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Review

Inflammatory impact of cigarette smoking on bone function and structure; a review of evidence

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Abstract

Cigarette smoking represents a major lifestyle risk factor for bone loss and skeletal disorders, with complex etiological mechanisms consisting both direct tissue effects and systemic alterations. Recent evidence demonstrates that tobacco smoking triggers an intricate cascade of cellular and molecular events that disrupts the delicate balance of bone remodeling, finally leading to decreased bone mass and increased fracture risk.

Keywords: Cigarette smoking, Bone loss, Parathyroid hormone, Calcium homeostasis, Vitamin D

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Introduction

Cigarette smoking represents a significant public health concern with widespread detrimental effects on the skeletal system (1). Recent evidence demonstrates that tobacco smoking causes an imbalance in bone turnover, leading to reduced bone mass and increased vulnerability to osteoporosis and fractures (2). With more than 7000 chemicals detected in tobacco smoke, the complex interactions between these compounds and bone tissue have emerged as a critical area of research in understanding smoking-related bone disorders (2). The impact of smoking on bone health operates through multiple pathways, both direct and indirect (3). Tobacco smoke influences bone mass through alterations in body weight, disruption of the parathyroid hormone (PTH)-vitamin D axis, changes in adrenal hormones, modifications in sex hormone levels, and increased oxidative stress on bone tissues (1,2). Furthermore, smoking may have mostly detrimental effects on bone health through its influence on calcium absorption and bone mineral density, making bone consistency vulnerable to osteoporosis and fracture (4). Smoking directly affects bone tissue through multiple cellular mechanisms. Cigarette smoking significantly affects osteoblast and osteoclast function, leading to decreased bone formation and increased bone resorption (5). Nicotine exhibits a dose-dependent effect on bone cells, where low levels may increase cell proliferation, however higher levels inhibit osteoblast production which results in cell death (6). The direct effects of nicotine and other tobacco components on bone tissue include inhibition of osteogenesis and angiogenesis (7). Moreover, the endocrine system plays a crucial role in smoking-induced bone deterioration (8). Tobacco smoking enhances estrogen metabolism, resulting in lower levels of estradiol (9). Women who smoke typically experience menopause two years earlier than non-smoking women, further compromising their bone health (10). The mechanism involves multiple pathways, including inhibition of aromatase enzyme, increased hepatic breakdown of estradiol, and elevated levels of serum sex hormone-binding globulin (11). Likewise, smoking induces significant oxidative stress in bone tissue, with studies showing that tobacco smoking is associated with elevated levels of free radicals (12). Smokers demonstrate significantly lower antioxidant enzyme levels and higher levels of oxidative stress products compared to nonsmokers (13). This oxidative imbalance contributes to increased bone resorption and decreased

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Implication for health policy/practice/research/medical education

Cigarette smoking causes substantial alterations in bone turnover mechanisms, leading to compromised bone mass and increased susceptibility to skeletal disorders

bone mass (14). The evidence clearly demonstrates that smoking has profound and multifaceted effects on bone health, operating through various pathophysiological mechanisms to compromise bone structure and function (1,14). The interaction between direct tissue effects, hormonal disruptions, and oxidative stress emphasizes the importance of smoking cessation in maintaining optimal bone health and preventing skeletal complications. In this review, we aimed to explain the molecular mechanisms of smoking-related bone disease through review of most recent data on this subject.

Search strategy

For this review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ) and Embase, using different keywords such as cigarette smoking, bone loss, parathyroid hormone, calcium homeostasis and vitamin D.

Smoking-induced inflammatory response in bone tissue

Cigarette smoking constitutes a major lifestyle risk factor affecting bone health through complex pathophysiological mechanisms. The deleterious effects of smoking on bone tissue manifest through both direct cellular damage and systemic inflammatory responses, leading to impaired bone remodeling and increased fracture risk (1,5). Cigarette smoking directly affects bone tissue through multiple pathways that disrupt normal cellular function. Several studies have demonstrated that smoke exposure causes significant alterations in bone cell activity, predominantly affecting the balance between bone formation and resorption (15-17). The direct impact of cigarette smoke on bone cells involves the activation of specific cellular pathways, notably through the RANKL/RANK/OPG system, as a regulator of osteoclastogenesis (17). Studies have also shown that smokers exhibit significantly lower median serum levels of osteoprotegerin (OPG) compared to nonsmokers (18). The reduction in OPG, combined with alterations in RANKL expression, creates an environment that favors increased bone resorption (19). Likewise, it has been shown that smoking exposure increases the RANKL/OPG ratio, promoting enhanced osteoclast activity across with bone resorption (20). Furthermore, cigarette smoke extract has been shown to reduce the migration, proliferation, and osteogenic differentiation of mesenchymal stromal cells in vitro, indicating a direct impairment of bone-forming capacity (21). Besides, the inflammatory response induced by cigarette smoke represents a critical mechanism in bone tissue dysfunction. Smoking triggers the release of various pro-inflammatory cytokines, including interleukin-1 beta (IL-1β), IL-6, and tumour necrosis factor alpha (TNF-α), which have been observed at elevated levels in bone tissue homogenates of smokers (22). These inflammatory mediators contribute significantly to the disruption of normal bone homeostasis. The increase in inflammatory markers is accompanied by enhanced oxidative stress (23). Recent studies have demonstrated that oxidative stress induced by cigarette smoking can lead to cellular damage and altered bone cell function. Beyond direct cellular effects, smoking induces systemic changes that indirectly impact bone metabolism (21). These alterations include disruption of hormone levels, particularly affecting the PTH-vitamin D axis, which plays a fundamental role in determining bone mineral density and calcium homeostasis (1,2). The study by Jorde et al, showed that smokers have lower vitamin D and PTH serum levels versus non-smokers, demonstrating a suppressive effect of tobacco on the production of these crucial bone-regulating hormones (24). Additionally, smoking affects the production of sex hormones, which are essential for maintaining bone mass and strength (2). The impact of smoking on bone tissue manifests primarily through its effects on the two main cell types responsible for bone remodeling, the osteoblasts and osteoclasts (7). Smoke exposure causes a significant imbalance between bone resorption and formation, while studies showing that even a brief 10-day exposure period can effectively induce osteoclast activity while simultaneously inhibiting osteoblast differentiation (5). Further, the study by Lu et al has demonstrated that smoke exposure induces DNA-binding activity of nuclear factor kappaβ (NFκβ) in osteoclasts, leading to alterations in bone remodeling-related gene expression (5). This mechanism triggering a cascade of cellular responses that eventually affects bone structure and function. The activation of these pathways results in increased osteoclast activity and decreased osteoblast function, creating an imbalance in the bone remodeling process (25). In another point of view, the impact of smoking on bone health extends to its effects on vascular function and angiogenesis. Prior studies have demonstrated that nicotine exerts a dose-dependent inhibitory effect on osteoblast development and vascular endothelial growth factor, which is essential for angiogenesis (2,26). This disruption of blood vessel formation and function can significantly impair bone healing and remodeling processes, as adequate vascular supply is crucial for maintaining healthy bone tissue and supporting new bone formation (27).

Molecular changes in bone structure

Smoking induces significant changes in bone cellular function, intensely affecting the critical balance between

bone-forming osteoblasts and bone-resorbing osteoclasts. In the study by Kohler et al, they have proved that cigarette smoke exposure leads to increased osteoblast apoptosis, compromising the bone formation process (22). Moreover, the bone cell dysfunction is accompanied by elevated levels of inflammatory mediators, including IL-1β, IL-6, and TNF-α in skeletal tissue, which further exacerbate the imbalance in bone remodeling (28). Additionally, studies have shown that smoking exposure results in decreased collagen type I deposition, a crucial component of bone matrix (22,29). A previous meta-analysis showed that smokers exhibit significantly reduced bone mass at various skeletal sites compared to non-smokers (30). Another study demonstrated that heavy smokers demonstrate approximately 4% lower total body bone mineral density and 6% lower total hip density compared to non-smokers (31). These alterations in bone mineral density are attributed to both direct cellular effects and indirect systemic mechanisms, including disrupted calcium metabolism and altered hormone function (32). Furthermore, smoking induces substantial changes in bone microarchitecture, affecting both trabecular and cortical bone components. A more recent study by Heilbronner et al utilized advance imaging techniques which found, smokers had significant alterations in trabecular bone structure, characterized by decreased trabecular volume and increased trabecular separation (33). These structural changes are accompanied by modifications in collagen composition too. Additional studies also showed a decreased type I collagen and increased type V collagen in smokers. These alterations in the molecular composition of bone matrix, contribute to the reduced bone strength and an increase of fracture frequency (22,29). Meanwhile other studies have exposed smoking impact on bone structure demonstrates notable sex-specific patterns (3, 34). Interestingly recent data also showed that male smokers typically experience more severe trabecular deterioration in both the spine and peripheral skeleton, while female smokers tend to exhibit more pronounced cortical deficits. These gender-specific differences in structural alterations suggest the interaction of sex hormones in mediating smoking's effects on bone tissue (34,35).

Hormonal and metabolic disruptions

The intricate relationship between tobacco smoke exposure and endocrine function demonstrates profound implications for skeletal integrity and mineral homeostasis. Smoking significantly impacts the vitamin D-PTH axis, creating a cascade of metabolic disturbances that affect bone metabolism (2,3). Likewise, tobacco exposure is negatively correlated with serum PTH levels, indicating that long-term contact may lead to parathyroid dysfunction (36). Importantly the study by Zaman et al have demonstrated that smokers exhibit reduced levels of both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D compared to non-smokers. This reduction in vitamin D metabolites may be attributed to the enhanced hepatic metabolism of vitamin D in smokers, leading to accelerated clearance and reduced bioavailability (37). The study by Fujiyoshi et al also detected a significantly lower PTH concentrations in smokers compared to non-smokers. This decline of the vitamin D-PTH system represents a crucial mechanism through which smoking affects skeletal health, potentially contributing to the increased risk of osteoporosis observed in smoking population (38). The influence of smoking on sex hormones presents another significant pathway affecting bone metabolism (34). Other studies also have demonstrated that smoking increases testosterone levels in women while potentially decreasing them in men, creating a complex hormonal imbalance that affects bone remodeling. This effect is mainly pronounced in women, where smoking has been shown to enhance estrogen metabolism, resulting in lower estradiol levels. The anti-estrogenic effect of smoking is further complicated by its impact on aromatase enzyme activity, which plays a crucial role in estrogen synthesis. These hormonal disruptions contribute to accelerated bone loss and increased fracture risk, predominantly in post-menopausal women who are already at elevated risk for osteoporosis (2,39,40).

Impact on calcium absorption

Smoking significantly affects calcium homeostasis through multiple mechanisms, including altered intestinal absorption and urinary excretion (38). Smokers also display a reduced calcium absorption versus non-smokers. This decrease in calcium absorption appears to be dose-dependent, since heavy smokers showing the most significant impairment (41). Several investigations also have revealed that with calcium and vitamin D supplementation, smokers exhibit a lower proportionate increase in urinary calcium excretion compared to non-smokers, suggesting fundamental differences in calcium metabolism (42). These alterations in calcium homeostasis may contribute to the accelerated bone loss observed in smoking population, remarkably in conjunction with other metabolic disruptions (43). The combined effects of these hormonal and metabolic disruptions manifest in altered bone turnover markers and accelerated bone loss. It should remember that, smokers exhibit significant changes in biochemical markers of bone metabolism, including reduced levels of bone formation markers such as osteocalcin (44). This effect appears to be particularly pronounced in specific skeletal sites, with studies showing accelerated bone loss at the femoral neck and total body in smokers compared to non-smokers (45). These metabolic alterations create an environment that favors bone resorption over formation, contributing to reduced bone mineral density and increased fracture risk

(45). Nicotine, a primary component of tobacco smoke, demonstrates a dose-dependent inhibitory effect on osteoblast development and vascular endothelial growth factor, which are essential for proper bone metabolism and calcium utilization (2,46). At lower concentrations, nicotine may increase cell proliferation, but at higher levels, it inhibits osteoblast production and can lead to cell death, further compromising the body's ability to maintain calcium homeostasis (46). In a comprehensive three-year study, researchers found that the mean calcium absorption fraction was significantly lower in smokers (12.9%) compared to non-smokers (14.6%), even after adjusting for several factors including gender, age, and dietary calcium intake. Heavy smokers, as those consuming at least 20 cigarettes per day, pointed as the lowest calcium absorption fraction at 12.1% (43).

Clinical implications

Effects of tobacco smoke on skeletal integrity manifest through complex interactions that influence bone metabolism, repair processes, and long-term skeletal health outcomes (1,47). More recent findings detected that smoker had significantly reduced bone mass across various skeletal sites, with an average deficit of approximately one-tenth standard deviation compared to non-smokers (30). The impact appears particularly pronounced in postmenopausal women, where prior studies indicated that bone loss accelerates by an additional 2% for every decade of smoking (2). This acceleration in bone loss translates to tangible clinical outcomes, with smoking increasing the lifetime risk of developing vertebral fractures by 13% in women and 32% in men (30). The mechanism of increased fracture risk includes both direct cellular damage and systemic effects on bone metabolism. The clinical manifestations of smoking are notably evident in hip fracture, where current smokers demonstrate an increased its risk that grows progressively with age, reaching as high as 71% by age 80 and 108% by age 90 years (48). The deleterious effects of smoking on bone healing represent a critical concern in orthopedic practice, mostly in the context of fracture management and surgical interventions. Correspondingly several clinical evidence demonstrate that smoking significantly impairs the bone healing process, leading to increased rates of delayed union and nonunion. To focus on tibia fracture, smokers require significantly longer healing times, with mean time to union extended by several weeks versus non-smokers. This finding appears particularly pronounced in open fractures, where smoking has been associated with a substantially higher risk of complications and delayed healing (49-51). The biological mechanisms underlying impaired bone healing in smokers involve multiple pathways affecting both cellular and vascular responses. Nicotine also hinders blood flow by increasing catecholamine release, across with vasoconstriction which is alongside of compromised tissue perfusion (52). Additionally, carbon monoxide another substance release from cigarette smoke impairs tissue oxygenation by binding to hemoglobin, potentially causing chronic tissue hypoxia in heavy smokers (53). Importantly, chronic exposure to tobacco smoke leads to persistent alterations in bone metabolism that may not fully reverse even after smoking cessation (54). In this regard, former smokers continue to exhibit an elevated risk of hip fracture compared to never-smokers, although this risk gradually diminishes with increasing duration of cessation. The persistence of these effects accentuates the importance of early intervention and smoking cessation in preserving bone health (55,56). To manage these individuals, vitamin D supplementation may be of particular importance; while they are frequently suffering from hypovitaminosis D due to altered skin function and metabolism (57).

Conclusion

The mechanisms underlying smoking-induced bone loss represent a complex interplay of cellular, molecular, and systemic effects. The evidence demonstrates that smoking disrupts normal bone homeostasis through multiple pathways, including direct effects on bone cells, activation of inflammatory and oxidative stress responses, hormonal disruptions, and alterations in crucial molecular signaling pathways. The compelling evidence for smoking's detrimental effects on bone metabolism through these various mechanisms underscores the critical need for preventive measures and early intervention strategies in smoking-related bone disorders.

Authors' contribution

Conceptualization: Yashar Shahbaz and Hooman Esfahani.
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Writing–original draft: All authors.
Writing–review and editing: All authors.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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