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BONE BIOLOGY

Do E-cigarettes and vaping have a lower risk of osteoporosis, nonunion, and infection than tobacco smoking?

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Cigarette smoking is significantly associated with reduced bone mineral density (BMD), increased risk of fracture, and reduced fracture healing.[1,2] Smoking is also independently associated with increased incidence of post-surgery complications such as infection and aseptic loosening following arthroplasty.[3-6] While cigarette consumption has declined over the past decade, the use of electronic cigarettes (E-cigarettes), or vaping, has risen dramatically, partly due to being regarded as a safer alternative to smoking.[7-9] Indeed, Public Health England guidance suggests that E-cigarettes are 95% safer than cigarettes, fuelling public perception of negligible risk.[8] Increased use of E-cigarettes will undoubtedly represent a harm reduction in comparison to cigarettes due to less exposure to carcinogens and toxicants.[2,10] However, E-cigarette usage still results in systemic exposure to numerous and potentially harmful vapour constituents, including nicotine (in nicotine-containing liquids), flavouring chemicals, and reactive aldehydes, particularly for highly vascularized tissues such as the bone.[2] Critically, recent data suggest that vaping may be considerably more harmful than first thought.[11] Despite this, there has been limited investigation into the impact of E-cigarette usage on bone health, particularly over extended time periods. Here we draw together data from studies that have investigated the impact of E-cigarette vapour and its major constituents on bone, highlighting the mechanistic and functional results.

E-cigarette vapour has been reported to have a substantial impact on bone architecture in vivo, with microfractures evident in the femurs of mice following six months of chronic exposure, even following exposure to aerosols free of flavourings and nicotine.[12] However, no effect on cortical bone strength, bone stiffness, or hydroxyapatite content was observed in this study.[12] In addition, nicotine-rich E-cigarette vapour has been demonstrated to induce apoptosis and cause a reduction in both mineralization and alkaline phosphatase activity of Saos-2 osteoblasts (a human osteoblast-like cell line, the main cell type responsible for bone formation).[13] Commercially available E-liquids also reduced cellular viability of Saos-2 and MG-63 cells (another osteoblast-like cell line), independent of the presence of nicotine.[14] Although application of E-cigarette liquid does not directly mimic usage, as the chemical composition of E-cigarettes can change upon vaping,[15-18] such data highlight potential harm to bone health. Furthermore, the differentiation of bone marrow-derived mesenchymal stem cells (MSCs) towards the osteoblast lineage plays an important role in the regulation of bone turnover, particularly post injury. In response to treatment with E-cigarette smoke extract, MSCs cultured in osteogenic conditions displayed reduced expression of osteoblast genes, including alkaline phosphatase and type 1 collagen messenger RNA (mRNA) expression, and decreased mineralization, potentially mediated by loss of connexin43.[19]

There is evidence that E-cigarette users self-titrate consumption to achieve a nicotine dose similar to that obtained from cigarettes.[20] Therefore, the impact of nicotine on bone following the use of nicotine-containing E-cigarettes may be comparable to that of conventional cigarettes. Critically, the expression of nicotinic acetylcholine receptor subunits has been reported in both human bone tissue and primary human osteoblasts, with expression upregulated in response to nicotine.[21,22] Nicotine appears to have a bimodal effect on proliferation of primary human osteoblasts, with low doses

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increasing proliferation and higher doses (> 0.1 μM) significantly reducing proliferation and inducing apoptosis.[21,23] Functionally, there is evidence that nicotine reduces human primary osteoblast alkaline phosphatase activity and osteogenic gene expression, including runt-related transcription factor 2 (RUNX2) and osteonectin.[24] Furthermore, nicotine has also been demonstrated to increase matrix metalloproteinases-1, 2, 3, and 13 mRNA expression in Saos-2 cells, and drive mitochondrial stress in murine osteoblast-like cells, resulting in increased reactive oxygen species production.[22,25,26]

In contrast to osteoblasts, osteoclasts are primarily responsible for bone resorption. Therefore a positive balance between osteoclast and osteoblast activity leads to a reduction in bone mass. Osteoclasts also express α1 to 5, 7, 9, and 10 nicotine receptor subtypes, with α7 mRNA increasing in response to nicotine treatment.[27] In vitro data examining the role of nicotine on osteoclast function are conflicting. On the one hand, nicotine increased RAW264.7 osteoclast carbonic anhydrase expression, promoting demineralization.[27] However, there is also evidence that nicotine reduces bone resorption by decreasing V-ATPase expression and the planar area of the resorption.[27] Contrasting results have also been observed in vivo. Firstly, knockout of α7 nicotine receptors in mice resulted in decreased osteoclastogenesis and increased bone mass.[28,29] However, nicotine-mediated activation of α7 receptors in mice has been demonstrated to upregulate receptor activator of nuclear factor kappa-B ligand (RANKL) expression, promoting osteoclast activation and bone resorption.[29]

The most common carrier agents/humectants used in E-cigarette liquids include propylene glycol and vegetable glycerine. E-cigarette use results in thermal degradation of such humectants, generating carbonyl compounds such as formaldehyde, acetaldehyde, and acrolein.[15,30] Importantly, increased amounts of aldehyde compounds were detected in exhaled breath after vaping, while exhaled formaldehyde concentrations were similar to traditional cigarettes (~5 μg·puff–1). [31] Although the effect of E-cigarette-derived carbonyl compounds on bone cell function has not been studied directly, there is evidence that aldehydes can reduce proliferation and increase cell death of U2OS cells (human osteoblastic cell line) in a dose-dependent manner,[32,33] and reduce osteoblast alkaline phosphatase activity and mineralization.[34] Acetaldehyde has also been shown to stimulate peroxisome proliferator-activated receptor (PPARγ) expression in murine osteoblasts, inhibiting osteoblast differentiation.[35] Additionally, genetic polymorphisms resulting in reduced aldehyde dehydrogenase, mitochondrial (ALDH2) cause a build-up of acetaldehyde in humans, lower BMD, and a significantly increased rate of hip fracture and osteoporosis.[36,37]

The wide variety of E-cigarette flavouring liquids available for consumption (over 8,000 to date) is a primary contributing factor to the rise in popularity of E-cigarette usage, especially among younger individuals and those who previously did not smoke cigarettes.[38-40] However, there is limited regulation and quality control of flavouring compounds present in E-cigarette liquids. Flavouring chemicals have been demonstrated to have harmful effects on other cell types such as immune cells,[11] and atomization of flavouring chemicals including linalool, dipentene, and citral causes free radical production.[41-43] Despite this, there is a dearth of studies investigating physiological effects of flavouring chemicals on bone directly.

Traditional cigarettes are associated with the inhalation of metal particulates, including chromium, cadmium, lead, and nickel, all of which are known to have a variety of harmful effects.[44-46] Emerging data have demonstrated that metal particulates and nanoparticles are also generated from E-cigarettes, with concentrations in many cases similar or exceeding those from cigarette smoke.[47,48] However, the effect of E-cigarette-derived metal particulates on bone has not yet been reported.

The development of E-cigarette devices has also resulted in their use to vape cannabidiol (CBD), the major non-psychoactive constituent of cannabis, due to its purported analgesic, anti-inflammatory, and anti-epileptic properties.[49-51] Again, although no direct study of the effect of vaping CBD on bone has been performed, data surrounding direct administration of CBD suggest a largely positive impact on bone, including reduced bone loss following the induction of periodontal disease,[52] promotion of fracture healing,[53] and recovery following injury in rats.[54,55] There is also evidence that CBD can suppress osteoclastogenesis and reduce the function of human osteoclasts.[56,57]

To date there has been little investigation into the effect of E-cigarette vapour on bone and bone cell function. Current data suggest that exposure of both osteoblasts and osteoclasts to high concentrations of nicotine may reduce their viability and impair function. Similarly, aldehydes and flavouring chemicals may also negatively impact osteoblast viability and ability to form bone. However, such findings are predominantly derived from studies using bone cell lines, with limited use of human osteoblasts or osteoclasts. Understanding how E-cigarette vapour components may mediate human bone cell function, in addition to long-term studies to determine the potential harm of chronic E-cigarette use on human bone, will be important to inform users and healthcare providers of potential risks, particularly regarding bone healing following orthopaedic surgery and injury.

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- T. Nicholson: Wrote the first draft of the manuscript, Reviewed, edited, and approved the final manuscript.
- A. Scott: Conceptualized the study, Reviewed, edited, and approved the manuscript.
- M. Newton Ede: Conceptualized the study, Reviewed and approved the final manuscript.
- S. W. Jones: Conceptualized the study, Reviewed, edited, and approved the manuscript.

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