orthodontic tooth movement in rats. J Islam Dent Assoc Iran 2016;28:86–91.

MacNaughton J, Banah M, McCloud P, Hee J, Burger H. Age related changes in follicle stimulating hormone, luteinizing hormone, oestradiol and immunoreactive inhibin in women of reproductive age. Clin Endocrinol 1992;36:339–345.

Malhotra N, Mithal A. Osteoporosis in Indians. Indian J Med Res 2008;127:263–268.

Manolagas SC. Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. Endocr Rev 2000;21:115–137.

Marcos JFL, Valle SGV, Iglesias ÁAG. Periodontal aspects in menopausal women undergoing hormone replacement therapy. Med Oral Pat Oral Cir Buc 2005;10:132–141.

Marino M, Galluzzo P, Ascenzi P. Estrogen Signaling Multiple Pathways to Impact Gene Transcription. Curr Genomics 2006;7:497–508.

Marrioti A. Sex Steroid Hormones and Cell Dynamicss in the Periodontium. Crit Rev Oral Biol Med 1994;5:27–53.

Martin KA, Manson JAE. Approach to the patient with menopausal symptoms. J Clin Endocrinol Metab 2008;93:4567–4575.

Mascarenhas P, Gapski R, Al-Shammari K, Wang HL. Influence of sex hormones on the periodontium. J Clin Periodontol. 2003;30:671–681.

Matkovic V, Jelic T, Wardlaw GM, Ilich JZ, Goel PK, Wright JK, Heaney RP. Timing of peak bone mass in Caucasian females and its implication for the prevention of osteoporosis. Inference from a cross-sectional model. J Clin Invest 1994;93:799–808.

Matthews K. Myths and Realities of the Menopause. Psychosom Med 1992;54:1–9.

Melby MK, Lock M, Kaufert P. Culture and symptom reporting at menopause. Hum Reproduct Update 2005;11:495–512.

Melsen B. 2012. *Adult orthodontics*, Wiley Online Library, 42-46.

Moher D, Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 2009;62:e1–34.

Morabia A, Costanza MC. International variability in ages at menarche, first livebirth, and menopause. World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives. Am J Epidemiol 1998;148:1195–1205.

Nelson H. Menopause. Lancet 2008;371:760–770.

Norton L. 1988. The effect of aging cellular mechanisms on tooth movement. Dental Clinics of North America, 32, 437-446.

Pacifici R. Cytokines, estrogen, and postmenopausal osteoporosis — The second decade. Endocrinol 1998;139:2659–2661.

Pepine CJ, Nichols WW. Estrogen and different aspects of vascular disease in women and men. Circ Res 2006;99:459–461.

Prince RL. Counterpoint: Estrogen effects on calcitropic hormones and calcium homeostasis. Endocr Rev 1994;15:301–309.

Prior JC. Perimenopause: The complex endocrinology of the menopausal transition. Endocr Rev 1998;19:397–428.

Proffit WR, Fields HW, Larson B, Sarver DM. Contemporary Orthodontics. St. Louis, Mosby Elsevier, 2019.

Raina A, Mutneja P, Dhawan P, Sharma G. Menopause and the oral cavity. Indian J Endocr Metab 2012;16:548-551.

Ray S, Rastogi R, Kumar A. Current status of estrogen receptors. Prog Drug Res 2002;59:201–232.

Raz R, Stamm WA. Controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. N Engl J Med 1993;329:753–756.

Riggs BL, Wahner HW, Seeman E, Offord KP, Dunn WL, Mazess RB, Johnson KA, Melton LJ. Changes in bone mineral density of the proximal femur and spine with aging.

Differences between the postmenopausal and senile osteoporosis syndromes. J Clin Invest 1982;70:716–723.

Roger VL, Jacobsen SJ, Pellikka PA, Miller TD, Bailey KR, & Gersh BJ. Gender differences in use of stress testing and coronary heart disease mortality: A population-based study in Olmsted County, Minnesota. J Am Coll Cardiol 1998;32:345–352.

Salazar M, Albino CC, Ramos AL, Micheletti KR, Nakamura Cuman RK, Hernandes L. Effect of teriparatide on induced tooth displacement in ovariectomized rats: A histomorphometric analysis. Am J Orthod Dentofacial Orthop 2011;139:e337–e344.

Salazar M, Hernandes L, Ramos, AL, Salazar BDO, Micheletti KR, Paranhos LR, de Mendonça MR, Cuoghi OA. Effect of alendronate sodium on tooth movement in ovariectomized rats. Arch Oral Biol 2015; 60:776–781.

Sandy JR, Farndale RW, Meikle MC. Recent advances in understanding mechanically induced bone remodeling and their relevance to orthodontic theory and practice. Am J Orthod Dentofacial Orthop 1993;103:212–222.

Sandy JR, Farndale RW, Meikle MC. Recent advances in understanding mechanically induced bone remodeling and their relevance to orthodontic theory and practice. Am J Orthod Dentofacial Orthop 1993;103:212–222.

Santen RJ, Stuenkel CA, Davis SR, Pinkerton JAV, Gompel A, Lumsden MA. Managing menopausal symptoms and associated clinical issues in breast cancer survivors. J Clin Endocrinol Metab 2017;102:3647–3661.

Santoro N, Brown JR, Adel T, Skurnick JH. Characterization of reproductive hormonal dynamics in the perimenopause. J Clin Endocrinol Metab 1996;81:1495–1501.

Santoro N, Randolph JF. Reproductive Hormones and the Menopause Transition. Obstet Gynecol Clin North Am 2011;38:455–466.

Schierbeck LL, Rejnmark L, Tofteng CL, Stilgren L, Eiken P, Mosekilde L, Køber L, Jensen JEB. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: Randomised trial. BMJ 2012;345:e6409.

Seifi M, Ezzati B, Saedi S, Hedayati M. The effect of ovariectomy and orchiectomy on orthodontic tooth movement and root resorption in Wistar rats. Dent Shiraz Uni Med Sci 2015;16:302–309.

Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015, elaboration and explanation. BMJ, 349, g7647

Sirisoontorn I, Hotokezaka H, Hashimoto M, Gonzales C, Luppanapornlarp S, Darendeliler MA, Yoshida N. Tooth movement and root resorption; The effect of ovariectomy on orthodontic force application in rats. Angle Orthod 2011;81:570–577.

Sirisoontorn I, Hotokezaka H, Hashimoto M, Gonzales C, Luppanapornlarp S, Darendeliler MA, Yoshida N. Orthodontic tooth movement and root resorption in ovariectomized rats treated by systemic administration of zoledronic acid. Am J Orthod Dentofacial Orthop 2012;141:563–573.

Smith EP, Boyd J, Frank GR, Takahashi H, Cohen RM, Specker B, Williams TC, Lubahn DB, Korach KS. Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. N Engl J Med 1994;331:1056–1061.

Sonja MM. The normal menopause transition : an overview. Maturitas 1996;23:137–145.

Soules MR, Sherman S, Parrott E, Rebar R, Santoro N, Utian W, Woods N. Executive summary: Stages of Reproductive Aging Workshop (STRAW). Climacteric 2001;4:267–272.

Speroff L, Glass RH, Kase NG. Clinical Gynecologic Endocrinology and Infertility,

Stefanick ML. Estrogens and progestins: Background and history, trends in use, and guidelines and regimens approved by the US Food and Drug Administration. Am J Med 2005;118:64–73.

Suri V, Suri V. Menopause and oral health. J Midlife Health 2014;5:115-120.

Taguchi A, Sanada M, Suei Y, Ohtsuka M, Nakamoto T, Lee K, Tsuda M, Ohama K, Tanimoto K, Bollen AM. Effect of estrogen use on tooth retention, oral bone height, and oral bone porosity in Japanese postmenopausal women. Menopause 2004;11:556–562.

Tan L, Ren Y, Wang J, Jiang L, Cheng H, Sandham A, Zhao Z. Osteoprotegerin and ligand of receptor activator of nuclear factor. Angle Orthod 2008;79:292–298.

Tan L, Wang J, Zhao Z, Jiang L, Zou R. Effects of osteoporosis on experimental tooth movement in aged rats. Sichuan Da Xue Xue Bao Yi Xue Ban 2006;37:449–451.

Tanaka M, Ejiri S, Toyooka E, Kohno S, Ozawa H. Effects of ovariectomy on trabecular structures of rat alveolar bone. J Periodontal Res 2002;37:161-165.

Tanaka M, Miyazawa K, Tabuchi M, Yabumoto T, Kadota M, Yoshizako M, Yamane C, Kawatani M, Osada H, Maeda H, Goto S. Effect of reveromycin A on experimental tooth movement in OPG−/− Mice. J Dent Res 2012;91:771-776

Theintz G, Buchs B, Rizzoli R, Slosman D, Clavien H, Sizonenko PC, Bonjour JP. Longitudinal monitoring of bone mass accumulation in healthy adolescents: Evidence for a marked reduction after 16 years of age at the levels of lumbar spine and femoral neck in female subjects. J Clin Endocrinol Metab 1992;75:1060–1065.

Thompson IOC, Van der Bijl P, Van Wyk CW, Van Eyk AD. A comparative light-microscopic, electron-microscopic and chemical study of human vaginal and buccal epithelium. Arch Oral Biol 2001;46:1091–1098.

Tsolakis AI, Khaldi L, Bitsanis I, Alexandridis C, Triantafyllou A, Spyropoulos MN, Dontas IA. The effect of osteopenia on tooth movement in ovariectomized rats. An experimental study. J Musculoskelet Neuronal Interact 2018;18:366–374.

Turner RT, Riggs BL, Spelsberg TC. Skeletal effects of estrogen. Endocr Rev 1994;15:275–300.

Tyrovola JB, Spyropoulos MN, Makou M, Perrea D. Root resorption and the OPG/RANKL/RANK system: a mini review. J Oral Sci 2008;50:367–376.

UK Public Assessment Report. Hormone-replacement Therapy: Safety Update. 2007.

Välimaa H, Savolainen S, Soukka T, Silvoniemi P, Mäkelä S, Kujari H, Gustafsson JA, Laine M. Estrogen receptor-β is the predominant estrogen receptor subtype in human oral epithelium and salivary glands. J Endocrinol 2004;180:55–62.

von Wowern N, Klausen B, Kollerup G. Osteoporosis: A risk factor in periodontal disease. J Periodontol 1994;65:1134–1138.

World Health Organization. Scientific Group on the Assessment of Osteoporosis at Primary Health, 2007.

World Health Organization. Technical Report Series 843. Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis: Report of a WHO Study Group. 1994.

Wronski TJ, Dann LM, Scott KS, Cintron M. Long-term effects of overiectomy and aging on the rat skeleton. Calcif Tissue Int 1989;45:360–366.

Xu Y, Zhao T, Xu W, Ding Y. Periodontal microstructure change and tooth movement pattern under different force magnitudes in ovariectomized rats: An in-vivo microcomputed tomography study. Am J Orthod Dentofacial Orthop 2013;143:828–836.

Yalcin F, Gurgan S, Gul G. Oral health in postmenopausal Turkish women. Oral Health Prev Dent. 2006;4:227–233.

Yamashiro T, Takano-Yamamoto T. Influences of ovariectomy on experimental tooth movement in the rat. J Dent Res 2001;80:1858–1861.

Zittermann A, Schwarz I, Scheld K, Sudhop T, Berthold HK, von Bergmann K, van der Ven H, Stehle P. Physiologic fluctuations of serum estradiol levels influence biochemical markers of bone resorption in young women. J Clin Endocrinol Metab 2000;85:95–101.

9. APPENDICES

Appendix I. Systematic review protocol used for registration with international prospective register of systematic reviews (PROSPERO).

Review question

To investigate current data on effect of pregnancy, lactation and menopause on orthodontic tooth movement

Context and rationale

Clinical practice has shown that the rate of orthodontic tooth movement and root resorption during treatment, tend to vary among individuals and might be influenced by factors such as nutrition, hormones, supplements, medications, and conditions. Adults and especially women, constitute a growing proportion of patients under orthodontic treatment. The objective of the present review is to systematically inspect and appraise the quality of the available evidence from animal studies regarding the effect of the hormonal changes that occur during pregnancy, lactation and menopause on the rate of orthodontic tooth movement and risk of root resorption.

Searches

Comprehensive electronic database searches will be undertaken without language restriction in the following databases:

MEDLINE via PubMed (http://www.ncbi.nlm.nih.gov/PubMed), Scopus (www.Scopus.com), Web of Science™ Core Collection (http://apps.webofknowledge.com/), Arab World Research Source (http://0-

web.a.EBSCOhost.com.amclb.iii.com) and ProQuest Dissertations & Theses Global database.

Efforts will be made to obtain conference proceedings and abstracts where possible. Authors will be contacted to identify unpublished or ongoing clinical trials and to clarify methodology and data as necessary. Reference lists of included studies will be screened for additional relevant research.

Study designs to be included

Inclusion criteria:

Controlled studies with a separate control group

Exclusion criteria:

Case studies, cross-over studies, studies without a separate control group.

Human disease modelled

Orthodontic tooth movement during pregnancy, lactation and menopause

Animals/population

Inclusion criteria:

Female animals during pregnancy, lactation or menopause

Exclusion criteria:

Male; ex vivo, in vitro and in silico models [humans are not going to be included],

Intervention(s), exposure(s)

Inclusion criteria:

All types of orthodontic interventions to induce movement of teeth, either during or

after orthodontic tooth movement.

Exclusion criteria:

Other kinds of interventions, like growth modification, etc

Comparator(s)/control

Inclusion criteria:

Animals not in pregnancy or lactation, healthy [not in menopause], naive animals

Exclusion criteria:

Male animals; humans; ex vivo, in vitro and in silico models

Other selection criteria or limitations applied

Inclusion criteria:

All languages, all publication dates.

Exclusion criteria:

None.

Outcome measure(s)

Inclusion criteria:

Rate of tooth movement and root resorption [quantified measurements]

Exclusion criteria:

Rate of tooth movement and root resorption [not quantified measurements]

Study selection and data extraction

Procedure for study selection

All assessments including titles and/or abstract screening and full text evaluation will

be performed independently and in duplicate by two reviewers. The investigators will not be blinded to the authors or the results of the research. Disagreements will be resolved by discussion.

Prioritize the exclusion criteria

1. Not animal study; 2. Not Pregnancy, lactation, menopause; 3. Not orthodontic tooth movement model; 4. Not quantified measurements on the rate of tooth movement and root resorption

Methods for data extraction

Extraction of data will be performed independently and in duplicate by two reviewers, from text and tables. In case of need authors of eligible studies will be contacted with e-mail to provide missing or additional data.

Data to be extracted: study design

Study design, number of groups

Data to be extracted: animal model

Species, age, weight, number

Data to be extracted: intervention of interest

Model of orthodontic movement

Data to be extracted: primary outcome(s)

rate of tooth movement [mm; continuous] and root resorption [number of resorption lacunae; resorption area (mm2) and volume (mm3); continuous; resorption area to total root area ratio; continuous]

Data to be extracted: secondary outcome(s)

Not applicable

Data to be extracted: other

bibliographical details, such as author, year and language.

Risk of bias and/or quality assessment

By use of SYRCLE's risk of bias tool.

The risk of bias in individual studies will be assessed independently and in duplicate. Discrepancies will be resolved by discussion.

Strategy for data synthesis

Planned approach

If more than 2 for pregnancy, lactation or menopause, at each time point, exist, then exploratory data synthesis will be carried out.

Effect measure

rate of tooth movement [mm; continuous - mean difference] and root resorption [number of resorption lacunae - mean difference; resorption area (mm2) and volume (mm3); continuous - mean difference; resorption area to total root area ratio; continuous - mean difference]

Effect models

random-effects

Heterogeneity

Heterogeneity will be assessed using both the χ^2 test and the I^2 statistic.

Analysis of subgroups or subsets

Subgroup analyses

Species, stage of pregnancy, timing since induction of menopause

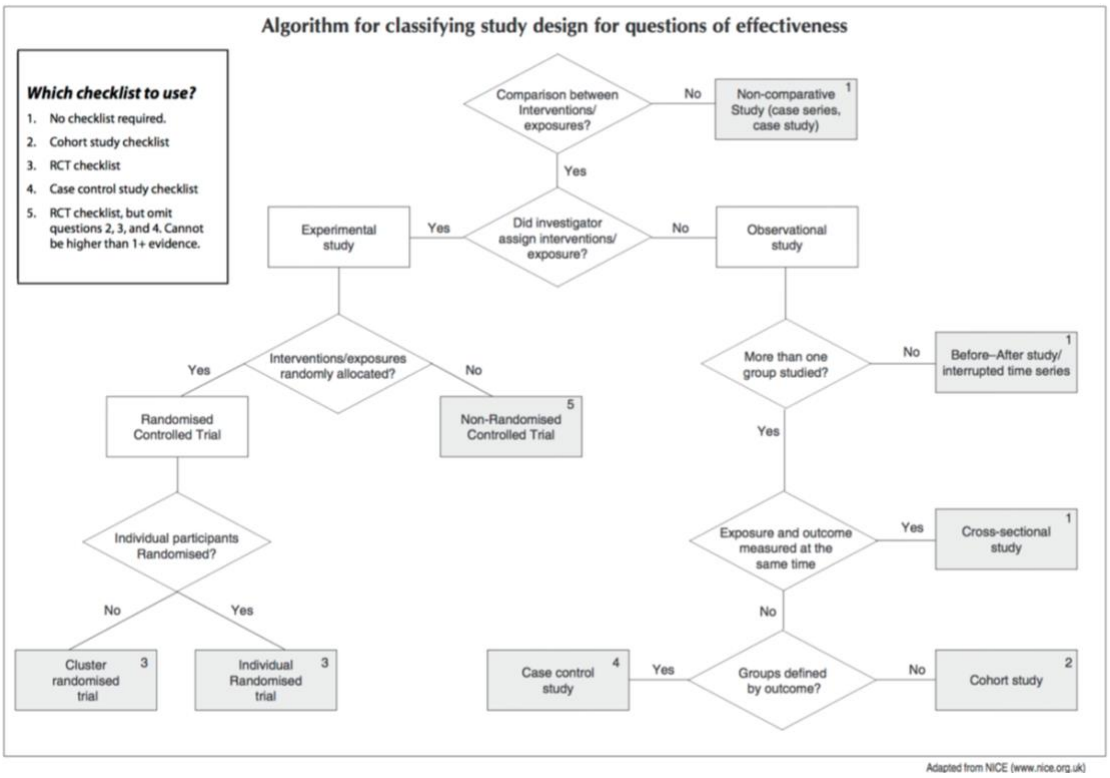
Sensitivity

None planned

Publication bias

For meta-analyses using the mean difference or risk ration as effect measure and containing at least 20 studies, we will produce funnel plots and assess publication bias using Egger's regression test.

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



Appendix III. Strategy for database search.

Database	Search strategy	Hits
PubMed	(premenopaus* OR postmenopaus* OR menopaus* OR perimenopaus* OR amenorrh* OR climacter* OR ovar* OR ovariect* OR oophorect* OR hysterectomy OR “ovarian failure” OR estrous OR estrogen* OR estradiol* OR oestradiol* OR estrone* OR oestrone* OR estriol* OR oestriol* OR progestogen* OR progesterone OR osteopor* OR ovulation) AND ("tooth movement" OR "orthodontic movement" OR "orthodontic anchorage" OR root resorption)	**140**
Cochrane Central Register of Controlled Trials	(premenopaus* OR postmenopaus* OR menopaus* OR perimenopaus* OR amenorrh* OR climacter* OR ovar* OR ovariect* OR oophorect* OR hysterectomy OR "ovarian failure" OR estrous OR estrogen* OR estradiol* OR oestradiol* OR estrone* OR oestrone* OR estriol* OR oestriol* OR progestogen* OR progesterone OR osteopor* OR ovulation) AND ("tooth movement" OR "orthodontic movement" OR "orthodontic anchorage" OR root resorption) in Title, Abstract, Keywords in Trials	**3**
Cochrane Database of Systematic Reviews	(premenopaus* OR postmenopaus* OR menopaus* OR perimenopaus* OR amenorrh* OR climacter* OR ovar* OR ovariect* OR oophorect* OR hysterectomy OR "ovarian failure" OR estrous OR estrogen* OR estradiol* OR oestradiol* OR estrone* OR oestrone* OR estriol* OR oestriol* OR progestogen* OR progesterone OR osteopor* OR ovulation) AND ("tooth movement" OR "orthodontic movement" OR "orthodontic anchorage" OR root resorption) {Including Limited Related Terms}	**0**
Scopus	TITLE-ABS-KEY(premenopaus* OR postmenopaus* OR menopaus* OR perimenopaus* OR amenorrh* OR climacter* OR ovar* OR ovariect* OR oophorect* OR hysterectomy OR "ovarian failure" OR estrous OR estrogen* OR estradiol* OR oestradiol* OR estrone* OR oestrone* OR estriol* OR oestriol* OR progestogen* OR progesterone OR osteopor* OR ovulation) AND ("tooth movement" OR "orthodontic movement" OR "orthodontic anchorage" OR root AND resorption)	**1045**
Web of Science™	TOPIC: ((premenopaus* OR postmenopaus* OR menopaus* OR perimenopaus* OR amenorrh* OR climacter* OR ovar* OR ovariect* OR oophorect* OR hysterectomy OR "ovarian failure" OR estrous OR estrogen* OR estradiol* OR oestradiol* OR estrone* OR oestrone* OR estriol* OR oestriol* OR progestogen* OR progesterone OR osteopor* OR ovulation) AND ("tooth movement" OR "orthodontic movement" OR "orthodontic anchorage" OR root resorption)) Timespan: All years. Search language=Auto	**251**
Arab World Research Source	TI tooth movement AND AB tooth movement	**2**
ClinicalTrials.gov	(orthodontic OR orthodontics) AND (tooth movement)	**34**
ProQuest Dissertations and Theses Global	(premenopaus* OR postmenopaus* OR menopaus* OR perimenopaus* OR amenorrh* OR climacter* OR ovar* OR ovariect* OR oophorect* OR hysterectomy OR “ovarian failure” OR estrous OR estrogen* OR estradiol* OR oestradiol* OR estrone* OR oestrone* OR estriol* OR oestriol* OR progestogen* OR progesterone OR osteopor* OR ovulation) AND ("tooth movement" OR "orthodontic movement" OR "orthodontic anchorage" OR root resorption)	**1**