Influence of smoking and vaping on bone-muscle crosstalk

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ABSTRACT

The intricate relationship between the skeletal and muscular systems involves a complex exchange of molecular signals, with muscles and bones functioning as endocrine and paracrine organs that produce bioactive molecules known as myokines and osteokines. These molecules are essential for maintaining the balance between bone and muscle tissue. However, various factors can disrupt this balance and negatively impact bone and muscle health.

Cigarette smoking, including the use of electronic cigarettes, is among the factors that affect communication between muscles and bones. While the exact mechanisms through which smoking influences muscle-bone signaling pathways are still being investigated, it is known that substances like nicotine in traditional cigarettes and other compounds in cigarette smoke can hinder fracture healing by decreasing the formation of new bone tissue. These substances also influence the levels of important molecules like RANKL, sclerostin, and osteocalcin, which are crucial for bone and muscle health. Additionally, the use of electronic cigarettes, including various flavored varieties, has been linked to an increase in proinflammatory cytokines that adversely affect the musculoskeletal system.

Finally, cigarette smoking has been associated with a higher risk of vitamin D deficiency through multiple pathways, leading to an increased risk of osteoporosis and falls. These findings underscore the importance of educating the public about the risks to musculoskeletal health posed by both traditional smoking and electronic cigarettes.

KEYWORDS

Traditional smoking, electronic cigarettes, bone-muscle crosstalk, myokines, osteokines.

Bone-muscle crosstalk

In the past, the relationship between the skeletal and muscular systems was understood primarily in mechanical terms, with bones known to function as levers and muscles as pulleys driving bodily movement. Although this perspective remains valid, it does not fully capture the intricate interplay between the two systems. Muscles and bones are recognized as being more than just mechanical structures. They also act as endocrine and paracrine organs, producing molecules respectively referred to as "myokines" and "osteokines."

Myokines, the molecules released by muscle fibers, can regulate biological and pathological processes in both local and distant tissues, including skeletal muscle, bones, and adipose tissue [1]. To date, more than 600 myokines have been discovered, such as irisin, myostatin, insulin-like growth factor-1 (IGF-1), and interleukin 6 (IL-6). Irisin is produced in response to vigorous physical exercise and triggers the "browning" process, i.e., the transformation of white adipose tissue into brown adipose tissue [2]. Moreover, irisin also enhances the growth and maturation of osteoblasts by activating the p38/ERK MAPK3 signaling pathways [3]. This leads to an increase in the synthesis and expression of important osteogenesis markers, including alkaline phosphatase, collagen I, RUNX family transcription factor 2, osteopontin, osteocalcin, and osteoprotegerin.

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On the other hand, myostatin, a powerful inhibitor of muscle growth, has a detrimental impact on bone turnover [4]. This cytokine works by suppressing the differentiation and function of osteoblasts [5], while also stimulating RANKL-induced osteoclastogenesis and MAPK signaling [6].

IGF-1 plays a crucial role in the healing process following muscle trauma as it stimulates bone formation and muscle regeneration [7]. IL-6, which is released in response to physical exercise, can promote osteoclastogenesis, and consequently increase bone resorption [8].

On the other hand, osteokines released by bones, such as receptor activator of nuclear factor κB ligand (RANKL), sclerostin, and osteocalcin, serve to maintain homeostasis between bone and muscle tissue. In particular, RANKL stimulates osteoclast proliferation by binding to its receptor RANK on osteoclast progenitor cells. This process involves activation of c-fos, NFATc1/NFAT2, as well as canonical and non-canonical NF-

κB pathways, ultimately leading to increased bone resorption [9]. However, it is important to note that RANKL also negatively affects muscle tissue, as the expression of the RANK receptor on muscle cells leads to muscle mass depletion [10].

At bone level, sclerostin inhibits the Wnt/beta-catenin signaling pathway, leading to a decrease in new bone tissue formation with a major impact on bone density and quality [11]. Moreover, recent research indicates that sclerostin may also have detrimental effects on muscle mass and strength [11].

In contrast to RANKL and sclerostin, osteocalcin plays a beneficial role in preserving muscle mass and function [12] by activating nutrient uptake in muscle cells through its receptor, G protein-coupled receptor family C group 6 member A, thereby promoting muscle growth and maintenance.

This bone-muscle connection, rooted in the fact that both tissues originate from mesenchymal stem cells, is also evident in osteosarcopenia, a condition in which osteoporosis and sarcopenia occur together [13]. All the above points underline the closeness of the relationship between bone and muscle, and also explain why bone fragility is correlated with skeletal muscle weakness.

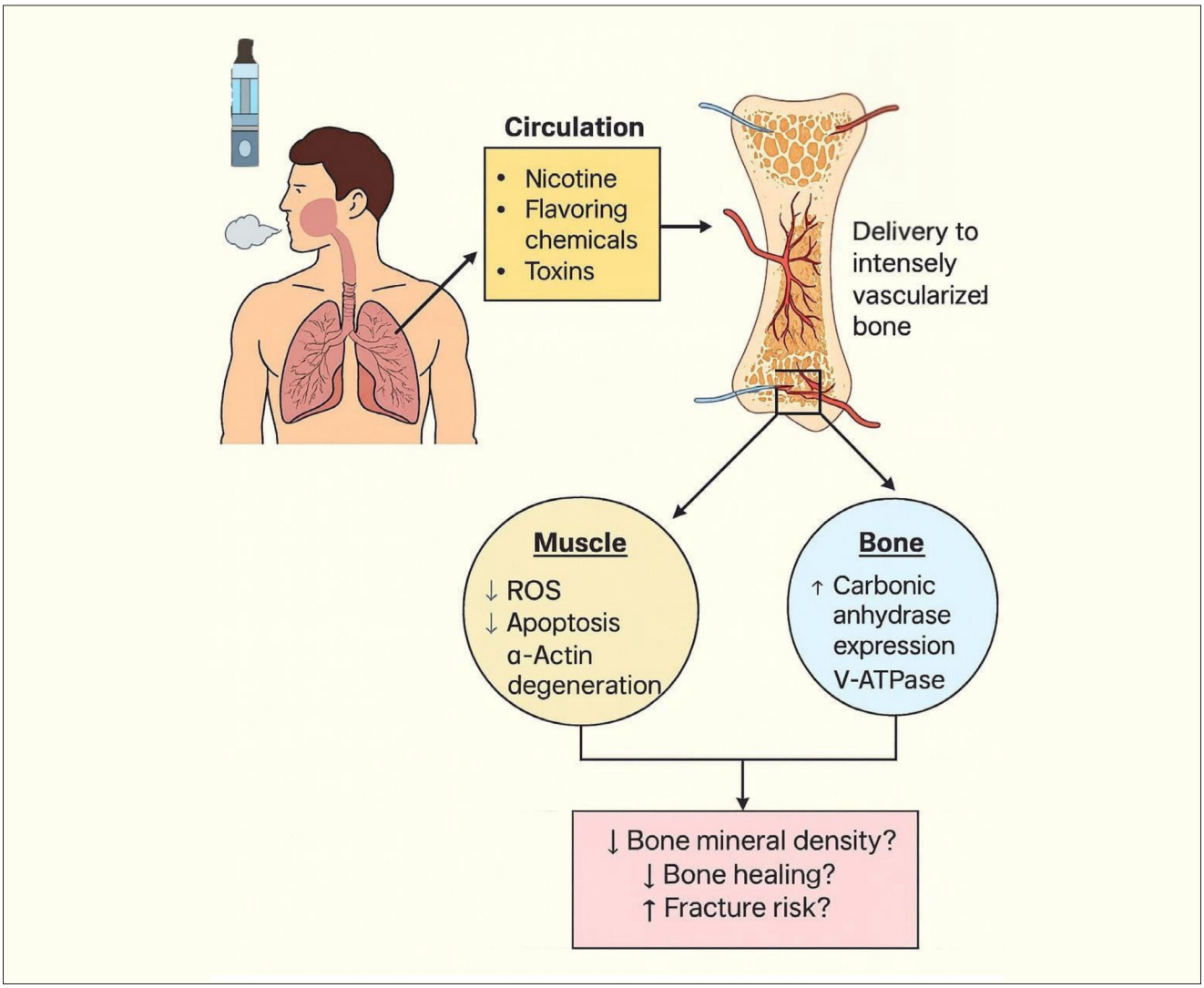
Environmental effects on bone-muscle crosstalk

Bone-muscle crosstalk is a complex mechanism influenced by a variety of factors. Genetic factors, aging, circadian rhythms, nutritional habits, physical activity, alcohol consumption, and smoking habits are among the key factors affecting this relationship. While the impact of smoking on the biological mechanisms of the musculoskeletal system is partially understood, the growing use of electronic cigarettes (e-cigarettes) has introduced new complexities that need further analysis.

Traditional cigarettes and e-cigarettes differ mainly in the substances that are inhaled. Traditional cigarette smoking involves tobacco combustion and inhalation of nicotine, whereas e-cigarettes are devices that heat and aerosolize liquids containing substances such as propylene glycol, glycerin, flavor additives, and possibly nicotine, but do not contain tobacco. The introduction of e-cigarettes has increased the number of smokers, and the long-term effects of this trend are still unknown.

Although the detrimental effects of smoking in terms of cancer, heart disease, and respiratory conditions are widely rec-

Figure 1 A potential mechanism between muscular d skeletal systems and the influence of smoking and vaping on this crosstalk.



ognized, awareness of the musculoskeletal damage caused by traditional cigarette smoking is limited (Figure 1), and the musculoskeletal effects of e-cigarettes remain largely unknown.

Influence of traditional cigarette smoking on bone-muscle crosstalk

Traditional cigarette smoking is a well-known risk factor for osteoporosis and fragility fractures [14], so much so that it is now included in the FRAX fracture risk assessment tool [14]. Smoking cigarettes can disrupt the balance of bone turnover processes, leading to a decline in bone mineral density (BMD). The effects of smoking on bone are both direct and indirect [15]. One of the molecules contained in traditional cigarette smoke is nicotine, which directly affects bone by binding to nicotinic receptors on bone cells. The impact of nicotine on the physiology of bone cells remains unclear, as its effects vary with concentration. Therefore, further studies are needed to fully clarify the role of nicotine in osteoblastogenesis and osteoclastogenesis [16]. Instead, the effect of nicotine on angiogenesis is well known: it inhibits the synthesis of vascular endothelial growth factor, thereby compromising the vascularization of bone tissue. Further studies are needed to explore other possible direct effects of traditional smoking, given that cigarette smoke contains not only nicotine but also large amounts of other chemical molecules that, combined, could be responsible for the bone loss reported in smokers of traditional cigarettes [17].

The indirect effects of smoking on bone health are mainly due to three mechanisms:

- The suppressive effect of nicotine on appetite, leading to weight loss. Smokers typically have a lower body weight compared with non-smokers, which may initially seem beneficial. However, lower body weight can result in decreased mechanical load on bones, stimulating osteogenesis and potentially leading to decreased bone density [18].
- Early onset of menopause in women. Estrogens play a crucial role in maintaining bone health and integrity, but women who smoke often experience menopause around two years earlier than non-smokers, due to smoking-related decreased estrogen levels. Smoking can affect estrogen production by inhibiting the enzyme aromatase, increasing hepatic degradation of estradiol, and raising levels of sex hormone-binding globulin, thereby ultimately reducing free estradiol levels [19].
- Increased osteoclast activity. Smoking leads to an imbalance in RANKL, sclerostin, IL-6, and IL-15 levels, resulting in heightened osteoclast activity and decreased osteoblast activity. This imbalance can contribute to bone loss and deterioration over time [20].

Impact of e-cigarette flavored liquids on human osteoblasts: results of *in vitro* studies

The harmful effects of traditional cigarette smoke on bone metabolism are similar to those of e-cigarette vapor containing nicotine [17].

A study examined the effects of various e-cigarette flavored liquids on human osteoblast-like cell lines (MG-63 and Saos-2) [21]. These cell lines were exposed to vapor from liquids, with and without nicotine, for 48 hours. The findings indicated a dose-dependent decrease in cell viability in all tested scenarios, regardless of the presence/absence of nicotine. In addition, flavored products had a more pronounced detrimental effect on osteoblast-like cells than unflavored liquids. There was also a noticeable difference in the level of osteotoxicity between the various flavored liquids tested. Coffee and fruit flavors exhibited a lower degree of cytotoxicity, while cinnamon flavor showed the highest cytotoxic impact. This heightened effect can be attributed to the presence of cinnamaldehyde, a compound derived from cinnamon that, when heated, can increase reactive oxygen species and, subsequently, oxidative stress in human osteoblast-like cells [22,23].

It is important to highlight that while many flavoring agents have been deemed safe for ingestion by the Flavor Extracts Manufacturers Association (FEMA), its classification does not take into consideration the potential consequences of inhaling these compounds after they have undergone thermal degradation.

Moreover, it has been emphasized that flavoring compounds found in e-cigarettes can result in elevation of pro-inflammatory cytokine production, potentially causing adverse effects on muscle and bone health [24].

Smoking and fracture risk

Research into the biological mechanisms through which cigarette smoking affects bone metabolism, especially in comparison with electronic devices, is still ongoing. Studies suggest that its effects may significantly impact clinical outcomes. Current data show that both current and former smokers are more likely than non-smokers to experience hip fractures [25]. Notably, individuals who have quit smoking still retain a slightly elevated risk in comparison to those who have never smoked, although this risk tends to decrease after at least five years of cessation of tobacco use [26].

Recent research has shown that the use of e-cigarettes can have similar negative effects. For example, a study demonstrated that mice exposed to e-cigarette vapors for three hours a day over a period of six months exhibited a notable increase in femoral microfractures compared with a control group. Surprisingly, fractures were also detected in mice exposed solely to propylene glycol and glycerin, suggesting that the harmful effects are not solely due to nicotine or flavoring agents [27].

During the thermal degradation of these compounds, carbonyl compounds such as formaldehyde, acetaldehyde, and acrolein are produced. These compounds have been shown to induce cell death in human osteoblasts and inhibit osteoblast differentiation [28]. Moreover, formaldehyde and acetaldehyde have been shown to have a dose-dependent impact on human osteoblast cell death [28].

Additionally, studies have shown that acetaldehyde increases the expression of peroxisome proliferator-activated receptor-gamma in murine osteoblasts. This transcription factor is known to inhibit osteoblast differentiation. In humans,

genetic variations that lead to decreased activity of aldehyde dehydrogenase 2, a key enzyme in acetaldehyde metabolism, can cause accumulation of acetaldehyde, which has been linked to reduced BMD and a higher risk of femoral fractures [29].

Recent research has emphasized that extended exposure to cadmium, which is found in both traditional cigarettes and e-cigarette liquids, is linked to an increased risk of osteoporosis and fractures [30]. It is well documented that recovery after bone fracture is complicated since tobacco smoke hinders wound healing and the formation of bone callus, impacting the activity of mesenchymal stem cells and fibroblasts [31]. In this regard, several studies demonstrate that nicotine, a powerful vasoconstrictor, decreases peripheral blood flow and thereby limits the supply of the nutrients and oxygen needed for tissue repair. This not only slows down wound healing following bone fracture surgery but also increases the risk of post-operative infections. Smoking-induced impaired angiogenesis also delays the healing process of fractures [32,33].

Knowledge of the impact of vaporized nicotine on the fracture healing process is currently limited. In an experimental study, 45 rats were divided into three groups and exposed to vaporized nicotine, cigarette smoke, or ambient air for six days a week for one month. Following this exposure, a iatrogenic femoral fracture was induced and repaired through intramedullary means. The rodents were then exposed for an additional four weeks before undergoing radiographic analysis. While no statistically significant differences were recorded, it was noted that the group exposed to vaporized nicotine exhibited comparatively less efficient bone healing than the other groups, resulting in a lower mineralized bone volume [34].

Hypovitaminosis D, smoking, and fall risk

Vitamin D has well-documented effects on skeletal muscle. Increasing data suggest that higher 25-hydroxyvitamin D [25(OH)D] serum concentrations are advantageous for health, with strong evidence supporting a role in fracture and fall prevention [35]. The main effect of the active vitamin D metabolite 1,25(OH)2D is to stimulate absorption of calcium from the gut. Vitamin D status is related to BMD and bone turnover. Vitamin D supplementation may decrease bone turnover and increase BMD [36].

It has long been observed that children with rickets, a condition caused by vitamin D deficiency, experience significant muscle deficits, known as "rachitic myopathy" [37]. This demonstrates the detrimental impact of vitamin D deficiency not only on bones but also on muscles. This effect has also been associated with the ability of vitamin D to inhibit myostatin, a key negative regulator of muscle mass. By inhibiting myostatin, vitamin D helps to prevent the infiltration of fat into muscle tissue, thus limiting adipogenesis [37]. A lack of vitamin D can lead to a decrease in muscle mass and strength, particularly in muscles responsible for maintaining posture and balance. This increases the likelihood of falls and other musculoskeletal disorders [37]. Recent studies have linked both active and passive smoking to a greater prevalence of vitamin D deficiency [38]. Various hypotheses have been proposed to explain how smoking could contribute to this deficiency [38]. One suggestion is that smoking may accelerate skin aging, thus inhibiting the conversion of 7-dehydrocholesterol (7-DHC) to precalciferol and ultimately decreasing the synthesis of vitamin D [39]. 7-DHC is a sterol that is both a precursor to cholesterol and a provitamin for vitamin D_3. The presence of 7-DHC in human skin enables humans and other mammals to synthesize vitamin D_3 (cholecalciferol) upon exposure to ultraviolet radiation in sunlight, via the intermediate isomer pre-vitamin D_3 [40]. Moreover, smoking has been shown to inhibit the synthesis of parathyroid hormone (PTH) [41]. The mechanism by which smoking affects PTH levels is not fully understood. PTH–vitamin D axis dysfunction has been observed in smokers [42].

Additionally, potential accumulation, in the kidneys, of heavy metals like lead and cadmium from cigarette smoke can decrease renal function and inhibit production of active vitamin D [43]. It should be noted that cadmium is also present in the vapor from e-cigarettes, making them ineffective in protecting against vitamin D deficiency and the associated increased risk of falls.

Conclusion

Smoking is a major public health concern that, beyond its well-known cardio-pulmonary effects, can also negatively impact the intricate relationship between bones and muscles. Recent scientific research is challenging the common belief that e-cigarettes are safer than traditional smoking. It is crucial to raise awareness of these findings and educate individuals on the importance of quitting smoking to preserve musculoskeletal integrity and function. However, additional long-term studies are needed to fully understand the pathological processes and clinical impact of different types of smoke on bone and muscle health.

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