CURRENT CONCEPTS REVIEW

The Musculoskeletal Effects of Cigarette Smoking

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- Cigarette smoking decreases bone mineral density and increases the risk of sustaining a fracture or tendon injury, with partial reversibility of these risks with long-term cessation of smoking.
- Cigarette smoking increases the risk for perioperative complications, nonunion and delayed union of fractures, infection, and soft-tissue and wound-healing complications.
- Brief preoperative cessation of smoking may mitigate these perioperative risks.
- Informed-consent discussions should include notification of the higher risk of perioperative complications with cigarette smoking and the benefits of temporary cessation of smoking.

Ever since the United States Surgeon General warned the public of a definite association between tobacco smoking and lung cancer in the 1960s, we have become more aware of the various harmful effects of smoking. While smoking rates have declined, nearly 20% of American adults continue to smoke[1].

Cigarette smoke consists of two phases: a volatile phase of nearly 500 different gases (e.g., carbon monoxide, carbon dioxide, nitrogen, ammonia, hydrogen cyanide, and benzene) and a particulate phase of approximately 3500 chemicals (e.g., nicotine, nornicotine, anatabine, and anabasine)[2]. Most of the known carcinogenic substances are found in the particulate phase[3]. Approximately 2 to 3 mg of nicotine and 20 to 30 mL of carbon monoxide are inhaled from each cigarette[4].

Nicotine has been established to be the addictive component of cigarette smoke and a cause of disease. Nicotine has numerous physiologic effects, including stimulating the sympathetic nervous system, causing vascular disturbances, and inducing cell death[3]. Primarily metabolized by the liver, the major nicotine metabolite cotinine is often used to assess recent cigarette smoking. It has a half-life of fourteen to twenty hours (versus three hours for nicotine) and can be detected in a smoker's urine for up to ten days after cessation. Nicotine and carbon monoxide decrease microperfusion and tissue oxygenation, inducing polycythemia, and increase platelet aggregation and cause endothelial damage, increasing blood viscosity and producing a state of hypercoagulation, resulting in microclotting[5-8]. Carbon monoxide also reduces the amount of oxyhemoglobin available by shifting the oxygen dissociation curve leftwards. An individual who smokes one pack of cigarettes per day is tissue hypoxic for fifteen to twenty hours per day[9]. Hydrogen cyanide primarily interferes with oxidative metabolism at the cellular level[10,11].

Cigarette smoking has numerous detrimental effects on the immune system, including decreased white blood-cell function (with leukocytosis), reduction in serum levels of immunoglobulins, reduced antibody response to various antigens, decreased T-cell response, and proliferation to mitogens, decreased mass and cellularity of lymphoid tissue, inhibition

Disclosure: None of the authors received payments or services, either directly or indirectly (i.e., via his or her institution), from a third party in support of any aspect of this work. One or more of the authors, or his or her institution, has had a financial relationship, in the thirty-six months prior to submission of this work, with an entity in the biomedical arena that could be perceived to influence or have the potential to influence what is written in this work. No author has had any other relationships, or has engaged in any other activities, that could be perceived to influence or have the potential to influence what is written in this work. The complete **Disclosures of Potential Conflicts of Interest** submitted by authors are always provided with the online version of the article.

of T lymphoblasts in the cell cycle, and impaired neutrophil function[12-19]. Despite reduced immunoglobulin levels, smokers tend to have increased levels of autoantibodies, particularly antinuclear rheumatoid factors[12,15,16].

Bone Metabolism, Bone Mineral Density, and Fracture Risk

Reduced blood supply, tissue hypoxia, and the effects of nicotine on arteriole endothelial receptors have been implicated for reduced bone metabolic activity in smokers[20,21]. Smoking has been hypothesized as being a cause of osteonecrosis because of its effects on the hematological system, including the development of a prothrombotic state and eventual interruption of the vascular supply[22,23]. A fourfold increase in the risk of the development of osteonecrosis of the femoral head among smokers was observed in a combined cohort of 230 patients with idiopathic osteonecrosis as compared with 404 matched control patients[24,25]. A correlation between passive smoking and the development of Legg-Calvé-Perthes disease in children has been reported in a series of ninety patients as compared with 183 control patients[26].

Components of cigarette smoke can be both stimulatory and inhibitory on osteoblast function and formation as measured by numerous metabolic assays, including DNA synthesis via ^{3}H-thymidine incorporation, alkaline phosphatase (ALP) serum levels and gene expression, activator protein 1 (AP1) and Runt-related transcription factors (RUNX), c-Fos, osteopontin, osteocalcin, collagen synthesis, total protein synthesis, and cell proliferation[27-30]. The effect of nicotine on osteoblast function and osteogenesis appears to be dose-dependent. Osteoblast formation and function are inhibited at high levels of circulating nicotine, corresponding to heavy smoking, whereas they are stimulated at low levels, corresponding to light smoking[28]. Carcinogens in cigarette smoke, particularly polycyclic aryl hydrocarbons and polychlorinated dibenzodioxins, inhibit osteoblast formation and differentiation through the aryl hydrocarbon receptor (AhR)[30-34]. Osteoblast-like cells exposed to high concentrations of both nicotine and cigarette smoke in vitro demonstrate decreased proliferation and impaired collagen synthesis[35-37]. Smaller osteocytes, decreased numbers of marrow cells and osteoblasts ($p < 0.01$), and significantly lower bone mineral density (BMD) were found in the femur ($p < 0.01$) and lumbar vertebrae ($p < 0.001$) of eight-week smoke-exposed rats in comparison with the findings in control animals[38]. However, tobacco extract not containing nicotine significantly reduced the mechanical strength of healing femoral fractures in rats, whereas nicotine alone did not ($p = 0.023$)[39].

Cigarette smoke constituents may also affect osteoclast function and formation. Rats that had been administered nicotine had increased bone-resorbing cytokine levels and negative effects on their trabecular bone (volume, thickness, formation, and mineralizing rate) as compared with control animals[40]. This effect may occur through osteoblast-mediated stimulation, through increased macrophage colony-stimulating factor (M-CSF) and prostaglandin E2 (PGE2) production, of osteoclast formation[41]. Smoke carcinogens also appear to affect osteoclasts through their action on AhR[30]. Significantly decreased bone density and dimensions have been noted in mice with constitutively activated AhR ($p < 0.05$), whereas an AhR antagonist was shown to decrease these negative effects on bone ($p < 0.05$)[42,43]. Smoke carcinogens also affect the ability of receptor activator of nuclear factor kappa-B ligand (RANKL) to induce the osteoclast cell-surface receptor (RANK) that binds to RANKL, a key factor in osteoclastogenesis[44,45]. Despite the inhibition on osteoclastogenesis, carcinogens may increase osteoclast resorptive activity as measured by increased C-telopeptide of type 1 collagen and tartrate-resistant acid phosphatase type-5b (TRAP5b) levels[42]. The degree of effect between decreased osteoclastogenesis and increased osteoclast activity is unknown.

Lymphocytes are vital for bone homeostasis, and another potential mechanism for the negative effects of smoking on bone may be the selective depletion of bone marrow B lymphocytes[46]. Decreased calcium absorption in smokers may also be a contributing factor to decreased bone formation and increased resorption[47].

Smoking has also been linked to altered sex hormones and stimulation of the adrenal cortical axis[48-50]. Female smokers tend to enter menopause two years earlier than nonsmokers and the effects of hormone replacement therapy with estrogen may be reduced in smokers[51,52].

Cigarette smoking leads to increased fracture rates of the hip, spine, and distal radius and other osteoporosis-associated fractures. Population-based studies in England[53,54] and Brazil[55] and in military veterans[56] all show an independent increased risk of fractures among smokers. Multiple other independent risk factors were reported, including the use of hormone replacement therapy, parental history of osteoporosis, menopausal symptoms, and gastrointestinal malabsorption and other endocrine disorders for women and age, body-mass index (BMI), alcohol use, rheumatoid arthritis, cardiovascular disease, type-2 diabetes, asthma, tricyclic antidepressant use, corticosteroid use, a history of falls, and chronic liver disease for both men and women[54]. These independent risk factors were noted in the United States, England, and Brazil. Analysis of 3617 cases of hip fractures (780 males, 2837 females) in England found that smokers ($n = 467$) were more likely to be male (35.3% versus 19.5%, $p < 0.0001$) and younger (seventy-two versus eighty-one years, $p < 0.0001$) as compared with nonsmoking patients who had hip fracture ($n = 3150$)[57]. A meta-analysis of ten large prospective studies that included nearly 60,000 men and women from around the world demonstrated an independent association between smoking and hip fracture risk both in men (risk ratio [RR] = 1.82; 95% confidence interval [CI], 1.34 to 2.49) and women (RR = 1.85; 95% CI, 1.46 to 2.34)[58]. When all osteoporotic fractures were evaluated, men (RR = 1.53; 95% CI, 1.27 to 1.83) were at increased risk from smoking as compared with women (RR = 1.20; 95% CI, 1.06 to 1.35). This has also been observed in other studies and suggests a dose-response relationship, as men tended to have higher usage than women, although the

duration of smoking has yet to be shown to be related to fracture risk[59,60]. Low BMD, however, accounted for only 23% of the increase in risk of hip fracture and 40% of the increase in risk of all osteoporotic fractures, with the independent risk that was associated with smoking remaining significant in men but not women after adjustment for BMD[58]. In a prospective study of 66,651 women, current smokers with a low intake of vitamin E and C had an odds ratio of 3.0 for hip fracture[61]. When these vitamins were taken at higher doses, the odds ratio fell to 1.1, suggesting a role for oxidant stress in the adverse effects of smoking on bone quality.

Smoking may exacerbate postmenopausal and aging-related bone loss. Postmenopausal women who smoke are more prone to vertebral fractures and have lower vertebral BMD than postmenopausal nonsmokers[62,63]. Daniell demonstrated an apparent cortical bone loss of 1.02% per postmenopausal year in thirty smokers as compared with 0.69% in fifty nonsmokers, with the rate increasing to 1.19% in eighteen nonobese postmenopausal smokers ($p < 0.001$)[62]. The level of osteocalcin, which is secreted solely by osteoblasts and used as a marker for bone formation, was decreased in recently menopausal female smokers[64]. On the other hand, increased rate of bone loss may be more a result of increased resorption than decreased formation. Biochemical markers of bone resorption are elevated in older smokers as compared with nonsmokers without a matched increase in bone formation[65].

Significant deleterious effects on BMD in adolescents and young adults (eighteen to twenty years of age) have also been observed in a study of 1068 men ($p = 0.01$)[50]. A mean BMD difference of 3.3% in the spine ($p < 0.01$) and 5% in the trochanter ($p < 0.01$) was seen in smokers after adjustment was made for age, height, weight, calcium intake, and physical activity. Cortical thickness ($p < 0.001$) and trabecular volumetric BMD ($p < 0.01$) were also significantly lower in smokers. The mean duration of smoking in this study was only 4.1 years, suggesting that the effects of smoking occur rapidly and may contribute to reduction in peak bone mass. In another study, BMD at baseline together with smoking and alcohol use during the study period accounted for 86.5% of the variation in BMD two years later[66]. The relative contributions of increased postmenopausal bone loss (as discussed previously) and reduced peak bone mass to the lower BMD in older smokers are unclear.

Lifestyle variables associated with smoking may also contribute to its effect on the skeleton, including decreased appetite, lower calcium intake, higher consumption of caffeine and alcohol, and lower levels of physical activity[65,67]. The importance of the associations between smoking, BMD, and bone structure did not change with adjustment for these variables[50]. Smokers, after adjusting for age, history of stroke, BMI, physical activity, and alcohol use, have decreased physical and neuromuscular performance (as measured via grip strength, triceps extension strength, quadriceps knee extension strength, hip abductor strength, a ten-second 23-cm step-up step-down test, chair stand-up test, foot-tap test, walking speed, tandem stand test of balance, and tandem walk test) that is nearly equivalent to that associated with five years of aging, suggesting that they are more prone to injury from increased risk of fall and with each fall[68]. Smokers in this study consumed an average of 15.9 (standard deviation [SD], 9.8) cigarettes per day but the duration of smoking was not specified. A survey of 10,059 senior citizens revealed that smoking was an independent predictor of unintentional injuries along with other independent factors, including education, alcohol use, rest and sleep patterns, support, interactions such as age and sex, activity limitations and sex, and home maintenance and sex[69].

Fracture-Healing and Distraction Osteogenesis

Smoking has been associated with delayed fracture union, nonunion, infection and poor wound-healing, in addition to overall worse health outcomes from both fracture and fracture fixation.

Most of the data regarding the effect of nicotine on bone-healing demonstrated either no detrimental effect or accelerated healing, but this effect may be dose-dependent, with higher doses being toxic and lower doses being stimulating[27,28,39,70-74]. The relative contributions of the two phases of cigarette smoke on fracture-healing or musculoskeletal physiology have not been directly investigated. The deleterious effects of smoking on fracture-healing may not be due to nicotine but to other chemicals in cigarette smoke[70]. Tobacco extract not containing nicotine significantly reduced the mechanical strength of healing femoral fractures in rats ($p = 0.023$), whereas nicotine alone did not affect mechanical properties[39]. The same group in a separate study also demonstrated increased fracture-healing strength with nicotine alone with a dose-dependent effect[71]. These studies suggest that nicotine replacement is safe with regard to bone-healing and may even accelerate fracture-healing. This is also supported by a study of 175 male patients who underwent hemicallotasis for knee deformity; in that study, snuff users had the shortest healing time of eighty-seven days and experienced the fewest complications, whereas smokers had a 100-day healing time and nonsmokers had a ninety-three-day healing time ($p = 0.03$)[72]. In contrast, in a rabbit model, fracture repair strength was biomechanically weaker and fractures were more prone to nonunion in animals that were exposed to nicotine as compared with those exposed to placebo[73,74]. In a mouse model, smoke exposure for one month prior to surgical tibial fracture resulted in delayed union through delayed chondrogenesis and cellular differentiation[75].

Humeral fractures are more prone to worse outcomes in smokers. Nonunions and complications were more prevalent for smokers with proximal humeral fractures treated with open reduction and internal fixation ($n = 16$ and 22, respectively; $p = 0.02$)[76,77]. Worse Constant scores were noted in those patients who smoked and had proximal humeral fractures that were treated with hemiarthroplasty ($n = 163$, $p < 0.05$)[78]. Diaphyseal humeral fractures treated with functional bracing were found to trend toward delayed union in smokers ($n = 19$, no p value provided)[79].

McKee et al., using the Ilizarov technique for reconstruction of the femur and tibia, demonstrated a significant association among the variables of smoking, slower bone formation, and prevalence of nonunion ($n = 84$, $p = 0.031$)[80]. Retrospective clinical studies have also demonstrated an increased risk of delayed union or nonunion for tibial fractures in smokers as compared with nonsmokers ($n = 146$ and 105, respectively; $p < 0.05$)[81,82].

The Lower Extremity Assessment Project (LEAP) reviewed the outcomes of 268 unilateral open tibial fractures treated operatively. The authors found that smokers were 37% more likely and former smokers were 32% more likely to develop nonunion. Additionally, the time to union was four weeks longer for smokers than for nonsmokers ($p < 0.05$) and was dependent on the grade of open fracture[83,84]. The effect of type of treatment (intramedullary nail versus external fixation) on time to union was not commented on in either study. Other comorbidities were not explored.

Smokers were more than twice as likely as nonsmokers to develop an infection and 3.7 times more likely to develop osteomyelitis ($p = 0.01$)[83]. Former smokers were 2.8 times more likely to develop osteomyelitis, but they were not at an increased risk of experiencing other types of infections ($p = 0.04$).

In another LEAP study, in which the outcomes of limb salvage procedures and amputations were evaluated in 397 patients by means of the Sickness Impact Profile, worse associated outcomes were reported both for limb-salvage and amputation procedures in patients who were smokers[85]. The impact from other comorbidities was not analyzed, although self-reported poor-health status prior to injury was associated with poorer outcomes following either treatment ($p < 0.05$). In another study, in which both open and closed tibial fractures were included ($n = 85$; with eighty-one patients treated operatively), smokers had a threefold to eighteenfold increased risk of impaired bone-healing[86].

In an analysis of forty-seven patients in whom a distal tibial fracture was treated with small-pin external fixation, it was found that a significantly delayed union took place in active smokers as compared with the time to union in nonsmokers[87].

Both operatively and nonoperatively managed ankle fractures are associated with worse results in smokers than in nonsmokers, either because of delayed healing (in nonoperatively managed patients) or increased perioperative complications (in operatively managed patients). A moderate correlation has been observed between smoking and delayed healing of nonoperatively managed ankle fractures ($n = 57$)[88]. Nåsell et al. reported the six-week follow-up data (available for 98.2% of patients) from their study of 906 patients (185 smokers and 721 nonsmokers) who underwent operative treatment for ankle fracture[89]. The authors found that smokers had a higher rate of complications overall when compared with nonsmokers (30.1% [fifty-five of 183 smokers] versus 20.3% [144 of 708 nonsmokers]; $p = 0.005$), with subanalysis showing a six times greater risk of infection for smokers. Diabetes mellitus was also noted as a risk factor for postoperative complications.

Smoking and diabetes mellitus have been reported to be independent risk factors for soft-tissue complications and worse outcomes in operatively managed calcaneal fractures[90-92]. Folk et al. reviewed wound-healing complications of 179 patients with 190 displaced intra-articular calcaneal fractures that were operatively treated. Forty-eight fractures were associated with wound complications, with forty (21%) requiring operative treatment[92]. Risk factors for wound complications included smoking (RR 1.2; $p = 0.03$), diabetes mellitus (RR 3.4; $p = 0.02$), and open fractures (RR = 2.8; $p < 0.0001$).

Operative treatment for fracture nonunions results in a higher incidence of persistent nonunion in smokers than in nonsmokers. After long-bone fracture, transforming growth factor beta 1 (TGF-β1) serum levels, a promising new marker of fracture-healing with differences in time courses noted between timely and delayed healing of fractures, was significantly reduced at four weeks after injury in fourteen smokers when compared with fourteen nonsmokers ($p = 0.007$), providing a possible mechanism of deficient bone-healing through a TGF-β1-mediated process[93]. Treatments for diaphyseal humeral fracture nonunion are associated with persistent nonunion in patients who smoke[79,94,95]. Vascularized and nonvascularized bone-grafting as well as allograft chips with demineralized bone matrix for scaphoid nonunions had lower rates of union in smokers than they did in nonsmokers ($p < 0.018$, $p < 0.01$, and $p = 0.005$, respectively)[96-99]. In a study of twenty-three femoral nonunions treated by exchange nail, two-thirds of smokers and all nonsmokers went on to union (no p value provided)[100]. On the other hand, Giannoudis et al., in their study of thirty-two femoral diaphyseal nonunions, found no association between smoking and nonunion[101].

Healing of Arthrodeses

Osteotomies and arthrodeses have also been associated with an increased risk for delayed union and nonunion in smokers than in nonsmokers. In a study of smoking and osseous union after ulna-shortening osteotomy in thirty-nine patients (forty wrists), ulna-shortening osteotomies for ulnocarpal abutment took longer to heal in smokers (7.1 months in smokers versus 4.1 months in nonsmokers, $p = 0.008$), and smokers were more likely to experience delayed union or nonunion (30% of smokers versus 0% of nonsmokers, $p = 0.02$)[102]. The Lapidus procedure for failed treatment of hallux valgus was associated with poorer outcomes among smokers on the basis of American Orthopaedic Foot & Ankle Society (AOFAS) scores, and all three nonunions in one series were in smokers ($n = 24$, $p < 0.05$)[103]. Cobb et al. found the risk for ankle arthrodesis nonunion in smokers to be 3.75 times that of nonsmokers ($n = 44$, $p = 0.0275$)[104]. Ishikawa et al. found the risk for hindfoot fusion nonunion in smokers to be 2.7 times that of nonsmokers ($n = 160$, $p = 0.04$)[105]. Nonunions were also more prevalent among smokers who had undergone isolated subtalar arthrodesis ($p < 0.05$) and, after adjusting for age and sex, smokers were 3.8 times more likely than nonsmokers to experience nonunion[106,107]. In patients who underwent hemicallotasis for knee deformity, smokers

needed 100 days to heal as compared with ninety-three days for nonsmokers (n = 175, p = 0.03)[72].

The association between smoking and spinal fusion nonunion has been well described. Brown et al. found the rate of pseudarthrosis in 100 lumbar spinal fusions to be five times higher in smokers (40% [twenty of fifty] versus 8% [four of fifty], p = 0.001)[108]. Smokers also had a lower success rate with regard to fusions for spondylolisthesis[109]. In eighty-six revision fusions for pseudarthrosis of the lumbar spine, there was a negative linear association with outcome scores and the number of pack years, and those who had quit smoking prior to their operation (duration was not specified) had better outcome scores and were more likely to return to work full time than those who did not (p = 0.03)[110]. In a series of 196 patients, smokers had lower fusion rates for multilevel anterior cervical interbody graft fusions (p < 0.02) but not for corpectomy and strut-grafting[111].

Rabbit models also demonstrated increased spinal fusion nonunions with systemic nicotine administration, with an improvement in fusion rates when nicotine was discontinued for the week before surgery[112,113]. In contrast, in a retrospective review of 158 patients who had undergone posterior cervical fusion, there was no difference in union rates between smokers and nonsmokers, but the functional scores of smokers were five times more likely to be diminished and associated with physical limitation[114]. In a retrospective review of ninety-six patients who underwent primary fusion for adult idiopathic scoliosis, there was no increase in the pseudarthrosis rate among smokers[115].

Soft-Tissue Healing

Fibroblasts, mesenchymal stem cells, acute phase proteins, and growth factors are crucial to the formation of granulation tissue. Poor wound-healing from cigarette smoke may be due to an alteration of the normal process of healing, including the migration and function of these players within the wound[116]. Additionally, nicotine causes an increase in catecholamines, promoting the formation of chalones that inhibit epithelialization and undermine the healing process[6]. Cigarette smoke itself creates numerous free radicals that can cause direct cellular damage[117].

Smokers are known to be at increased risk for wound and soft-tissue complications as compared with nonsmokers[10,118-120]. Patients with spinal cord-injuries who smoke have a higher prevalence of pressure sores, and these sores are often more extensive than those that occur in nonsmokers[121]. Increased risk of free and local flap failure among smokers has been described[84,118,119]. A higher incidence of delayed wound-healing and infection in smokers has also been reported in patients after spine surgery[122].

Tendon-healing and ligament-healing appear to be negatively affected by cigarette smoking, although the data are sparse. In a rat rotator cuff tear model, nicotine delayed tendon-to-bone healing and was associated with prolonged inflammation[123]. Mice exposed to cigarette smoke had weaker medial collateral ligaments four weeks after injury and demonstrated lower type-I collagen gene expression and cellular density[124,125]. In comparison with nonsmokers, smokers had lower increases in the University of California at Los Angeles (UCLA) scores with either open or arthroscopic rotator cuff repair for degenerative tears and were found to have larger tears with a dose-dependent relationship[126-128]. In a survey of 402 patients who had a primary anterior cruciate ligament reconstruction[129], smokers had 0.36 times the odds of success as nonsmokers, as measured with use of patient-reported outcomes (International Knee Documentation Committee Subjective Knee Form), and smoking cessation was advised for improved long-term outcomes[130,131].

Recent studies have also suggested that smoking is a risk factor for tendon injuries. A higher prevalence of degenerative rotator cuff tears in smokers with a dose-and time-dependent relationship has been reported, although no specific range of dose exposure or duration was specifically looked at[132,133]. In one study, a history of smoking was a risk factor for rotator cuff tear (odds ratio [OR] = 1.74; 95% CI = 1.23 to 2.4, increasing to 4.24; 95% CI = 1.75 to 10.25, if within last ten years), with one to two packs per day becoming significant (OR = 1.66, p = 0.009) and more than two packs per day doubling the risk of sustaining a rotator cuff tear (OR = 3.35, p = 0.0007)[133]. Carbone et al., through an analysis of covariance model that was adjusted for age and sex, showed that the total number of cigarettes smoked in life differed significantly (p = 0.032) between patients who had a small rotator cuff tear and those who had medium or larger rotator cuff tears but did not specify the difference or a significant dose exposure or length[127]. Smokers also had a 7.5 times higher risk of distal biceps tendon rupture in one series[134].

Back Pain

The smoking of cigarettes is associated with increased risk of back pain and degenerative disc disease. A recent meta-analysis of forty studies showed that current smoking was associated with increased prevalence of low back pain within the past twelve months, with a pooled odds ratio of 1.31[131]. Furthermore, the odds ratios for current smokers having chronic low back pain or disabling back pain were 1.79 and 2.14, respectively. Former smokers ranked in prevalence between persons who had never smoked and current smokers. Adolescent smokers also had a higher incidence of low back pain, with an odds ratio of 1.82. The multifactorial etiology of back pain makes interpreting this association difficult. Smokers tend to have poorer mental and physical health scores, have more musculoskeletal disorders, and have chronic pain[136-138]. In studies that control for psychological or workload factors, the results were similar. Publication bias may also have favored the positive results[135].

Elevated levels of proinflammatory mediators have been seen in smokers and can amplify pain[139,140]. Studies on twins, including 600 patients, have attempted to isolate the habit of smoking and, with the use of magnetic resonance imaging (MRI), have found an 18% greater disc degeneration score in smokers as compared with nonsmokers; however, no clinical

difference was found[141]. Proposed mechanisms include reduced perfusion and malnutrition of the discs from vasoconstriction, atherosclerosis, and microclotting, which may lead to progressive degeneration[142-144].

Arthritis

The relationship between smoking and osteoarthritis is controversial. Smoking has been thought to protect large weight-bearing joints from osteoarthritis through its osteopenic effect, in which subchondral bone is made more pliable and conformable to loads, through the anabolic stimulation of chondrocytes by nicotine, and because smokers tend to be thinner[145-150]. However, smaller studies have shown increased knee cartilage loss among smokers, as measured by MRI[151-153]. Smoking does not offer protection from osteoarthritis in interphalangeal joints of the fingers[150]. In addition, smoking is a well-known risk factor for rheumatoid arthritis and smokers with rheumatoid arthritis have been shown to be less responsive to anti-tumor necrosis factor (anti-TNF) agents[154-159].

Cessation and Perioperative Management

There are no definitive guidelines on perioperative cessation. Immune function appears to recover after two to six weeks of abstinence; wound-healing, after three to four weeks; and pulmonary function, after six to eight weeks[11,160-167].

The effects of smoking on the skeleton may at least be partially reversible. Former smokers have been found to have lower fracture risk than current smokers, but it may take ten years after cessation to demonstrate any reduction in hip fracture risk[58,168]. In a cohort study including 2322 men, fracture risk was more than halved during the first ten years after cessation but remained increased until thirty years after cessation[59]. A decrease in urinary N-telopeptide, a marker of bone resorption, was seen after six weeks of abstinence in postmenopausal women[169]. In 837 middle-aged men, no significant difference in BMD was observed between former smokers (mean duration of cessation of 5.6 ± 4.6 [SD] years) and those who never smoked, indicating that cessation had a positive effect on BMD[170]. The duration of smoking was negatively associated with lumbar vertebrae BMD ($p = 0.004$).

Former smokers had consistently improved outcomes compared with current smokers with regard to systemic postoperative complications, infections, outcome scores, return to work, and recovery rates. In a retrospective study of 3309 patients undergoing primary total hip replacement, heavy tobacco use (40+ pack-year history) was associated with an increased risk of systemic postoperative complications ($p = 0.004$), including venous thromboembolism, cardiac or cerebrovascular events, postoperative anemia, blood transfusion, gastrointestinal bleeding, urinary tract infection, pneumonia, and death[171]. As compared with nonsmokers, former and current smokers had a 43% and 56% increased risk, respectively, of a systemic postoperative complication, and the heaviest tobacco smoking group had a 121% increased risk. Smoking for more than fifteen years was found to be a predisposing factor to failure of lumbar discectomy for radiculopathy due to disabling low back pain ($p < 0.01$)[172]. Conversely, smoking alone had no adverse effect on recovery rate after cervical laminoplasty but had a negative interactive effect with diabetes mellitus[173].

The most common perioperative complications associated with smoking are wound-healing, infection, and cardiopulmonary complications[11,165,174-180]. Seven prospective studies of the effect of cessation on perioperative complication have been identified, with quit rates of 40% to 89%[176-178,181-184]. A recent systematic review of six randomized trials[176,177,183,185-187] demonstrated a pooled relative risk reduction of 41% (95% CI, 15% to 59%; $p = 0.01$) for postoperative complications, with each week of cessation prior to surgery increasing the magnitude of effect by 19%[179]. Cessation programs beginning at least four weeks preoperatively were shown to have a significantly larger treatment effect than shorter trials ($p = 0.04$)[179]. The review also included fifteen observational studies that demonstrated a relative risk reduction of 0.76 (95% CI, 0.69 to 0.84, $p < 0.001$) on total complications, with longer periods (more than four weeks) of cessation producing an average 20% larger reduction in complications than shorter periods. Similar results were reported in a prior meta-analysis of six randomized controlled trials[180].

There are only a handful of randomized smoking cessation studies involving orthopaedic patients. In a study that included two groups of sixty patients undergoing knee or hip replacement, the group of patients who underwent six to eight weeks of smoking cessation intervention prior to their operation had significantly fewer complications requiring treatment as compared with a control group (52% [twenty-seven of fifty-two] as compared with 18% [ten of fifty-six], respectively [$p = 0.003$]), especially with regard to wound complications (31% [sixteen of fifty-two] as compared with 5% [three of fifty-six], respectively [$p = 0.001$]), but no significant effect of smoking reduction (at least 50%) on complications was observed[176]. In another study, which included 117 men and women who were randomized to either a four-week smoking-cessation program or a control group prior to undergoing hernia repair, laparoscopic cholecystectomy, or a hip or knee replacement, postoperative complications (including hematoma, wound infection, seroma, gastrointestinal complication, or urinary tract complication) were reduced from 41% (twenty-two of fifty-four) in the control group to 21% (ten of forty-eight) in the intervention group ($p = 0.03$), with the number needed to treat being five to avoid a complication[177]. Interestingly, an analysis per protocol demonstrated that abstainers (15%) had fewer complications than those who only reduced smoking (35%) or those who continued to smoke (37%), although this was not significant ($p = 0.14$).

In a multicenter, single-blinded controlled trial, 105 smokers with fractures were randomized to either a control group or to six weeks of smoking intervention that was initiated during their hospitalization. The odds of having a complication was 2.51 times higher in the control group than in the intervention group, with the number needed to treat being 5.5 to avoid a complication[178]. A randomized study of seventy-eight

healthy subjects who had experimental incisions made just lateral to the sacrum demonstrated a higher infection rate in smokers, with four weeks of abstinence reducing wound infections to the level of a subject who never smoked[182].

Conclusions

Tobacco smoking has important negative effects on multiple organ systems, including the musculoskeletal system, which increases the risk of injury, illness, and perioperative complications. The musculoskeletal effects include decreased BMD, fracture-healing complications, and wound complications. Perioperative cardiopulmonary complications are increased with smokers. Orthopaedic surgeons should encourage all patients who are contemplating elective procedures to quit smoking four to six weeks in advance of the proposed procedure and should advise them of the serious negative outcomes associated with active smoking in the perioperative period. Abstinence from smoking can be monitored with a urine cotinine test. By reducing smoking, a major burden of economic and emotional costs for the patient will be lessened. ■

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