REVIEW
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Effect of Antidepressants and its Orthodontic Implications

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Abstract

Antidepressants are widely prescribed medications used to treat depression, anxiety, and obsessive-compulsive disorders. Commonly used antidepressants include selective serotonin (5-hydroxytryptamine [5-HT]) reuptake inhibitors (SSRIs). The main component of SSRIs is fluoxetine. It acts by increasing extracellular 5-HT levels in the peripheral system. The 5-HT reuptake receptors are mostly found on bone cells. Studies have shown that antidepressants may cause decrease in bone formation owing to increased extracellular 5-HT levels on bone cells. Anti-inflammatory effects of antidepressants have also been reported. On the basis of these findings, in this review, we aimed to explain the possible interactions between antidepressants and orthodontic applications.

Keywords: Bone formation, bone resorption, fluoxetine, inflammatory response, orthodontic tooth movement, selective serotonin reuptake inhibitor

Introduction

In recent years, depression has become one of the major public health problems internationally. It is also very common in younger age groups. According to a cross-national comparison made by the World Health Organization, the prevalence of mood disorders is expected to increase over successive generations.[1] Depression is mainly caused by irregularities in the serotonin (5-hydroxytryptamine [5-HT]) level.[2] 5-HT is a monoamine compound acting as a neurotransmitter, synthesized from an essential amino acid, tryptophan. 5-HT has a complex and multifactorial biological mechanism that modulates mood, cognition, learning, memory, and various physiological processes such as vomiting and vasoconstriction.[3] To regulate 5-HT level in patients, the first-line drugs prescribed are antidepressants, mostly selective 5-HT reuptake inhibitors (SSRIs), which have been cited as one of the top 200 drugs used in the USA in 2018.[4] Increasing consumption of antidepressants has created concerns about their side effects on human metabolism, especially on gastrointestinal (GI) tract and cardiovascular and skeletal systems.[5] Even if the effect of 5-HT on the skeletal system has not been clearly identified in the literature, the gene study by Yadav et al.[6] was a game changer and explained the effect of 5-HT on bone physiology extensively. Subsequently, studies on dentistry have been published, especially on maxillofacial surgery and periodontology.[7-14] However, the effect of serotonergic system on tooth movement still remains controversial.[15-17] In this review, we aimed to explain and summarize the influence of SSRIs on orthodontic tooth movement through the perspective of previous bone mass and inflammatory response studies.

Effect of 5-HT on Bone Metabolism

5-HT may affect bone physiology oppositely, depending on the site of synthesis (brain and duodenum). In total, 5% of 5-HT secretion is controlled by the central nervous system, which regulates neuronal response and acts as a neurotransmitter to enhance bone formation. The non-neuronal response of 5-HT is controlled by the peripheral nervous system and affects the GI tract and cardiovascular and skeletal systems. Peripherally produced 5-HT has a negative effect on bone mass by limiting bone formation.[18,19] 5-HT cannot cross the blood-brain barrier; hence, altering its concentration peripherally does not influence its central levels or vice versa.[20] Therefore, 5-HT's central and peripheral functions may be completely dissociated. The opposite actions of 5-HT on bone metabolism are also related to a rate-limiting enzyme called tryptophan hydroxylase

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(Tph). The 2 isoforms of Tph, Tph1 and Tph2, are expressed in the periphery and in the brain, respectively.[21]

Low-density lipoprotein (LDL) receptor is an important genetic mechanism for Tph enzyme production. The *in vivo* study by Yadav et al.[6] examined the effect of LDL-receptor related protein 5 (Lrp5) on bone metabolism. The main objective was to clarify whether there was a difference between *Lrp5* gene–activated and *Lrp5* gene–knocked-out (*Lrp5* −/−) mice on osteoclast and osteoblast prevalence and accordingly between the resulting actions. A most distinctive difference was the overexpression of Tph1 in *Lrp5*−/− bones. The authors concluded that overexpressed Tph1 and higher blood 5-HT levels might have played a role in decreased bone formation and bone mass in *Lrp5*−/− mice. Therefore, they believed that Lrp5 had an active role in bone formation through its duodenal expression. The study also revealed that decreased bone mass of *Lrp5*−/− mice was associated with decreased osteoblast counts and decreased bone formation, whereas osteoclast counts were not affected.

Antidepressants

According to the 2013 Medical Expenditure Panel Survey, 12% of daily prescribed drugs were antidepressants in the USA.[22] Even though SSRIs are the most prescribed types of antidepressants, there are 4 major members of the antidepressant family, which are SSRI, selective norepinephrine reuptake inhibitor (SNRI), tricyclic antidepressants (TCA), and monoamine oxidase inhibitors (MAOI).

SSRI

In total, 65% of antidepressant users are prescribed SSRIs, which are primarily preferred for the medication of adults and children because of their fewer side effects.[23] The most commonly used SSRIs (commercial names and chemical agents) are Celexa (citalopram), Lexapro (escitalopram), Luvox (fluvoxamine), Paxil (paroxetine), Prozac (fluoxetine), Viibryd (vilazodone), and Zoloft (sertraline).

SNRI

The second most widely used antidepressants are SNRIs, whose action is similar to the SSRIs, inhibiting the reuptake of norepinephrine and 5-HT.[24] Some examples of commonly used SNRIs (commercial names and chemical agents) are Cymbalta (duloxetine), Effexor (venlafaxine), and Fetzima (levomilnacipran).

TCA and MAOI

These antidepressants are characterized by their nonspecific pharmacologic action and higher incidence of adverse effects than SSRIs.[24] They are prescribed when SSRIs and SNRIs are contraindicated. They are thus known to be the third-line treatment for depression.

Main Points

- Selective serotonin reuptake inhibitors (SSRIs) are the most commonly used antidepressants.
- The effect of SSRIs on bone metabolism and inflammation may alter the responses to orthodontic treatment and forces.
- Orthodontic patients using SSRIs should be closely monitored because there might be changes in bone density.

SSRIs and Bone

An SSRI agent, fluoxetine (Prozac®), plays a role in blocking 5-HT transporter (5-HTT; SERT) (Figure 1). The absence of active 5-HTT prevents reuptake of 5-HT, resulting in prolonged activation of the 5-HT receptor and an accumulation of 5-HT within the synaptic cleft. The action of SSRIs on serotonin signaling pathway takes place in the same manner as on bone cells (osteoblast, osteoclast).[25] In addition, SSRIs remain longer in the bone marrow than in the brain or plasma.[26] Owing to their high levels of concentration in the bone marrow, studies have mostly focused on the side effects of SSRIs on bone metabolism.[7,8,13, 27-29] There are 14 receptors that recognize serotonin in the human body, but only 3 of them are expressed in the osteoblast (Htr1b, Htr2b, and Htr2a).

According to gene deletion studies,[6,30,31] inactivation of Htr1b prevents recognition of 5-HT by osteoblasts, whereas inactivation of Htr2b or Htr2a does not affect osteoblasts and bone metabolism. Moreover, high levels of gut-derived 5-HT in circulation suppresses osteoblast proliferation resulting in excessive binding to 5-Htr1b. Therefore, it is proposed that peripheral 5-HT inhibits bone formation and yet does not affect bone resorption, whereas brain-derived 5-HT enhances bone formation by inducing osteoblast proliferation and decreasing bone resorption.

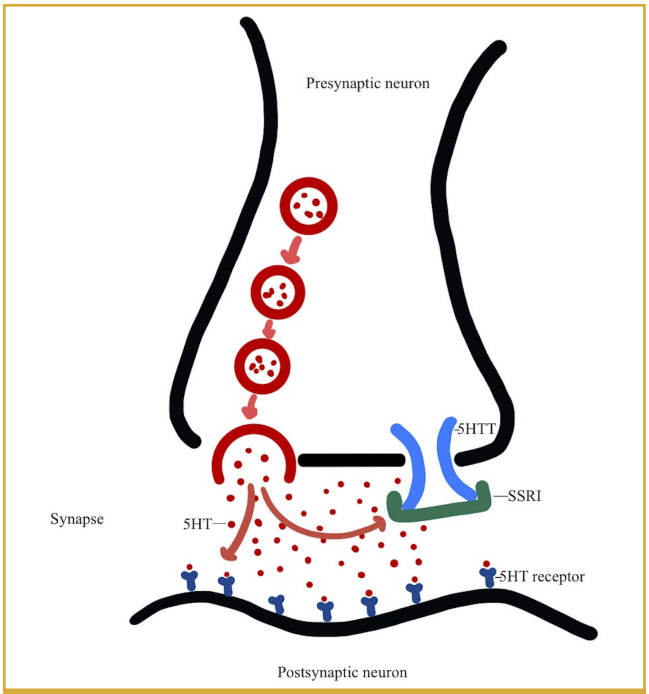

Figure 1. Effects of SSRI to serotonin 5-HT signaling by inhibiting 5-HTT.

In a systematic review,[28] the effects of SSRIs on bone mineral density (BMD) were found to be treatment time dependent, causing a decrease in BMD with prolonged SSRI consumption at older ages.

Yadav et al.[6,30,31] and Tsapakis et al.[29] claimed that SSRIs have a negative effect on bone formation via inhibiting osteoblast proliferation, although the *in vitro* study by Battaglino et al.[32] indicated that 5-HTT may be found not only in osteoblasts but also in osteoclasts. As these cells have opposite effects on bones, the effect of SSRIs on bone metabolism seems to be more complex *in vivo*.

SSRIs and Dentistry

Only a few studies in dentistry based on SSRIs have been reported. The interaction between bone metabolism and SSRI are susceptible to cause complications in dental procedures especially in oral-maxillary surgery, periodontology, and orthodontics.[7-17] It has also been emphasized that altered effects of SSRI on the jaw bone might be useful to diagnose and explain idiopathic osteoporosis.[7] In addition, mandibular bone fractal analysis and panoramic mandibular indices may be used to observe SSRI related osteoporosis.[8] The study by Gupta et al.,[7] evaluating the jaw bone morphology and bone mass index on panoramic radiographs of 64 SSRI users, concluded that SSRI intake was associated with lower BMD. Another study questioning the effect of SSRIs on human mandible using fractal analysis method on 212 dental panoramic radiographs indicated that there was no statistical significant difference between different ages and sexes. The study also revealed that the trabecular rich sites were more affected by SSRI related hormonal changes than the mandibular cortical sites.[8] As the changes in bone metabolism could influence the osseointegration, the study by Wu et al.[9] aimed to explain the relation between SSRIs and the risk of failure in osseointegrated dental implants. After 67 months of follow-up, they observed that 38 dental implants failed and 784 succeeded in the nonuser group, whereas 10 failed and 84 succeeded in the SSRI user group. The failure rate was 4.6% in the nonuser group and 10.6% in the SSRI user group meaning that SSRI users were more susceptible to implant failure. Similar results were found by Altay et al.[11] and Chrcanovic et al.[12] However, those studies could not reach the statistical significance level to reveal an accurate hypothesis among the assigned groups. Later, Vila[10] published an extensive thesis on the effect of different types of antidepressants on dental implants. The study stated that the SNRIs had the most significant implant failure rate, whereas SSRIs had the lowest failure rate among all the antidepressant types and yet could not reach an actual result.

Recent studies have shown that in addition to antipsychotic effects of fluoxetines, they also have anti-inflammatory, immunomodulatory, and additional analgesic effects. In their study, Branco-de-Almeida et al.[13] aimed to estimate the effect of fluoxetine on bone loss and inflammatory response on ligature induced periodontitis in rat models. The study indicated that *COX-2 mRna* expression was reduced in the gingival tissues after SSRI treatment, suggesting that fluoxetine possibly down-modulated prostaglandin E (PGE) 2 generation by suppressing the production of COX-2 protein at the inflamed sites, thus contributing to the reduction of bone loss in furcation areas. After experimental studies on rat models, an observational study was published including 236 patients who had chronic periodontitis and clinical depression. The study results have shown that patients using fluoxetine had lower bleeding on probing percentages and reduced attachment loss.[14]

5-HT and Orthodontic Tooth Movement

Orthodontic tooth movement is a combination of bone remodeling and inflammatory response. Bone remodeling during tooth movement is composed of bone formation on the tension side and bone resorption on the compression side. This process is initiated by an inflammatory response to the action of cytokines, chemokines, and prostaglandins.[33]

In the initial phase of tooth movement, the periodontal ligament adjacent to the lamina dura receiving dental pressure is exposed to elastic deformation and compression. Under heavy forces, this compression prevents blood flow and induces cell death leading to hyalinization. During the hyalinization phase, osteoclasts cannot reach the site of compression to resorb the alveolar bone on movement direction. Tooth movement proceeds on resorption of the hyalinized tissue by macrophages, followed by direct resorption of the alveolar bone by osteoclast reaching the adjacent alveolar bone. On the tension site, bone apposition is initiated by osteoblasts. Thus, tooth movement resumes through a combination of bone resorption and apposition.[33]

Two physiological processes may accelerate tooth movement because of decreased bone density and increased bone turnover rates. The mechanism of bone turnover is controlled by the balance between receptor activator of nuclear factor kappa-B and receptor activator of nuclear factor kappa-B ligand (RANKL). RANKL and osteoprotogerrin (OPG) are both known to be produced by osteoblasts and have important roles in regulating osteoclasts.[34] It has been proposed that several factors can regulate the RANKL/OPG ratio and thus regulate osteoclastogenesis. Although RANKL induces bone resorption, OPG plays a role in blocking the process. The force at the compression side causes inflammation and an increase in RANKL/OPG ratio meaning resorption of bone on that side; however, on the tension side, RANKL/OPG ratio decreases and bone formation occurs.[35] In addition to physiological bone remodeling, inflammation induced orthodontic tooth movement is mediated by PGE), IL-1, IL-6, and tissue necrosis factor-a, which are released from the cells of the periodontal ligament. These mediators activate osteoclasts by stimulating RANKL or depressing OPG. In summary, RANKL and OPG are both known to be produced by osteoblasts and have important roles in regulating osteoclasts.[34] The effect of 5-HT on these agents is discussed and explained in a study by Chabbi-Achengli et al.[36] According to the study, RANKL enhances the expression of Tph1, which leads to an increase in the 5-HT level secreted by the osteoclasts. When RANKL is produced by osteoblasts, 5-HT synthesized by osteoclast

precursors could act synergistically with RANKL signaling and further increase osteoclast differentiation. In conclusion, they stated that 5-HT may increase osteoclast differentiation. Therefore, antidepressant-related increased extracellular 5-HT levels may contribute to an increase in RANKL mediated osteoclast differentiation resulting in decreased bone density. Hence, it may end with enhanced orthodontic movement of the teeth. However, anti-inflammatory effect of antidepressants may induce depression on inflammatory mediators, leading to a decrease in orthodontic tooth movement. These theoretical contradictions raise the significance of *in vivo* trials in understanding the overall impact of antidepressants on orthodontic tooth movement.

Clinical and Research Consequences

In the literature, there are 3 *in vivo* studies[15-17] about the effects of SSRIs on orthodontic tooth movement. In the first study, fluoxetine (SSRI) was administrated intraperitoneally (10 mg/kg) to 9-week-old Wistar rats.[15] Orthodontic tooth movement was observed after daily fluoxetine injections for 30 days through closed coils fixed and activated on maxillary first molars and incisors. The rats were sacrificed after 3, 7, and 14 days, and each specimen was evaluated using polarization microscopy and microcomputed tomography. This study revealed that fluoxetine did not interfere with the rate of tooth movement and trabecular bone in rats.[15]

The second study published by Rafiei et al.[16] evaluated the effect of fluoxetine on root resorption, alveolar bone remodeling, and the rate of orthodontic tooth movement during orthodontic force application. This study differed from the other studies in terms of the timing of appliance removal and specimen investigation techniques. In this study, appliances were removed after 21 days, which was longer than the other studies,[15,17] and histologic evaluation was performed. The study showed that fluoxetine reduced the rate of tooth movement owing to its anti-inflammatory action. However, the results were not statistically significant. Bone apposition and root resorption rates did not show statistical differences between the control and experimental groups.

The study by Mirhashemi et al.[17] focused on the effects of fluoxetine on orthodontic tooth movement. The standardization of the study was provided as in the previous *in vivo* studies[15,16] and yet the removal time of the appliance was only in accordance with the study by Rafiei et al.[16] The evaluation method and evaluated regions differed from the previous studies. The bone mass was evaluated by bone densitometry in 4 different regions (mandibular bone, alveolar bone, hard palate, and skull). The findings of this study were not in accordance with the findings of previous studies.[15,16] This study found that the decrease in bone density caused an increase in orthodontic tooth movement. Furthermore, it demonstrated that osteoclast numbers did not statistically differ between both the groups. These results support the fact that 5-HT causes a decrease in bone density by reducing osteoblast numbers but not by increasing osteoclasts counts.

Conclusion

Although there is no consensus in the literature, dentists should keep in mind that side effects of SSRIs might alter the results of dental treatments. Moreover, decreased bone formation, reduced inflammatory response, and altered orthodontic tooth movements are likely to occur in patients using SSRI. Although further studies are required, we must be careful during dental procedures such as orthodontic treatment, implant placement, tooth extraction, and prolonged treatments.

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