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REVIEW ARTICLE

Antioxidant supplements: Positive or negative actors in orthodontic treatment

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ABSTRACT

Antioxidant supplements are popular and commonly considered healthy benefits such as reducing the risk of disease. It should be noted that their advantages/disadvantages are still unclear. Some research on antioxidants shows that they may reduce the risk of cancer, heart disease, neurodegenerative diseases, and some chronic diseases, and have various health benefits such as a positive effect on bone metabolism by supporting bone regeneration. Some of them show that the benefits of antioxidant supplements are not clear and indicate to increase the risk. The effects of antioxidants on orthodontic treatment are now being studied extensively due to their widespread use. Antioxidants that regulate bone modulation can be used to reduce orthodontic treatment time, accelerate tooth movement, or in some cases prevent unwanted tooth movement, but their unconscious use can adversely affect the orthodontic treatment. Understanding the mechanisms of action of antioxidants and their effects on orthodontic treatment can increase the success of treatment and prevent adverse situations that may occur due to the use of antioxidants.

Many inflammatory mediators play a role in the response to mechanical forces in orthodontic treatment. Increased expression of pro-inflammatory cytokines is associated with oxidative stress. Antioxidants can affect remodeling processes in which osteoblast and osteoclast cells play a role, such as relapse, anchorage, and bone formation after maxillary expansion in orthodontic treatment. The use of antioxidants in orthodontic treatment may increase tooth movement and shorten retention time by increasing osteoblastic activity after maxillary expansion, or on the contrary, slow tooth movement and prolong treatment time by reducing oxidative stress and inflammation. Accordingly, factors such as the desired effect in orthodontic treatment and the phase of treatment should be considered when using antioxidants. We aimed to provide information and suggestions for evaluating the effectiveness of antioxidant use in orthodontic treatment with basic information about antioxidants.

Keywords: Antioxidant supplements, orthodontic treatment, oxidative stress

INTRODUCTION

The process of oxidation in the human body damages cell membranes and other structures (cellular proteins, lipids, DNA, etc.) by creating unstable molecules called free radicals (Buczko, Knas, Grycz, Szarmach, & Zalewska, 2017). Over time the damage caused by an overload of free radicals may become irreversible and lead to cellular dysfunctions and certain diseases or cancers. Oxidation can be also accelerated by stress, physical conditions, chemicals, sunlight, and other factors. Nevertheless, as it is well known, antioxidants are man-made or natural substances, which are produced from several sources including minerals, vitamins or food and herbal supplements, that scavenge free radicals from the body cells and may prevent or reduce the health issues caused by oxidation. Antioxidants are classified into basic groups: synthetic and natural on their origin, or endogenous and exogenous depending on their source, or enzymatic or non-enzymatic depending on their action, or water- and lipid-soluble depending on their solubility (Pizzino et al., 2017).

Unconscious use and high doses of exogenous antioxidants can cause oxidative damage by showing a pro-oxidant effect (Sotler et al., 2019). Even if use of antioxidant supplements has been found to be healthy; their protective potentials have become scientifically interesting compounds. High doses of antioxidant supplements can be harmful in some cases. For example, taking high-dose beta-carotene supplements increases the risk of lung cancer in smokers, and using high-dose vitamin E supplements increases the risk of hemorrhagic stroke and prostate cancer (Virtamo et al., 2003). In the dental field, the effect of antioxidant use is controversial.

Orthodontic tooth movement (OTM) occurs as a result of the remodeling of teeth and surrounding tissues by the appli-

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cation of mechanical force. During orthodontic treatment, the periodontal ligament (PDL) compresses on the compressive side and stretches on the tension side when force is applied to the tooth. Compression of the PDL is associated with osteoclast activity and stretching of the PDL is associated with osteoblast formation, resulting in bone formation (Masella & Meister, 2006; Verna, Zaffe, & Siciliani, 1999). Osteoclastic activity and bone resorption are considered rate-limiting factors in OTM (Seong et al., 2022). Osteoclasts remove the hyalinized necrotic tissue in the PDL, allowing the tooth to move within the alveolar bone (Salomao et al., 2014). Although the main factor affecting OTM is force, there are studies reporting that pharmacological active substances, chemical agents, antioxidants, and food supplement applications affect tooth movement by affecting the remodeling mechanisms of the PDL in tension and pressure regions. In addition to pharmacological interventions such as vitamin D, thyroxine, dihydroxycholecalciferol and prostaglandin E2 (PGE2) administration, invasive and non-invasive surgical techniques have been tried to accelerate OTM and modify the limiting step of bone resorption (Chen et al., 2016; Kacprzak & Strzecki, 2018; Kale, Kocadereli, Atilla, & Asan, 2004)

Oxidative stress is one of the biological responses to orthodontic treatment (Buczko, et al., 2017). Orthodontic force is considered a type of physical stress placed on the PDL. Hypoxia and compression occurring in PDL stimulate the production of free radicals (Arai et al., 2010). Oxidative stress, caused by excessive free radical production and/or impaired antioxidant defenses, can adversely affect bone formation by impairing the formation of osteoclasts, osteoblasts, and osteocytes (Kara et al., 2012). Many inflammatory mediators are involved in the response to mechanical forces during orthodontic treatment (Buczko et al., 2017). Oxidative stress and inflammation can be easily induced by each other (Fan et al., 2017). Antioxidants play a role in the anti-inflammatory response by preventing oxidant formation and reducing inflammation and may be effective on OTM (Chae et al., 2011).

In some cases, in orthodontic treatment, besides accelerating tooth movement, tooth movement should be suppressed/optimized for anchor applications that prevent unwanted tooth movement. Although various cytokines and compounds, including PGE2, vitamin D3, calcitonin and bisphosphonates, have been considered as drug candidates to optimize tooth movement by modulating osteoclasts, they have been reported to be unsuitable for clinical use due to their potential adverse effects (Shoji-Matsunaga et al., 2017). Antioxidants may be effective without the risk of oral tissue damage due to mechanical application and side effects of pharmacological agents. Besides, inhibition of osteoclast differentiation and promotion of osteoblast differentiation by regulating bone modulation could support the effectiveness of treatment in clinical applications such as preventing relapse in orthodontic treatment, accelerating the bone formation process after maxillary expansion, and anchoring methods that suppress/optimize unwanted tooth movement (Gad & Soliman, 2023). At the same time, considering that OTM may slow down with the use of antioxidants, issues such as orthodontic treatment duration, orthodontic force activations and appointment frequency should be considered in treatment planning (Bilici Geçer, 2023).

Several authors have investigated the effects of topical and systemic medications, including antioxidant supplements, on OTM. A significant number of patients seeking orthodontic treatment may benefit from medication for common health problems. Furthermore, given the general trend towards increased use of dietary supplements in the populations, it would be helpful to understand the effects of different agents on OTM in order to plan treatments and predict the timing of these treatments.

The duration of fixed orthodontic treatment can be approximately 1 to 3 years, depending on the severity of the malocclusion and the treatment applied. Lifestyle changes in patients undergoing orthodontic treatment have a significant impact on the patient's dietary intake and nutritional requirements (Al-Dlaigan, Shaw, & Smith, 2001). During orthodontic treatment, eating habits are affected by pain and functional limitations, especially in the first 3 to 5 days after treatment, patients may avoid raw vegetables, fruit and hard foods to prevent adequate chewing due to tooth sensitivity and bracket breakage during treatment (Ozdemir, Ilhan, Gorucu-Coskuner, Taner, & Bilgic, 2021). This condition significantly reduces the intake of protein, calcium, fiber and some vitamins, and blood levels of antioxidants such as vitamins C and E may be lower in orthodontic patients (Miresmaeili, Mollaei, Azar, Farhadian, & Mani Kashani, 2015; Ozdemir et al., 2021).

It is well known that the use of antioxidants is common in adults today. Although there are some studies investigating the relationship between orthodontic tooth movement and osteoclastic activity and age, the results are controversial. It has been suggested that alveolar bone and PDL remodeling is slower in adults than in adolescents, due to factors such as reduced cellular activity, vascularity and changes in bone composition. While it has been reported that there was no significant difference in the number, size or activity of osteoclasts in alveolar bone during orthodontic tooth movement in rats (Kabasawa, Ejiri, Hanada, & Ozawa, 1996; Jager & Radlanski, 1991), another study reported that osteoclast formation was slower in adult rats than in young rats (Ren, Kuijpers, & Maltha, 2005). It has also been suggested that orthodontic retention may take longer in adults to prevent relapse (Li et al., 2016). Considering the lower bone dynamics and osteoclastogenic activity during orthodontic treatment in adults, it should be considered that the use of antioxidants may prolong the duration of orthodontic treatment in adult patients, but may contribute to the post-treatment retention process.

As people become more concerned about their oral health,

dental care is becoming more detailed. This article focuses on the use of antioxidants in orthodontic treatment. Different types of antioxidants, different mechanisms of action and amounts of antioxidants used in OTM were reviewed. Challenges and safety assessment of these materials in the current field were also discussed. This review provides background information on antioxidants, summarizes the scientific evidence on antioxidants and health, and suggests additional sources of information on orthodontic treatment.

Exogenous antioxidants are dietary antioxidants found in significant amounts in widely consumed fruits, vegetables, nuts and cereals. Examples include vitamin C (ascorbic acid), vitamin E (alpha-tocopherol), carotenoids, polyphenols (phenolic acid, flavonoids, resveratrol etc.) and some minerals (Zn, Mn, Cu, Se, etc.). Endogenous antioxidants include glutathione, melatonin, uric acid, bilirubin, albumin, coenzyme Q10 (CoQ10), alpha-lipoic acid, ceruloplasmin and transferrin produced by the body (Mironczuk-Chodakowska, Witkowska, & Zujko, 2018; Pizzino et al., 2017).

Vitamin C

Vitamin C is an important water-soluble antioxidant that has been shown to neutralize the effects of free radicals on body fluids and reverse free radical damage at the cellular level (Bolat et al., 2020; Ishikawa, Iwasaki, Komaki, & Ishikawa, 2004). A major source of vitamin C, naturally occurring in citrus fruits, tomatoes, potatoes, broccoli, red and green peppers, kiwisand strawberries (Miresmaeili et al., 2015; Yalcin Bahat, Ayhan, Ureyen Ozdemir, Inceboz, & Oral, 2022; Gregory, 1993; Mangels et al., 1993). The recommended daily intake is 45 mg for 9 to 13 year olds, 65-70 mg for 14 to 18 year olds and 75-90 mg for 19 year olds (Monsen, 2000). For vitamin C, the most common effects are diarrhoea, nausea and abdominal cramps (Jacob & Sotoudeh, 2002; Monsen, 2000). Vitamin C may cause chromosomal and/or DNA damage by acting as a pro-oxidant and should be used with caution (Kazmierczak-Baranska, Boguszewska, Adamus-Grabicka, & Karwowski, 2020).

Vitamin C levels in the blood of orthodontic patients have been found to be 17 to 75% lower than desired (Miresmaeili et al., 2015). Vitamin C is known to be an important factor in bone remodelling and collagen synthesis in the PDL. Its deficiency can lead to a complete halt in osteogenesis, disturbance in the organisation of the PDL and an increase in bone resorption (Fujita, Hirano, Itoh, Nakanishi, & Tanaka, 2001; Van den Berg, Yu, Lemmens, & Beynen, 1994). Vitamin C has been shown to play a critical role in osteoclast stimulation, which occurs during tooth movement (Ozdemir et al., 2021). It also enables stem cells to transform into osteoblasts through collagen type I synthesis, interaction with integrins, activation of protein kinase signalling and phosphorylation of osteoblast-specific transcription factors (Miresmaeili et al., 2015). It has been reported to increase collagen production and induce tooth movement, and its deficiency may reduce OTM due to inhibition of collagen remodelling (Fujita et al., 2001; Motoji, To, Hidaka, & Matsuo, 2020; Van den Berg et al., 1994).

Miresmaeili *et al*., (2015) evaluated the effect on OTM in rats given dietary vitamin C. To achieve the desired blood level, vitamin C (1% water) added to the daily drinking water 7 days before the start of the experiment and applied for 17 days. It has been reported that the amount and rate of OTM and the number of osteoclasts increase. Bolat *et al*., (2020) evaluated the systemic and local effects of vitamins C and E on OTM. Systemically, 150 mg/kg (i.p.) of vitamins C and E were administered once a day. Locally, vitamins C and E (20 µL) were injected into the PDL every three days. It was reported that the most tooth movement was in the local vitamin C group, the least tooth movement was in the local vitamin E group, there was no significant difference in the number of osteoclasts, and the number of osteoblasts increased with the application of the vitamin. Özdemir *et al*., (2021) stated that vitamin C deficiency during orthodontic treatment reduces tooth movement by reducing tissue healing and regeneration in the PDL. Consuming less than the daily requirement of vitamin C may prevent collagen degradation and reformation necessary for tooth movement (Litton, 1974).

A long retention period after maxillary expansion is required to prevent early relapse. Therefore, it is important to promote osteogenesis of the expanding midpalatal suture to prevent relapse. Farhadian *et al.*, (2015) evaluated the effect of dietary vitamin C on osteogenesis of the midpalatal suture in rats during maxillary expansion, and they planned application periods of 3, 9 and 17 days. To achieve the desired blood level, 10 kg/m3 of vitamin C was added to the daily drinking water 7 days before the start of the experiment. It was observed that vitamin C had no significant effect on osteoclasts during maxillary suture expansion in rats, it had a stimulating effect on osteoblast differentiation at the beginning (day 3), but later (day 17), a negative effect on osteoblasts was observed.

Uysal *et al*., (2011) evaluated the effects of vitamin C administration on bone formation in the expansion of the maxillary suture in rats by histomorphometry. A single dose vitamin C (0.5 mg/kg) was administered locally and systemically to rats as an intramuscular and subcutaneous injection. The experimental period consisted of a 5-day expansion period and a 15-day retention period. Systemic administration of vitamin C with rapid maxillary expansion may shorten the duration of the procedure and improve the quality of the regenerated bone, whereas local injection of antioxidants has been reported to be detrimental to bone formation.

Dehis *et al.*, (2018) evaluated the efficacy and safety of local vitamin C injection on impacted canine traction speed and preservation of periodontal integrity in patients with unilateral impacted canines. The use of vitamin C was reported to increase the speed of movement during traction of the impacted

tooth. Healing was evaluated for 12 months after canine maintenance surgery and it was found that the alveolar bone level was preserved, the gingival biotype and the width of keratinized gingival tissues increased. Vitamin C was found to accelerate the eruption of canines by maintaining the integrity of the periodontium.

Vitamin E

Vitamin E is a powerful lipid-soluble antioxidant (Seong et al., 2022). It is found abundantly in olive and sunflower oils, as well as nuts, soybeans, avocados, wheat, and green leafy vegetables (Colombo, 2010). There are eight different forms of vitamin E known to occur in nature: four tocopherols (α, β, γ and δ isomers) and four tocotrienols (α, β, γ and δ isomers) (Clarke, Burnett, & Croft, 2008). Alpha-tocopherol has the highest antioxidant activity and is the most bioavailable in human tissues (Borhanuddin, Mohd Fozi, & Naina Mohamed, 2012; Huang, Chang, Huang, & Chen, 2003). Protects cell membranes from oxidation by lipid radicals generated during the lipid peroxidation chain reaction (Herrera & Barbas, 2001). In addition to being a potent biological antioxidant, it suppresses the production of pro-inflammatory mediators that have been reported to increase bone resorption, such as interleukin (IL)-1, IL-6, PGE2 and tumor necrosis factor-α (TNF-α) (van Tits, Demacker, de Graaf, Hak-Lemmers, & Stalenhoef, 2000). Vitamin E also has anti-inflammatory effects, inhibits platelet aggregation and improves immunity (Seong et al., 2022). The Food and Drug Administration (FDA) has classified α-tocopherol as "Generally Recognized as Safe (GRAS)" (Bolat, 2014). The recommended daily intake is 11 mg for children aged 9 to 13 years and 15 mg for children aged 14 years and over (NIH, 2021).

Many inflammatory mediators are involved in the response to mechanical forces during orthodontic treatment (Buczko et al., 2017). Vitamin E alters cytokine production (Esenlik, Naziroglu, Acikalin, & Ovey, 2012; Xu, Watkins, & Seifert, 1995), suppresses the harmful effects of free oxygen radicals in cells during bone formation (Xu et al., 1995), stimulates bone formation and has beneficial effects on new bone formation (Kurklu et al., 2011) during orthodontic treatment.

In rats, the supplementation with tocotrienol and alpha-tocopherol maintained corticosterone levels at a value appropriate for cellular homeostasis (Nur Azlina & Nafeeza, 2008) and reduced the stress state and inflammation caused by orthodontic force (Sufarnap et al., 2021). In rats fed a vitamin E diet (600 IU/kg), OTM increased on days 4 and 14, the number of osteoclasts increased, and bone volume decreased on day 14 (Seong et al., 2022). They suggested that high levels of vitamin E may help stimulate bone formation by increasing osteoblastic activity and preventing relapse during the retention phase. Although no systemic effects on bone turnover were found, it has been reported that long-term administration of high levels of vitamin E during orthodontic treatment can cause unwanted side effects. Indeed, the several studies reported that it may increase tooth movement by increasing osteoclastic activity (Seong et al., 2022; Sufarnap, Siregar, & Lindawati, 2020), and may reduce OTM by reducing inflammation (Esenlik et al., 2012; Q. Jiang, 2014; Sufarnap et al., 2021).

Wistar rats were given vitamin E (60 mg/kg) by oral gavage 14 days before appliance placement and during the 14-day experiment. It has been reported that vitamin E can reduce cortisol and IL-1β levels, and accordingly reduce the stress caused by orthodontic force (Sufarnap et al., 2021). Another similarly designed study reported that vitamin E increased tooth movement and the number of osteoblasts, but did not affect the number of osteoclasts (Sufarnap et al., 2020).

The results of studies of vitamin E on bone mineral density, markers of bone formation and bone health in humans are inconsistent. While some studies have found a negative association between serum vitamin E levels and markers of bone turnover and bone mineral density (Hamidi, Corey, & Cheung, 2012; Zhang, Hu, & Zhang, 2017) others have found that, on the contrary, higher dietary vitamin E intake is associated with higher bone mineral density (Mata-Granados, Cuenca-Acebedo, Luque de Castro, & Quesada Gomez, 2013; Shi et al., 2016). Esenlik et al., 2012 evaluated the changes in oxidant and antioxidant levels in gingival crevicular fluid in patients receiving orthodontic treatment with vitamin E (300 mg/day) for one month. Vitamin E has been reported to reduce lipid peroxidation levels in the anterior region.

Omega-3

Omega-3 fatty acids, which are polyunsaturated fatty acids, consist of alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Omega-3 fatty acids have anti-inflammatory effects by reducing levels of inflammatory mediators such as pro-inflammatory cytokines and arachidonic acid-derived eicosanoids (PGE2 etc.) (Calder, 2006; Gad & Soliman, 2023). Omega-3 fatty acids have beneficial effects on bone and cardiovascular diseases due to their immunomodulating and anti-inflammatory effects (Gad & Soliman, 2023). The use of EPA and DHA, separately or together, reduces oxidative stress. This effect is thought to be related to the immunomodulatory effect of polyunsaturated fatty acids and the reduction of leukocyte activation (Mori & Beilin, 2004). The icosapent ethyl and omega-3 acid ethyl esters, which are omega-3 fatty acid products, have been approved by the FDA, and the recommended daily intake are 1-1.2 g for 9 to 13 year olds, 1.1-1.6 g for 14 to 18 year olds and over 19 year olds. Although there are harmless side effects such as fishy smell, indigestion, diarrhea, bloating and nausea, it is generally safe and it has been reported that EPA and DHA intake should not exceed 3 g per day (Krupa, Fritzy, & Parmar, 2023; NIH, 2023).

Omega-3 has been shown to inhibit osteoclast activity and bone resorption, while stimulating osteoblast activity and new

bone formation (Sun et al., 2003). Omega-3 has a beneficial effect on bone health by increasing Ca absorption in the intestine, increasing osteoblast differentiation and activity, and supporting mineral deposition in bone (Gad & Soliman, 2023). Diet rich in omega-3 fatty acids suppresses the inflammatory response, like non-steroidal anti-inflammatory drugs, and the inhibition of prostaglandin synthesis and suppression of the inflammatory response results in osteoclast activation and a decrease in the rate of OTM (Iwami-Morimoto, Yamaguchi, & Tanne, 1999). Gad & Soliman, (2023) evaluated the effect of oral administration of omega-3 fatty acids (200 mg/kg/day) for 21 days on OTM in rabbits and a decrease in active resorption areas was observed due to the strong osteoclastic inhibitory effect of omega-3 fatty acids. It was reported that while an increase in osteoblastic activity was observed, the use of omega-3 reduced the amount of OTM. Similarly; Ogrenim *et al*., (2019) administered oral omega-3 fatty acids (400 mg/kg/day) for 14 days. It has been reported that while omega-3 increases total antioxidant status, it decreases total oxidant status, receptor activator of NF-κβ ligand (RANKL), proinflammatory cytokine levels such as IL-6 and IL-1β, and thus slows the rate of OTM.

Coenzyme Q10 (CoQ10)

CoQ10 is a lipid-soluble, vitamin-like benzoquinone compound that is endogenously synthesized in the human body from tyrosine and functions as a coenzyme in key enzymatic reactions during cellular energy production (Bilici Gecer, 2023). CoQ10, a non-enzymatic antioxidant, is the only lipophilic antioxidant that can be synthesized de novo by cells and has enzymatic mechanisms to regenerate its reduced form (Arenas-Jal, Sune-Negre, & Garcia-Montoya, 2020). CoQ10 is the most widely used dietary supplement after fish oil and multivitamins (Yang et al., 2022). CoQ10 is not FDA-approved for the treatment of any medical condition, but is widely used as a dietary supplement over the counter. Oral formulations are available in doses from 30 to 600 mg. It has been found that CoQ10 supplements are generally well tolerated, with rare side effects such as stomach upset, nausea, vomiting and diarrhea. No toxic effects have been reported even at doses of 1200 mg/day (Sood & Keenagham, 2022)

Beneficial effects of CoQ10 have been reported in many conditions including cardiovascular disease, inflammatory disease, diabetes and cancer (Arenas-Jal et al., 2020). CoQ10 is used as a preventive and supplement in neurodegenerative diseases such as Alzheimer's and Parkinson's, which are associated with ageing and increased oxidative damage (Lopez-Lluch, Rodriguez-Aguilera, Santos-Ocana, & Navas, 2010). Recently, the use of CoQ10 in dermocosmetic products has become widespread due to its skin repair and anti-aging properties. The effects of CoQ10 and selenium on oxidative stress and inflammation in viral infections have been investigated in COVID-19 infection and it was found that they could be used as a supportive approach in the prevention and treatment of diseases (Hargreaves & Mantle, 2021).

The high antioxidant activity of CoQ10 is explained by its intramembranous localization and redox properties (Varela-Lopez, Giampieri, Battino, & Quiles, 2016). Thanks to its highly hydrophobic isoprene side chain, CoQ10 prevents the initiation of lipid, protein and DNA peroxidation by interacting with oxygen-derived free radicals and protects cells from oxidative damage by preventing damage to biomolecules (Crane, 2001). Unstable free radicals become stable with an electron from ubiquinone. The ubiquinol and semi-quinone forms of CoQ10 provide regeneration of the reduced forms of antioxidant compounds such as vitamins E and C (Kawamukai, 2002). CoQ10 has been reported to have an anti-inflammatory effect by inhibiting the expression of RANKL-dependent genes. It has also been shown to increase the peroxisome proliferator-activating receptor-dependent anti-inflammatory response and inhibit the release of cytokines such as TNF-α and IL-6 (Fan et al., 2017; Varela-Lopez et al., 2016).

Bilici Gecer, (2023) evaluated the effects of CoQ10 (100 mg/kg/day) on OTM in rats. It has been reported that CoQ10 reduces orthodontic tooth movement, reduces the number of osteoclasts due to the inhibition of ROS formation, and the morphology of osteoblasts changes to a cubic/cylindrical form, showing osteoblastic alignments, new ossification areas are prominent and wide, and bone matrix formation is more advanced. In immunohistochemical evaluation, it was stated that RANKL and vascular endothelial growth factor (VEGF) levels increased with orthodontic force application and decreased with CoQ10. At the same time, it was stated that while total oxidant status levels decreased in CoQ10 groups, total antioxidant status levels increased. Another study evaluating the effects of CoQ10 (25 mg/kg/day) for 21 days on relapse after orthodontic treatment in rabbits reported that there was no significant difference in the amount of tooth movement due to relapse after removal of the orthodontic appliance, but the number of osteoclasts decreased significantly (Madian et al., 2020).

Resveratrol

Resveratrol, an exogenous antioxidant in the group of polyphenols found naturally in a variety of foods such as grapes, grape seeds, blueberries, peanuts and red wine, is known to have anti-inflammatory, anti-carcinogenic, antioxidant, anti-aging and protective effects on the cardiovascular system and bone tissue (Liu et al., 2020; Okubo, Ishikawa, Sano, Shimazu, & Takeda, 2020). Clinical studies have shown that taking resveratrol in amounts up to 5 g per day is technically safe, but taking more than 2.5 g per day can cause abdominal side effects such as cramping, bloating, and nausea (Ramirez-Garza et al., 2018). Resveratrol increases cellular resistance to oxidative stress, supports osteogenesis by increasing the differentiation of bone mesenchymal cells, and stimulates the prolifera-

tion and differentiation of osteoblasts by inducing the production of alkaline phosphatase and bone morphogenetic protein-2 (BMP-2) (Y. Jiang et al., 2020; Xia, Daiber, Forstermann, & Li, 2017). It also inhibits receptors involved in osteoclast differentiation through RANKL and induces apoptosis of differentiated osteoclasts (Boissy et al., 2005). Resveratrol reduces the production of inflammatory mediators through inhibition of the cyclooxygenase-2 (Cox-2) cascade (Okubo et al., 2020). Resveratrol has no known significant toxic side effects (Russo, 2007) and is being promoted as a complementary alternative medicine candidate for pain management (Okubo et al., 2020).

Several studies have been conducted in the field of dentistry, reporting on the antioxidant capacity of phenolic compounds in the structure of grape seed extract and its beneficial effects on bone tissue. The effects of resveratrol on OTM and orthodontic root resorption at doses of 5 and 10 mg/kg/day for 14 days were investigated and it was observed that resveratrol significantly reduced OTM and orthodontic induced root resorption, decreased RANKL expression and increased the expression of osteoblast-related mediators such as OPG (Liu et al., 2020). Demir, (2020) reported that during rapid maxillary expansion in rats, 150-300 mg/kg/day of grape seed extract administered by oral gavage resulted in increased bone formation in the midpalatal suture, thus shortening the fixation period and preventing relapse. Okubo *et al*., (2020) reported that when resveratrol was administered to rats at a dose of 2 mg/kg (i.p.), it suppressed peripheral and/or central sensitization and reduced mechanical ectopic hyperalgesia induced by experimental tooth movement, making it a potential therapeutic agent for this purpose.

Curcumin

Curcumin is a substance derived from the root of the turmeric plant, which has the characteristic of being a yellow or orange pigment (Unlu, Nayir, Dogukan Kalenderoglu, Kirca, & Ozdogan, 2016). It is increasingly being investigated for its various therapeutic properties, including analgesic, antioxidant, anti-inflammatory and antimicrobial activities. Curcumin inhibits inflammatory cytokine production by regulating lipoxygenase activities. Inhibits RANKL activation for osteoclastogenesis (Cesur et al., 2018). According to EFSA (European Food Safety Authority) reports, up to 3 mg/kg body weight per day is allowed (EFSA, 2014). In another study, some subjects receiving 0.45 to 3.6 g/day curcumin for one to four months reported side effects such as nausea and diarrhea (Hewlings & Kalman, 2017).

Asefi, Seifi, Fard, & Lotfi, (2018) investigated the effect of curcumin (0.03 mL local injection) for 21 days on the OTM rate in rats. Curcumin had no significant effect on OTM, but significantly inhibited root and bone resorption, osteoclastic activity and angiogenesis. In another study investigating the potential effect of topical curcumin (1%) on periodontal tissues and myeloperoxidase activity in the gingival crevicular fluid (GCF) during the first phase of orthodontic movement in patients undergoing orthodontic treatment, it was reported that the curcumin gel formulation reduced myeloperoxidase activity in the GCF 14 days after arch wire placement (Samita, Verma, Sharma, Moinuddin, & Ahad, 2022).

Melatonin

Melatonin is the major pineal hormone synthesized from tryptophan. It stimulates osteoblastic cell proliferation and type I collagen synthesis. Due to its antioxidant properties, it inhibits bone resorption by influencing osteoclast differentiation and protecting bone from oxidative damage (Cesur et al., 2018). Acute toxicity of melatonin is very low in both animal and human studies. Melatonin can cause mild side effects such as headaches, insomnia, skin rashes, upset stomach, and nightmares (Malhotra, Sawhney, & Pandhi, 2004). After rapid maxillary expansion in rats, curcumin (150 mg/day/kg, i.p.) and melatonin (75 mg/day/kg, i.p.) induce new bone formation and may shorten the retention phase (Cesur et al., 2018). However, the clinical trials should be conducted before the agents can be used prophylactically in humans. In a study investigating the effect of simulated orthodontic pressure and tension forces on periodontal ligament fibroblasts, melatonin increased collagen synthesis and expression of inflammatory mediators without effects on genes involved in bone remodeling (Schroder et al., 2022).

CONCLUSION AND CLINICAL RECOMMENDATIONS

Unconscious use and high doses of antioxidants used as dietary supplements can cause oxidative damage by having a pro-oxidant effect. The use of antioxidant supplements has sometimes been found to be healthy, but studies have also shown that they are not effective in treating or preventing disease. Therefore, their protective potential has made them scientifically interesting compounds. High doses of antioxidant supplements can be harmful in some cases, as well as beneficial in orthodontic treatment, and adverse effects may be observed. It is thought that antioxidants, which are widely used today, may be effective in OTM due to their effects on oxidative stress and pro-inflammatory cytokines. In some cases, in addition to accelerating tooth movement, tooth movement should be suppressed/optimized for anchor applications that prevent unwanted tooth movement in orthodontic treatment. In addition, shortening the retention period and increasing bone formation in patients undergoing maxillary expansion are important in reducing the duration of orthodontic treatment. The effective use of antioxidants without the risk of side effects of pharmacological agents may have positive effects in clinical use as well as negative effects such as prolongation of treatment and slowing of tooth movement in unconscious use.

Antioxidants can reduce inflammation during OTM through their effects on oxidative stress and proinflammatory cytokines. Reduced expression of proinflammatory cytokines such as RANKL, IL, TNF-a may result in decreased osteoclast formation and thus tooth movement. Considering that OTM may be reduced, issues such as orthodontic treatment duration, orthodontic force activations and frequency of appointments may need to be considered in treatment planning.

Antioxidants can be effective without the risk of oral tissue damage from mechanical application and the side effects of pharmacological agents. In addition, it can support treatment efficacy in clinical applications such as inhibiting osteoclast differentiation and promoting osteoblast differentiation by regulating bone modulation, preventing relapse in orthodontic treatment, accelerating the bone formation process after maxillary expansion, and anchoring methods that suppress/optimize unwanted tooth movement. It can support the retention process in preventing relapse due to tooth movement after orthodontic treatment and accelerate the bone formation process after maxillary expansion. Local applications in anchorage methods, such as slowing/suppressing tooth movement, can help increase the effectiveness of treatment. Considering the different mechanisms of action of antioxidants and their effects on remodeling during the orthodontic treatment process, clinicians can determine at which stage of treatment they should be used and play an important role in increasing the effectiveness of treatment. In addition, considering the nutritional value of antioxidants, the patient's diet may be as important as the pharmacological drugs in the medical history. Given that OTM may be slowed with the use of antioxidants, issues such as the duration of orthodontic treatment, orthodontic force activations, and the use of antioxidants should be considered.

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