THE MUSCULOSKELETAL EFFECTS OF SMOKING

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In 1964, the Surgeon General warned the American public of a definite association between smoking and lung cancer.¹⁰⁵ Since this report we have become increasingly aware of other harmful effects, including peripheral and cardiovascular disease as well as other forms of cancers. Although smoking rates have declined, 26 percent of American adults continue to smoke. The individual who smokes not only places him or herself at risk, but also places others in danger through the emission of passive smoke. Society must bear the cost for the smoker's habit, but unlike many risk factors for disease, smoking represents a factor which can be minimized or even eliminated.

Smoking affects every organ system in the human body, including those of the musculoskeletal system. The deleterious effects are dose-related, and at least partially reversible by the cessation of smoking. Unfortunately, smoking usually begins under the age of 21, and frequently continues throughout life.⁷ As the treatment for tobacco-related heart and lung disease becomes more successful, and people who smoke live longer, these musculoskeletal effects will become increasingly evident.

CIGARETTE SMOKE

As a cigarette burns, both tobacco and paper are vaporized, resulting in the emission of more than 4,000 compounds.⁴⁴ The substances are actively inhaled by the smoker in the form of **mainstream smoke**, but are also passively inhaled by the nonsmoker in the form of **side-stream smoke**, as it is emitted from the burning tip. Side-stream smoke is chemically different from mainstream smoke. Since smoke knows no boundary, environmental tobacco smoke (ETS) is unwittingly consumed by smokers and nonsmokers alike.

The active ingredients of cigarette smoke include **nicotine**, the addictive substance, and unfortunately two prominent gases: **carbon monoxide** and **hydrogen cyanide**, among others. Smoke also contains particles of tar and other irritants which are also believed to be carcinogenic.⁶⁶

As each cigarette is smoked, approximately 2 to 3 milligrams of nicotine and 20 to 30 milliliters of carbon monoxide are inhaled by the smoker.⁹⁵ These substances affect every tissue in the human body. The cardiovascular effects of nicotine and carbon monoxide have been studied extensively, and these same substances are believed to affect the musculoskeletal system by the same mechanisms.

NICOTINE

Nicotine is a toxic alkaloid which represents the addictive substance in tobacco smoke. The effect of nicotine is complex since evidence suggests that it acts simultaneously as a ganglionic depressant and stimulant. As the cigarette is smoked, and nicotine is consumed, catecholamine levels rise in the bloodstream^{79 80} which stimulate the heart to increase output, but also causes adrenergic vasoconstriction.^{18 63 111 115} Peripheral vasoconstriction results in a decrease in blood flow to the extremities with a reduction in forearm blood flow and a subsequent decrease in digital blood flow.^{11 90 91} The inhalation of two cigarettes was found to diminish blood flow to the hand by 29 percent.¹⁰⁷

In addition to vasoconstriction, nicotine has a direct effect upon blood coagulation. An increase in platelet adherence results in platelet aggregation with sludging of blood in small vessels, resulting in an overall decrease in microvascular profusion.⁷² Nicotine also results in an increase in fibrinogen levels which increases blood viscosity and induces a state of hypercoagulation.³³

Nicotine also has many endocrine effects. Elevated levels of plasma vasopressin, Bendorphin, ACTH and cortisol have been noted. With high doses of nicotine, growth hormone and prolactin levels also are increased.^{79 92 93}

Evidence also suggests that nicotine exerts a direct effect at the cellular level, resulting in toxicity to the osteoblast, ^{25 30} fibroblast and macrophage.^{95 77} Components of tobacco smoke also have been shown to create damage to the vascular endothelium, leading to the development of atherosclerosis.⁵⁸

CARBON MONOXIDE

Incomplete combustion of paper and tobacco results in the production of carbon monoxide. This toxic gas has an affinity for hemoglobin which is 200 times greater than oxygen and binds preferentially with the hemoglobin molecule to form **carboxyhemoglobin**. The creation of carboxyhemoglobin instead of oxyhemoglobin has two major effects. First, the amount of oxyhemoglobin available for oxygen transport is reduced. Second, the oxygen dissociation curve shifts leftward, so that available oxygen is less able to dissociate from hemoglobin. The end result is tissue hypoxia.^{77 82}

Cigarette smoke contains 2 to 6 percent carbon monoxide. During active smoking, as much as 2 to 15 percent of hemoglobin is converted to carboxyhemoglobin with an

average of 5 percent among smokers.⁴⁴ This results in chronic tissue hypoxia which is entirely unrelated to the presence or absence of nicotine in the cigarette.¹

Chronic exposure to carbon monoxide also results in polycythemia which contributes to the increase in blood viscosity caused by nicotine.⁹ Like nicotine, carbon monoxide increases platelet aggregation^{22 74} and further elevates fibrinogen levels.⁷⁰ These qualities also contribute to increased blood viscosity and eventually to microvascular clotting.^{38 70}

Jensen and Goodson have demonstrated that smoking for 10 minutes results in a reduction of tissue oxygen tension for 1 hour. An individual who smokes one pack of cigarettes per day is tissue hypoxic for 15 to 20 hours each day.⁵²

OTHER SUBSTANCES

The second compound which is prevalent in cigarette smoke is hydrogen cyanide. This noxious gas is detected in significant quantities in the bloodstream of smokers. Its primary effect is at the cellular level, interfering with the enzymatic systems necessary for oxidative metabolism at the tissue level.⁷²

An additional component of tobacco smoke is known as **tar**. This is the aggregate particulate matter after moisture and nicotine are removed. Many components of tar are carcinogenic and a specific fraction, the polyaromatic hydrocarbons, are known to increase the metabolism of a wide variety of drugs by induction of hepatic microsomal enzymes of the p450 system.¹⁰ Patients who are heavy smokers, therefore, may require larger quantities of medications to achieve the desired therapeutic effect, and can develop toxicity to these drugs, when smoking is abruptly discontinued. Only drugs which are metabolized by microsomal enzymes are affected.

EFFECT OF SMOKING UPON BONE

After reaching peak bone mass at the age of 33, human bone loss occurs at a relatively fixed rate approximating 0.5 percent per year in women and 0.3 percent per year in men (Type II osteoporosis). At menopause, due to sudden estrogen deprivation, bone loss accelerates to 2 to 3 percent per year for the next 6 to 10 years (Type I osteoporosis), following which the rate of loss returns to its former, baseline level, 0.5 percent per year.^{20 84}

At the age of 65, or 15 years postmenopause, bone mineral content varies; however most women have lost 33.5 percent of one-third of their bone mass, due to the combined effects of Type I and II osteoporosis. Men have lost 10 percent of bone mineral, due to

Type II osteoporosis. This loss in bone mineral results in skeletal weakness and increased fracture rates in the distal radius, spine and hip. Women are particularly vulnerable, due to this increase in skeletal fragility and the greater likelihood of trauma since the female life span is five years greater than men.

Smoking presents added stress to the skeletal system by accelerating the loss of bone mineral in both men and women.^{45 60 99 100 102} The exact mechanism for this effect has never been determined with certainty. Slender women seem to be affected to a greater degree, ^{14 21} however, body weight alone cannot adequately explain loss of bone mineral.^{35 45 48 55 86 101}

Women who are smokers enter menopause, on the average, two years earlier than nonsmokers⁶ and, according to some investigators, lose bone mineral more rapidly after menopause than nonsmokers.^{45 56} Hopper, in a study of female twins, found evidence of increased bone resorption and high levels of FSH and LH which suggest relative estrogen deficiency.⁴⁸ Several investigators have demonstrated an increase in estrogen degradation.^{21 51 67 65 113 114} Moreover, postmenopausal estrogen therapy is less effective in smokers, and higher doses may be required to achieve the desired result.^{51 55}

Estrogen deficiency, however, does not explain the increase in osteoporosis found among men who smoke. Nicotine has an apparent toxic effect upon the osteoblast³⁰ with a resultant decrease in bone formation.²⁵ Calcitonin resistance has been induced by smoke extracts and has also been hypothesized as a cause for loss of bone mineral.⁴⁶ A decrease in calcium absorption from the gut has also been implicated among smokers.⁵⁶

Studies which investigate the relationship of smoking to loss of bone mineral are frequently confounded by other addictive behaviors. For example, heavy drinkers also tend to be heavy smokers.²⁶ Nevertheless, smoking must be considered an important risk factor for the development of osteoporosis, and the summation of alcohol and nicotine addiction may accelerate bone loss even further. Slemenda believes that for those who both smoke and drink excessively, bone loss is approximately twice that of the normal rate of 0.3 percent to 0.4 percent per year, after age 33. This results in an eventual decrease in bone mass which is a full standard deviation (SD) beyond that which is normally anticipated at age 65. This significant decrease has serious implications for the older population since a decrease in bone density by one standard deviation approximately doubles the rate of fracture.^{99 100}

Hopper and Seeman, in a study of twins, were able to reduce the impact of confounding factors. A significant decrease in bone density was observed in the smoking group with an obvious dose-response relationship. The results indicate that the twin with a 20

pack/year history of smoking developed a 5 to 10 percent greater decrease in bone density in a comparison to the nonsmoking twin.⁴⁸ In vitro studies indicate that a 10 percent decrease in bone mineral confers a threefold increase in rate of fracture.¹⁷ A 10 percent deficit in mineral content represents a decrease in bone density of one full SD⁸⁴ and over a period of 10 years, confers a 44 percent increase in rate of hip fracture.⁷¹

Unfortunately, this increase in skeletal fragility is accompanied by an increase in accident rate. Smokers are 1.5 times more likely to become involved in an automobile collision and 1.4 to 2.5 times more likely to be injured at work.^{76 87} The reasons for this propensity for accident is unclear. General weakness, with poorer balance and impaired neuromuscular performance, has been demonstrated among both active smokers and former smokers.⁷⁶ In another study, smokers had a 4.1 fold increase in risk of tibial shaft fractures. Moreover, the fractures were more comminuted in the smoking population.⁵⁹

BONE HEALING

Smoking affects the rate and quality of bone healing. Animal studies indicate a reduction in the quantity and quality of bone at osteotomy sites.¹⁰⁶ Studies using the Ilizarov device demonstrate that a nonsmoker can make 1 cm of bone in two months, however a smoker requires three months to make 1 cm of bone, with a 90 percent failure of complete bony union at the osteotomy site.¹¹² Fractures of the tibia that occur in smokers also require a longer mean time for clinical union with an increase in the rate of delayed union.⁵⁹ Animal studies have indicated a tendency for bone resorption at fracture ends with subsequent interference in bone healing.⁶²

Arthrodesis is also adversely affected by smoking. In a study of ankle arthrodesis, Cobb found the risk for nonunion in smokers to be 3.75 times that of nonsmoking controls. Brown found a 40 percent rate of pseudarthrosis in lumbar spinal fusion compared to an 8 percent rate in nonsmokers.¹⁸ Hanley and Levy also demonstrated a higher failure rate among smokers in a review of fusions for spondylolisthesis.³⁹

There are many possible explanations for these findings. At the cellular level, nicotine has been found to be toxic to the osteoblast, and may also interfere with calcitonin. Hydrogen cyanide interferes with cellular metabolism and carbon monoxide interferes with oxygen transport. Oxygen levels have been measure at the fusion site, and as predicted, a significant decrease in pO2 among smokers has been demonstrated.¹³ As a result of these and other studies, heavy smoking is now considered to be a relative contraindication for spinal fusion.

WOUND HEALING

Delayed healing of a hand wound in a smoker was initially described by Mosely and Finseth in 1977.⁷² Spinal cord patients who are smokers have a higher incidence of pressure sores and the areas of necrosis are more extensive.⁶¹

Postoperative wound complications in cosmetic procedures is significantly higher in smokers.^{82 83 98} A study comparing the cosmetic results of incisions with smokers and nonsmokers found that the smokers, in general, had inferior cosmetic results.⁹⁶

These results can be analogized to postoperative orthopaedic patients. A higher incidence of wound infection and delayed would healing has been verified in patients undergoing spine surgery.¹⁶ Additional studies are needed to investigate the true impact of smoking upon orthopaedic surgical patients.

Mechanisms for delayed healing include tissue ischemia produced by vasoconstriction, increased platelet adhesives and microvascular clotting, with diminished oxygen transport due to the combined effects of carbon monoxide and nicotine toxicity.⁹⁵ In addition, the catecholamine release in response to nicotine may stimulate the formation of **chalones** or hormones which inhibit epithelialization, and undermine wound repair.⁷³

Nicotine is toxic to fibroblasts and macrophages,⁷⁷ both of which transport healing substances to the wound area. In addition, fibroblasts manufacture collagen which is necessary for scar formation. Hydrogen cyanide can inhibit the enzyme systems required for oxidative metabolism and oxygen transport at the cellular level.⁷²

OSTEONECROSIS

Since the human femoral head is entirely intrascapular, its blood supply is fragile. A variety of conditions can interrupt the flow of blood and result in ischemia and eventual osteonecrosis. These conditions include trauma with tearing of the epiphyseal arteries, arterial thrombosis or arterial embolism due to fat or sickled cells, and obstruction of venous outflow.

Hirota had demonstrated a four-fold increase in the risk of osteonecrosis of the femoral head among smokers.⁴³ Matsuo also found an increase in risk of osteonecrosis among current smokers.⁶⁸ An additional correlation between inhalation of passive smoke and the development of Legg-Calve-Perthes disease has been noted.⁷⁸

The hematologic effects produced by nicotine and carbon monoxide are the probable reason for this condition. These substances result in narrowing of the epiphyseal vessels due to vasospasm and the development of a prothrombotic state with platelet aggregation,⁹⁴ increased plasma viscosity, and elevated fibrinogen levels.⁶⁹ This hypercoagulable state, in conjunction with vascular stasis and endothelial damage leads to microvascular sludging, clotting and eventual interruption of the vascular supply to the femoral head.

LOW BACK PAIN

The association of smoking with back pain remains controversial. Since 80 percent of mankind will develop back pain at some time during life, and since the cause of back pain is multifactorial, direct linkage to smoking is subject to debate.

Smoking has been implicated as a general cause for musculoskeletal pain in a study of 6,681 people in Norway.¹³ Smoking is also correlated with extremity pain, in addition to back pain.¹²

Several investigators have noted a correlation between cigarette smoking and general low back pain.^{4 29 54 64} A dose-response relationship to cigarettes smoked and degree of pain has also been identified.^{25 37} Most authors agree that confounding factors such as genetic predisposition, lifestyle and occupational differences may be operating in these studies. Battie, et al, attempted to isolate the habit of smoking in a study of identical twins who were disconcordant for smoking and found an 18 percent greater incidence of disc degeneration in smokers when compared to nonsmokers. Furthermore, the distribution of disc degeneration was somewhat unusual among smokers, with a higher incidence of disc deterioration in the upper lumbar spine rather than the lower lumbar spine. This pattern suggests that systemic factors in addition to the usual mechanical factors are operating to cause disc degeneration among smokers.⁸

The reasons for the higher incidence of back pain among smokers is theoretical at present. Since smokers have diminished bone density, microfracturing of the vertebral bodies has been proposed.¹⁰³ Repetitive damage due to the transitory increases in intradiscal pressure associated with chronic coughing also has been hypothesized.^{54 75} Malnutrition of the disc due to diminished blood flow and interference with oxygen transport at the cellular level are also potential mechanisms.^{8 37 47} Since smoking impairs fibrinolysis, fibrin deposition which leads to inflammation and scarring also has been implicated.⁵⁰

SMOKING AND ARTHRITIS

Osteoarthritis

Surprisingly, most studies indicate a negative correlation between cigarette smoking and the development of osteoarthritis in weight bearing joints. Two separate studies have found a negative association with osteoarthritis of the knee^{31 88} and one study noted a negative correlation with osteoarthritis of the hip.⁵⁷

Smoking may have a protective effect for the development of osteoarthritis in weight bearing joints and the reasons for the relationship are unclear. A inverse correlation between osteoporosis and osteoarthritis has been identified.^{34 24} Since most studies also indicate an association of osteoporosis among smokers, it is possible that the decrease in bone density associated with smoking may be the important factor. It is interesting to note, however, that smoking does not offer protection from Heberden's Nodes or degenerative osteoarthritis of the distal interphalangeal joints of the fingers.⁴⁰

Rheumatoid Arthritis

Environmental factors are considered important for the development of rheumatoid arthritis. Several authors have noted a significant increase in frequency of rheumatoid arthritis among smokers.^{108 32 41 42 110} Fischer notes that tobacco was introduced to Europe from the New World in 1600. It was not until 1800 that rheumatoid arthritis was initially described in Europe, possibly related to the rise in tobacco use.³²

In an effort to separate environmental factors from genetic factors, Silman investigated twins with rheumatoid arthritis. A strong association between smoking and the development of rheumatoid arthritis was present among both monozygotic and dizygotic twins.⁹⁷ The biological reason for the association of smoking and rheumatoid arthritis remains to be determined.

DUPUYTREN'S CONTRACTURE

The relationship of Dupuytren's Contracture to cigarette smoking has been recognized in the past.³⁶ Other associations include epilepsy, alcoholism, chronic lung disease, trauma,⁴⁹ and diabetes mellitus.²⁷ Smoking results in changes in connective tissue of the hand which ultimately leads to joint stiffness, and contracture of the palmar fascia.²⁸

The biological reason for the proliferation of fibrous tissue which occurs in Dupuytren's Contracture is unknown. With smoking, a significant decrease in blood flow to the hand

has been identified.^{89 90 91 107 111} Following years of smoking, microvascular occlusion is also believed to occur resulting in fibroblastic proliferation and contracture.⁵

REFLEX SYMPATHETIC DYSTROPHY

Reflex sympathetic dystrophy (RSD) is commonly associated with orthopedic trauma, although it also can occur following other problems such as myocardial infarction, cerebrovascular disease and cervical radiculopathy.^{3 81} Stimulation of the sympathetic nervous system has been implicated, with an inappropriate increase in sympathetic tone and secondary vasospasm.

An and others noted a high correlation between smoking and the development of RSD.³ Nicotine stimulates the sympathetic nervous system resulting in a marked increase in levels of epinephrine, and norepinephrine^{20 63 79 80} and a secondary decrease in peripheral blood flow.^{11 90 91 111} This increase in sympathetic tone is believed to predispose the smoker to the development of RSD following orthopaedic trauma.

CONCLUSIONS

Chronic smoking has many consequences, many of which are directed to the musculoskeletal system. Nicotine alone causes vascular constriction, increased platelet adhesiveness, and increased fibrogen levels. At the cellular level, it is toxic to the osteoblast, macrophage and fibroblast. The effects of nicotine are compounded by carbon monoxide which interferes with oxygen transport and further increases blood viscosity, and hydrogen cyanide which interferes with oxidative metabolism. Other substances in tobacco smoke may have additional unrecognized consequences upon smokers and nonsmokers alike.

Smoking is emerging as a powerful risk factor for the development of osteoporosis in women as well as men. Cigarette use leads to the skeletal fragility, and when injury occurs, it also interferes with wound and bone healing. In addition, cigarette smoking represents a risk factor for the development of rheumatoid arthritis, disc degeneration, back pain and pain in general. Due to hemodynamic effects in the upper extremity, tobacco places smokers at increased risk for the development of Dupuytren's Contracture, and reflex sympathetic dystrophy. Similar effects in the hip place the smoker at higher risk for the development of osteonecrosis. Although smoking may have a protective effect for the development of osteoarthritis, the risks of smoking far outweigh any possible benefit.

Cigarette smoking is probably the greatest potentially reversible risk factor in the area of public health, and unlike many risk factors, is totally under individual control.

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