

# Influence of menopause on endodontic treatment

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## ABSTRACT

Menopause is one of the physiological changes characterized by the end of menstrual and ovulatory cycles occurring in women in their fourth and fifth decade of life. Thereat, production of estrogen, an important hormone that acts in many physiological process of the individual such as the regulation of skeletal system, decreases. The decline in estrogen levels results in loss of bone mineral density, increased fracture risk, as well as bone diseases such as osteoporosis, a pathological process in which there is increased resorption of cavities that are not completely filled by newly formed bone. Furthermore, estrogen deficiency can cause many changes in an individual's oral health. In the presence of bacterial infection of pulp tissue,

this deficiency can aggravate apical periodontitis. Several drugs have been studied as potential therapeutic agents to compensate for deficiency of estrogen. These drugs aim to reduce the likelihood of fractures and prevent bone loss as well as cardiovascular and mental disorders resulting from postmenopausal hormone disabilities. Raloxifene (RLX) is one of the most studied drugs therapies and proves to prevent bone loss. Even though raloxifene is indicated for and produces benefits to bone metabolism and maintenance of bone density, additional studies are warranted to further investigate the role of raloxifene in endodontic infection of osteopenic organisms.

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## Introduction

The growing number of older people has been increasingly evident and, for this reason, has raised health concern over this age group mainly due to physiological changes and increased susceptibility to diseases.

Menopause is one of the physiological changes that occur during women fourth and fifth decade. It characterizes the physiological end of menstruation<sup>1</sup> and decline in the level of estrogen, which results in loss of bone mineral density, increased fracture risk and bone diseases such as osteoporosis.<sup>2</sup>

Estrogen is key to the physiological processes of the individual, including cell growth and development, as well as regulation of reproductive, neuronal, immune, cardiovascular and skeletal systems.<sup>3,4</sup> Furthermore, estradiol plays an important role in inflammatory diseases, which can interfere in the proliferation of cytokines.<sup>5,6</sup>

Deficiency in estrogen level can affect ones body, including oral health.<sup>7</sup> Estrogen is capable of recruiting immune and skeletal cells modulating the progression of pathological tissue.<sup>6,8</sup>

Bacterial infection of pulp tissue can cause periapical lesion, in which case inflammatory cells are stimulated to produce factors that increase the activity of osteoclasts and, as a result, lead to alveolar bone resorption.<sup>9</sup> Since estrogen plays an important role in the process of alveolar resorption, its deficiency can aggravate apical periodontitis.<sup>10</sup>

Several drugs have been studied as potential therapeutic agents to compensate for estrogen deficiency. Among these, we highlight the selective estrogen receptor modulator (SERM). It is a class of non-hormonal molecules that, depending on the estrogen receptor that it binds to, may produce agonist or antagonist effects on estrogen in different target tissues.<sup>11</sup> Raloxifene hydrochloride (RLX), a second generation of SERM, mimics the beneficial effects of estrogen without stimulating breast and endometrium tissues.<sup>12</sup> SERM molecular mechanism of action involves high binding affinity with estrogen receptor, causing a conformational change in the structure of the receptor, as well as its dimerization and association with specific DNA response elements for RLX.<sup>13</sup> Studies reveal that raloxifene treatment results in increased bone mineral density, thereby significantly reducing the incidence of fractures.<sup>14,15,16</sup>

## Osteoporosis

The increase in worldwide life expectancy is causing the proportion of elderly people to grow faster than any other age group.<sup>17</sup> The elderly have higher vulnerability and incidence of pathological processes, such as osteoporosis. These conditions affect quality of life and increased mortality, representing an important issue for the health of people in this age group.<sup>18,19</sup> In this context, there is great concern about the health of the elderly and prevention of diseases resulting from the aging process,<sup>20</sup> which leads to further studies that can improve the quality of life of these individuals.

The elderly presents several physiological changes that predispose them to pathological conditions typical of aging.<sup>21</sup> Osteoporosis is a pathological process resulting from the decline in estrogen that occurs in menopausal women.<sup>22</sup> These changes result in increased resorption cavities not completely filled by newly formed bone, causing bone density loss and thereby increasing the risk of fracture.<sup>23,24</sup>

## Estrogen

Adult skeleton is maintained due to regeneration that occurs by the process of bone remodeling: the continuous process of resorption and bone formation.<sup>25</sup> Bone metabolism is regulated mainly by estrogen an essential hormone that acts on the cells involved in bone remodeling, such as osteocytes, osteoblasts and osteoclasts<sup>26</sup> which, in turn, can be influenced by systemic and local factors.<sup>27</sup>

Estrogen has beneficial effects on skeletal tissue, minimizing bone resorption and acting directly or indirectly on cells of bone metabolism. Estradiol can also act in the expression of osteoprotegerin (OPG) and as receptor activator of nuclear factor kappa- $\beta$  ligand (RANKL). Furthermore, this hormone stimulates secretion of OPG and inhibits RANKL, thereby promoting bone formation.<sup>28</sup>

## Osteoporosis X Periapical lesions

Bone changes caused by decreased production of estrogen may impair maxillary regions, specially the alveolar process, thereby resulting in the loss of bone in this region.<sup>29</sup> This is proved by some authors who suggest that lack of this hormone promotes intense resorption of the alveolar process in female rats.<sup>8</sup>

Therefore, the same signs and symptoms that occur in long bones as a result of decreased estrogen (fractures, pain and loss of function) may also affect maxillary bones, causing abscesses, mobility and tooth loss.<sup>30</sup>

Estrogen also acts in inflammatory sites, as it is the case of chronic inflammatory and degenerative diseases.<sup>5</sup> Estrogen deficiency may therefore influence periapical and periodontal disease, increasing the intensity of bone resorption.<sup>10</sup> These disease processes involve different cells such as osteoblasts and osteoclasts of which function determines the development of bone loss.<sup>31</sup> Periapical diseases do not involve bone cells only, but also include cytokines such as IL-1 and TNF-alpha, also observed in osteoporosis. Thus, the cellular and molecular mechanisms leading to bone loss are similar between inflammatory processes and osteoporosis.<sup>32</sup>

Periapical lesion is common in pulp inflammatory processes, necrosis and contamination. Bacterial growth reaches the root canal system, recruiting inflammatory cells, inducing cell bone metabolism and causing bone resorption in the periapical region.<sup>33,34,35</sup> Systemic factors such as osteoporosis may interact with local factors, (for instance, apical periodontitis) and aggravate bone loss.<sup>36</sup> Given that estrogen influences the process of bone resorption, deficiency of this hormone can worsen the condition of apical periodontitis.<sup>10</sup>

Osteoporosis and apical periodontitis are both involved with bone resorption; however, osteoporosis is not the primary cause of apical periodontitis, a systemic disease that can contribute to the progress of the lesion. Studies conducted with mice report that decreased concentration of estrogen aggravates alveolar bone resorption, which can be reduced with estrogen infusion.<sup>37,38</sup>

### Hormone replacement therapies

Several therapies are available in the market to treat and prevent diseases arising as a result of menopause. Hormone replacement therapy with bisphosphonates, raloxifene and calcitonin is one example.<sup>39</sup> These drugs aim to reduce the risk of fracture, in addition to preventing bone loss as well as cardiovascular and mental disorders resulting from postmenopausal hormone deficiency.<sup>20</sup> However, depending on the medium, some important side effects should be considered before using these drugs, given that some medications may have effects

on patient's breast and uterus causing tumors.<sup>40</sup> Estrogen hormone replacement is an example of these side effects, in which case women also complain or discontinue treatment due to swelling and tenderness after replacement.<sup>41</sup> Therefore, raloxifene is an alternative drug therapy in the treatment of osteoporosis in postmenopausal women.<sup>42</sup>

Raloxifene (RLX) is one of the drug therapies widely studied and discussed nowadays. After approval, its indication for prevention and treatment of osteoporosis in postmenopausal women increased.<sup>14</sup> Studies reveal that raloxifene also prevents bone loss and secondarily suppresses its formation, thereby resulting in decreased bone remodeling in ovariectomized rats.<sup>43</sup> Moreover, it acts on bone tissue without stimulating other tissues, such as breast and endometrium, due to its different action that depends on the receptor.<sup>11</sup>

Raloxifene is classified as SERM (selective estrogen receptor modulator) with different effects depending on the tissue target of estrogen action.<sup>44</sup> Due to its different mechanisms of interaction with different estrogen receptors, it selects the tissues it acts upon. Thus, depending on the target organ, it produces antagonistic effects (as in breast and uterus) and does not stimulate estrogenic processes;<sup>45</sup> or agonist effects, in which case it exerts its antiresorptive function.<sup>46</sup> Raloxifene is recommended for patients with a family history of breast and/or endometrial cancer, or in cases in which classic hormonal replacement is contraindicated.<sup>20</sup>

Even though the indication, performance and benefits of the drug on bone metabolism and maintenance of bone density are well-known, there are no studies focusing on its action over apical periodontitis in osteopenic organisms treated with raloxifene. To date, the literature comprises studies that assess the effect of raloxifene in case of fracture, alveolar repair after tooth extraction, bone mineral density in postmenopausal women and osteoclastogenesis.

Bone metabolism is influenced by several mechanisms in which bone cells participate. These cells are modulated by factors such as the presence of proteins rank/rankl/opg.<sup>47</sup> Differentiation and activation of osteoclasts are mediated by a member of the TNF family and TNF-receptor in conjunction with other factors, such as hormone levels and the presence of inflammatory cells.<sup>48</sup> OPG is produced by osteoblast

lineage and binds to RANK receptor present in osteoclasts, thereby preventing RANKL from binding to its receptor and, as a result, inhibiting the activity of osteoclasts. Therefore, OPG is essential for bone metabolism, since it is closely related to bone resorption.<sup>49</sup> A study assessing the effect of raloxifene and estradiol on alveolar repair of ovariectomized rats demonstrated that raloxifene treatment yielded more satisfactory results than estradiol treatment. Additionally, the alveolar repair of rats treated with raloxifene is stabilized faster than in the group treated with estradiol, given that the serum levels of OPG increased while RANKL decreased.<sup>27</sup>

In addition to OPG, RANKL also participates in osteoclastogenesis as a cytokine present in osteoblasts of which function is essentially related to bone metabolism. When RANKL binds to RANK, osteoclasts are activated, thereby increasing bone resorption.<sup>50</sup> Therefore, studies aiming to assess bone remodeling and disease are commonly performed by measuring the levels of RANKL. A study investigating the role of raloxifene in women with osteoporosis demonstrated that treatment with raloxifene had a negative effect on the levels of RANKL, significantly decreasing their number and increasing bone mineral density. For these reasons, it supported the hypothesis that raloxifene may reduce the activity of osteoclasts.<sup>51</sup>

Other studies show that the use of raloxifene in postmenopausal women increases bone density by producing agonist effects on tissue and inhibiting the action of osteoclasts.<sup>11,14,52</sup> There is also another study assessing the effect of raloxifene and resedronate on tibia of ovariectomized rats. This study reveals that both drugs, used alone or in combination, decreased the number of

osteoclasts.<sup>53</sup> Furthermore, the authors noted that rats treated with these drugs had increased activity of alkaline phosphatase and calcium in plasma. Alkaline phosphatase is considered a marker of osteoblast and affects bone mineralization.<sup>45,54</sup> Some authors suggest that raloxifene increases calcium absorption in the gastrointestinal tract, thereby indirectly benefiting bone tissue.<sup>55,56,57</sup>

Another method used to assess the activity of bone remodeling is by tartrate-resistant acid phosphatase (TRAP), a marker of osteoclasts which is directly related to bone resorption. One study<sup>58</sup> assessing the effect of raloxifene on osteoclastogenesis revealed significant decrease in the number of osteoclasts in the presence of the drug. In addition to increased enzymatic activity of alkaline phosphatase and osteoblastic activity.

In addition to having antiresorptive activity, raloxifene action on the differentiation of osteoblasts is evident.<sup>59,60</sup> These cells are influenced by the presence of alkaline phosphatase.<sup>54</sup> Based on this information, it is reasonable to conclude that raloxifene increases alkaline phosphatase activity.<sup>61</sup>

## Conclusion

Raloxifene is widely discussed as an alternative hormone replacement therapy for postmenopausal women. With agonist or antagonist effects, depending on the target organ, raloxifene has proved effective in improving the quality and quantity of bone without causing malignant effects on breast and uterus. Despite the indications and benefits of raloxifene, additional studies are warranted to further investigate the role of raloxifene in endodontic infection of osteopenic organisms.

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