The Effect of Nicotine on Bone Healing: A Systematic Review and Application to Total Joint Arthroplasty

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Introduction:

Nicotine, a primary component of tobacco products, is known to have widespread effects on various physiological processes, including those critical to bone healing. As the global prevalence of smoking remains significant, understanding the impact of nicotine on the healing processes is crucial, especially in the context of orthopedic procedures such as total joint arthroplasty, an increasingly common surgery. While many studies have been conducted demonstrating the detrimental effects of smoking cigarettes on bone healing, joint health, and orthopedic surgical outcomes, few human studies have been performed evaluating the effect of nicotine alone on these outcomes. Further investigating the effects of nicotine alone is becoming more relevant, as the prevalence of e-cigarette use, nicotine gum, patches, and other forms of nicotine replacement therapy continues to increase each year. Comparing the risk of nicotine use to traditional cigarette and tobacco use may offer a solution to populations unable to maintain nicotine abstinence in the months preceding an operation. As traditional smoking use is proven to worsen fracture healing and rates of nonunion, and leads to higher rates of mechanical complications, medical complications, and mortality in those undergoing total joint arthroplasty. Bone healing and joint repair are complex biological processes that can be influenced by multiple factors, including vascular supply, cellular activity, and the local environment of the affected tissues. This systematic review aims to comprehensively evaluate the current evidence on how nicotine affects these processes in cellular, animal, and human models, with an additional context for patients undergoing total joint arthroplasty. By synthesizing the available literature, we seek to provide insights that could inform clinical practices and optimize patient-centered care.

Methods:

A search was conducted on May 3rd, 2024 in Ovid Medline, Embase, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature Plus, Scopus, and the Web of Science Platform. All dates were included up to 2024, and included studies that show the effect of nicotine without tobacco products on bone or joint healing, health or growth. Primary outcomes included the effects on bone healing, health or growth from solely nicotine in both humans and animals, and excluded studies using nicotine with tobacco only, as opposed to isolated nicotine, or other ingredients contained in cigarette smoke.

Results:

The search and screening resulted in 84 studies to be included (Figure 1.), including numerous animal models and in vitro studies.

Bone Healing: Animal models exposed to nicotine demonstrated delayed bone healing, decreased new bone formation, increased necrosis, and increased chondrocyte density evidencing nicotine-induced tissue hypoxia, which can contribute to abnormal mineralization. Hypoxic effects were attributed to increased hypoxia-inducible factor-1alpha and VEGF, while BMP-2 changes were inconsistent among studies. Furthermore, in these models nicotine increased osteoclast activity, leading to higher bone resorption and necrosis, along with decreased new bone formation. Some evidence shows nicotine-treated bone defects healed with greater porosity indicating poorer fracture toughness. One study demonstrated nicotine significantly reduced femur bone histomorphometric parameters which were not reversed even after nicotine cessation. However, there remains little to no evidence of nicotine having negative effects on mechanical properties of healed bone. While nicotine generally was shown to inhibit new bone formation, multiple studies demonstrated a biphasic relationship with low nicotine concentrations stimulating osteoblast proliferation and high concentrations inhibiting it. Nicotine demonstrated inconsistencies in its effects on histomorphometric bone mineral density and bone mineral content.

Physiologic & Inflammatory Markers: Nicotine's impact on physiologic and inflammatory biomarkers is unclear, and there is conflicting evidence upon review of the literature. While many in vitro studies show a decrease in bone inflammatory cytokine profile with nicotine administration, animal studies show mixed results of increased and decreased inflammatory cytokines such as IL-1 and IL-6. One study demonstrated no decrease in serum calcium or phosphorus level with nicotine administration; however, serum Vitamin D was significantly reduced, and parathyroid hormone trended down.

Osseointegration: Nicotine clearly slows osseointegration of titanium implants in rat and rabbit femurs and tibias, reducing implant stability and bone-to-implant contact. Specifically higher doses of nicotine demonstrated inhibitory effects on osteoblast proliferation, increased necrosis and new bone formation, and negatively affected osseointegration.

Discussion:

The evidence suggests nicotine has an overarching negative effect on bone healing, bone growth, and integration of implants into bone in various animal and in vitro studies performed thus far. While there have been conflicting results regarding nicotine's impact on various inflammatory cytokines and markers, such as IL-1 and IL-6, the most representative studies reveal nicotine impairs bone healing by disrupting vascular and cellular processes essential for bone regeneration. This includes increasing vasoconstriction and reducing angiogenesis, a key factor in bone regeneration, and through inhibiting osteogenesis and increasing bone resorption. Osseointegration studies demonstrate nicotine's impact on bone healing around a titanium implant, which is useful for theorizing nicotine's effects on implant-bone interface healing and adaptation in TJA. The evidence of this type of study points to a dose-dependent detriment on bone formation around implants and delay in integration of such implants. While nicotine may cause these effects in animal models and in vitro studies, there is a severe paucity of human studies evaluating the effect of nicotine, without tobacco or cigarette smoke, on bone healing or orthopedic surgery outcomes, serving as the main limitation of this review. Further, there has been shown to be a distinct effect of cigarette smoke in comparison to nicotine on bone healing. This warrants the need for more human studies comparing the effects of cigarette use and nicotine replacement therapy in patients undergoing orthopedic surgeries and total joint arthroplasty.

Significance/Clinical Relevance:

This study is significant in providing insight to the potential effects of nicotine on bone healing in orthopedic surgery, specifically in the context of clinical decision-making for patients undergoing total joint arthroplasty and with a smoking history or nicotine use disorder.

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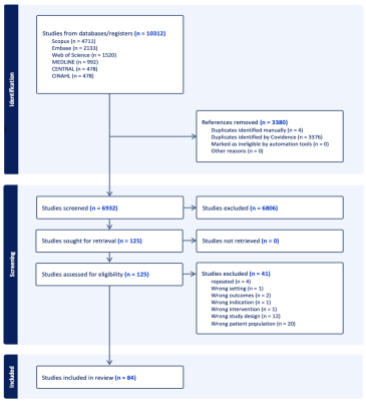

Figure 1. PRISMA flow diagram for studies searched, included and excluded from the systematic review.