



## ■ BONE FRACTURE

# Tobacco and bone fractures

A REVIEW OF THE FACTS AND ISSUES THAT EVERY ORTHOPAEDIC SURGEON SHOULD KNOW

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## Objectives

The aim of this study was to review the impact of smoking tobacco on the musculoskeletal system, and on bone fractures in particular.

## Methods

English-language publications of human and animal studies categorizing subjects into smokers and nonsmokers were sourced from MEDLINE, The Cochrane Library, and SCOPUS. This review specifically focused on the risk, surgical treatment, and prevention of fracture complications in smokers.

## Results

Smokers have an increased risk of fracture and experience more complications with delayed bone healing, even if they have already stopped smoking, because some adverse effects persist for a prolonged period. Some risks can be reduced during and after surgery by local and general prevention, and smoking cessation is an important factor in lessening this risk. However, if a patient wants to stop smoking at the time of a fracture, the cessation strategies in reducing tobacco use are not easy to implement. The patient should also be warned that using e-cigarettes or other tobaccos does not appear to reduce adverse effects on health.

## Conclusion

The evidence reviewed in this study shows that smoking has a negative effect in terms of the risk and treatment of fractures.

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## Introduction

The smoking of tobacco in the form of cigarettes was popularized in the early decades of the 1900s; by 1945, nearly 75% of men and 25% of women in Europe were smokers.<sup>1</sup> By 1950, studies had appeared in the medical literature linking cigarette smoking to lung cancer,<sup>2-4</sup> and by the 1990s, it was known that smoking causes harm to the entire musculoskeletal system.<sup>5-8</sup> Smoking has a negative impact on bone mineral density (BMD), reducing calcium absorption and lowering levels of vitamin D, changes hormone levels, and reduces body mass.<sup>9-11</sup> Smoking is also associated with a higher risk of bone fracture, slower healing, and nonunion.<sup>12</sup>

In 1939, Ochsner and DeBakey<sup>13</sup> reported on pneumonectomies performed for lung

cancer and proposed that smoking contributed to the development of malignancy, although the tobacco industry insisted that the published statistics were not conclusive.<sup>14</sup> This dismissal of epidemiological evidence was a strategy used repeatedly by the tobacco industry to downplay the consequences of smoking.<sup>1,15</sup> In the end, it was the accumulation of evidence from many sources, rather than a single report, that showed smoking to be an irrefutable cause of lung cancer.<sup>2,3</sup>

Regarding the relationship between tobacco and bone diseases, we have not progressed far beyond the level of evidence demonstrated by Ochsner and DeBakey<sup>13</sup> in 1939 for smoking and lung malignancy. The number of reports on the relationship between tibial fractures and smoking remains

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limited, with only 778 tibial fractures in smokers (between 1993 and 2015) included in the most recent meta-analysis on the subject.<sup>16</sup> The incidence of tibial shaft fractures in the world has been reported to be between 16.9/100 000 and 50.1/100 000 per year.<sup>17,18</sup> The number of smokers is currently estimated to be approximately one billion (i.e. at least 15% of the world population).<sup>19</sup>

The aim of this study was to review the impact of smoking tobacco on the musculoskeletal system, and on bone fractures in particular.

## Materials and Methods

**Analysis and data synthesis.** The search strategy was designed to examine the effects of smoking on bone. The studies involved epidemiological studies and clinical interventions, ranging from conservative treatment, such as cast immobilization, to surgical procedures. In addition, arms of clinical trials comparing different interventions that reported results separately for smokers and nonsmokers were included. The following inclusion criteria were applied: 1) publications written in the English language; 2) human and animal studies; and 3) studies categorizing subjects into at least two groups (smokers and nonsmokers). Articles were excluded if they were not available or were duplicated. Keywords were: “cigarette”, “nicotine”, “tobacco”, “bone”, “delayed union”, and “nonunions”. Three electronic databases were consulted by the lead author (JH): MEDLINE, The Cochrane Library, and SCOPUS.

**Definitions.** Causality: the association between smoking and bone fracture may be confounded by several established risk factors. For example, alcohol abuse is regarded as one of the most important potential confounders because alcohol is also a risk factor for fracture, decreased bone mineral density (BMD), and decreased bone healing. Alcohol abuse is also positively correlated with smoking.<sup>20,21</sup> This bias is present in meta-analyses where data are pooled across various strata, such as smoking status, without considering alcohol as a confounder. For this reason, causality was determined by looking at the range of available evidence, as in chronic disease epidemiology.<sup>22</sup> Every year, lung cancer causes more than 1.6 million deaths resulting from direct tobacco use or from passive smoking.<sup>19,23</sup> Globally, cigarette smoking is responsible for over 80% of all lung cancer cases.<sup>23</sup> Tobacco is recognized as a cause of lung cancer, but not as a cause of fracture or nonunion.

**Strength of association:** this refers first to magnitude of association, and secondly to statistical strength. The larger the association between factors and the greater their statistical significance, the lower the probability that the observations are influenced by bias, chance, confounding factors, or uncontrolled data.

**Temporality:** exposition to a factor needs to precede the disease in order to be considered as a cause. Temporality alone is not a predictor of causality, but no association can

be considered to satisfy criteria for causality when temporality is not fulfilled. For example, 890 000 deaths result each year from exposure to passive smoking;<sup>19,23</sup> however, for influence on bone healing, no results from exposure to second-hand smoke exist at the present time.

**Specificity:** this term refers to the extent to which exposure to a suspected cause can predict the outcome of a disease. Epidemiological and biological factors need to be analyzed and compared. For example, not all cigarette smokers will have cancer, and not all lung cancers are related to smoking cigarettes. However, there is ‘a high degree of specificity’ between tobacco and lung cancer (80% of all lung cancer cases). For nonunion, the relative risk (risk ratio: 1.67) for nonunion in smokers exists,<sup>16</sup> and a certain proportion of nonunions might be related to cigarettes, but this attributes only low specificity to the relationship between nonunion and smoking.

**Analogy, plausibility, and coherence:** all these criteria, when taken together, suppose that the relationship between the cause and the disease does not defy elementary scientific principles. From a biological point of view, it must be in agreement with all experimentally proven biological mechanisms.

**Experiment:** this refers to natural observations that might be considered as ‘experiments’, imitating the conditions of an experiment that is conducted in a defined scientific environment. The outcomes of these natural observations can have the force of a true scientific experiment. An example of a ‘natural observation’ is an evaluation of the consequences of quitting cigarettes. To attribute health improvements to factors other than smoking cessation would require proof of other influences, as well as evidence that continuing smokers also experienced health improvements where this other influence was observed.

**Response-dose gradation:** this refers to an augmented effect (for example, increased frequency of the disease) as a consequence of an augmented dose (longer duration of smoking or increased number of cigarettes). This relationship strongly supports a cause effect, except when a confounder, varying in the same way as the observed dose, has not been identified and could be the cause of the observed association.

**Biological plausibility:** this criterion refers to animal or *in vitro* studies that have addressed mechanisms by which smoking may increase fracture risk. For example, multiple lines of evidence support the biological plausibility of causal relationship of tobacco smoke with delayed healing and with number or functional decrease of mesenchymal stem cells (MSCs).

## Smoking, low bone mineral density, and fractures

**Low bone mineral density.** There is a causal link between smoking and low BMD.<sup>24</sup> This association with low BMD was previously thought to be exclusive to older women;

however, there is now a consensus that smoking is also a risk factor for low BMD and bone loss in men older than 50 years of age.<sup>24</sup> It is important to demonstrate, independently of the normal activities of daily living,<sup>25,26</sup> that smoking leads to low BMD and hip fracture.<sup>27,28</sup> While the majority of BMD variation (60% to 80%) is explained by predetermined factors, such as genetics,<sup>29</sup> the remaining 20% to 40% is attributable to nonmodifiable risk factors, such as age, and modifiable risk factors, such as smoking, which is a long-established contributing risk factor.<sup>30</sup> The biological plausibility of loss of BMD in later life as a consequence of smoking is linked to the effects of nicotine and cadmium of cigarette smoke on bone cells,<sup>31</sup> and to the fact that the BMD of a smoker may also be altered through decreased absorption of calcium and vitamin D,<sup>32</sup> as well as a modified function of some hormones.<sup>33</sup> Smoking also affects oestrogen levels and the effectiveness of hormonal replacement therapy.<sup>33,34</sup> The United States Department of Health and Human Services report concluded in 2004 that smoking causes low BMD in menopausal women.<sup>35</sup> Each year, BMD decreases by an extra 2% in smokers compared with nonsmokers, prompting a distinction of about 6% by the age of 80 years.<sup>36</sup> A review of 40 000 patients on the effect of smoking on BMD demonstrated that smoking has a more negative impact on bone mass for men than for women.<sup>35,37</sup> While considerable evidence associates tobacco use with low bone mass and increased fracture risk in older people,<sup>28,36</sup> research has emerged more recently with strength of association linking smoking at a young age with unfavourable bone geometry and density, as well as a reduction in peak bone mass.<sup>38,39</sup> A Belgian study of 677 healthy men and women at the age of peak bone mass (25 to 45 years of age) found that patients who start smoking early (16 years of age or younger) had decreased BMD, a decreased cortical bone area at the tibia, and decreased trabecular and cortical BMD at the radius compared with smokers who started smoking after 16 years of age, as well as compared with nonsmokers.<sup>38</sup> Furthermore, in a large population of more than 1000 young Swedish men (mean age 18.9 years (SD 0.6)), significantly lower BMD of the total body, lumbar spine, femoral neck, and trochanter was observed in current smokers (at least one cigarette per day) compared with nonsmokers.<sup>39</sup> The authors concluded that the impact of smoking on bone mass may occur relatively quickly, due to the fact that the mean duration of smoking was 4.1 years (SD 2.1).<sup>39</sup>

**Fractures.** Hip and spine: smoking decreases BMD and raises the frequency of osteoporosis. Therefore, an observation of augmented risk of bone fractures might be expected. An augmented frequency of spine fracture by 32% in men and 13% in women has been demonstrated.<sup>35</sup> For hip fractures, the increased risk caused by cigarettes was projected to reach 40% in men and 31% in women.<sup>28,35-37</sup> The burden of hip fractures should not

be underestimated. Mortality rates as high as 20% to 24% have been reported in the year after a hip fracture,<sup>26,40</sup> with an increased risk of death persisting for up to five years afterwards.<sup>41</sup> It has been reported that a 50-year-old woman has an equal chance of dying from a hip fracture as from breast cancer.<sup>42</sup>

Any fracture: a fracture meta-analysis conducted by Kanis et al<sup>28</sup> reported results of 60 000 people, and observed a 25% increased risk for any fracture, as well as an 84% increased risk for hip fracture, among the smokers. This analysis suggests that there is strength of association between smoking and the risk of any fracture, probably independently of its effect on BMD. When adjusted for body mass index (BMI), BMD, and age, a 12% significant increase in any fracture risk was still observed with use of cigarettes. This effect in smokers could be related to poor physical function. In addition, self-reported fractures described in a study by Taes et al<sup>38</sup> had a higher prevalence in early and current cigarette smokers, and this remained significant after exclusion of child fractures and after adjustment for alcohol use, weight, age, and education. In the United Kingdom,<sup>28,43</sup> a systematic review comprising nearly 60 000 individuals concluded that current smokers were at a significantly increased risk of any fracture compared with nonsmokers, and that this risk was significantly higher in men than in women.

### Reducing the risk of fracture in smokers

**Risks associated with smoking in the perioperative period.** Smoking is a risk factor for heart disease and bronchopulmonary disease. A smoker with heart failure or with bronchitis has an increased risk of perioperative mortality, which, while not directly related to smoking, is linked to each of these diseases.<sup>44-46</sup> Smoking increases the concentration of carbon monoxide (CO) and reduces the blood's oxygen transport by haemoglobin (Hb). Smokers have a HbCO level of 7%, which can exceed 15% at the end of the day in some heavy smokers, and several days of detoxification are necessary before reaching undetectable levels in the blood.<sup>47</sup> This decrease in oxygen transport may be related to the ST segment depression on the electrocardiogram when the exhaled CO exceeds 35 ppm. Therefore, smokers have to receive oxygen supplementation for a longer time following surgery compared with nonsmokers.

**Regional risk: vascularization and tourniquet use.** Smoking is a cause of atherosclerotic peripheral arterial disease (PAD). There is a solid dose-response connection between the quantity of cigarettes consumed and the probability of developing PAD even after adjustment for other risk factors.<sup>35</sup> It has also been demonstrated that occasional but regular smoking (more than one pack per week, over a time period of more than one year) is linked with both acute and chronic alteration of arterial function in healthy

young people.<sup>48</sup> Likewise, an investigation into the impact of long-term smoking on arterial stiffness among young smokers (mean age 24.3 years (SD 2.4)) compared with nonsmokers (mean age 20.2 years (SD 1.3)) found significantly higher arterial rigidity among the smokers.<sup>49</sup> Tobacco consumption at a young age, particularly cigarette smoking, is highly linked to thromboangiitis obliterans (Buerger's disease), a recurrent inflammatory, nonatherosclerotic vaso-occlusive disease.<sup>50</sup> Typically, this specific complication of smoking tobacco leads to progressive inflammation and thrombosis of arteries of the limbs, and also leads to ulcers and necrosis because of vascular ischaemia.<sup>51</sup>

These PAD patients have an increased risk of complications when arterial tourniquets are used. Patients who had previous vascular surgery have a high risk of arterial occlusion when tourniquets are applied to the limb. Similarly, while risks with tourniquet are low in healthy patients with a short procedure, they are much higher in elderly patients with comorbidities such as trauma and peripheral vascular disease. Long operation times and high tourniquet pressures are also associated with high risk. Therefore, the risks and benefits should be assessed for each patient, considering their smoking status, before deciding whether to use a tourniquet. Kam et al<sup>52</sup> suggested that mechanical pressure due to the tourniquet may be the cause of traumatism on atheromatous vessels, with fractures of the plaque and lack of blood flow as a result of thrombosis in atherosclerotic vessels. The tourniquet should be avoided in patients with poor capillary return, absent distal pulses, calcified vessels, or previous vascular surgery on the involved limb.

### Local risk: skin, bone fixation, and prevention of infection

**Skin incision.** There is a strong association between smoking and delayed wound healing after surgery.<sup>53</sup> The risk of complications such as infection, skin dehiscence, and erosion (destruction of tissue surfaces) is increased. To avoid these wound healing complications, one should consider minimally invasive surgery.

Psoriasis lesions should be avoided at the site of incision. Smoking is a risk factor for psoriasis, an autoimmune pathology characterized by plaque psoriasis present on the surface of the skin.<sup>54,55</sup> The biological plausibility of an association between smoking and psoriasis is that smoking causes inflammatory reactions by decreasing immune cell processes. Furthermore, nicotine impairs the function of T lymphocytes by decreasing their calcium reserves.<sup>56</sup> Palmoplantar pustulosis, confined to the palms of the hands and the soles of the feet, is a form of psoriasis strongly correlated with tobacco; 95% of these patients are smokers.<sup>54,55</sup> Palmoplantar pustulosis is therefore a specific complication of smoking and should be diagnosed before treating hand or foot fractures.

**Fracture fixation.** Alternate or supplemental fixation that provides greater strength to the fracture can offset the low bone stability of the callus (due to reduced bone mineralization and collagen synthesis) observed during the first weeks in smokers. Smokers have lower calcium absorption rates.<sup>57</sup> Concerning the synthesis of collagen, nicotine administration in rabbits lowered the levels of collagen types I and II.<sup>58</sup> Nicotine also decreased callus formation and bone stability in rabbits.<sup>59</sup> As a result, bone instability may appear at the site of the callus. In an experiment of closed tibial fracture in a mouse, exposure to cigarette smoke delayed chondrogenesis during healing.<sup>60</sup> Cigarette smoking also seems to negatively impact endochondral ossification.<sup>60</sup> This may be related to smoking-induced hypoxia, which alters cartilaginous callus formation.<sup>60</sup> As a result, calcium supplementation and mode of fixation according to the site of fracture can be discussed in some patients; even if plaster has no risk of delayed wound healing, it is not the best fixation.<sup>61</sup> When plates are used, locked plates should be recommended.<sup>62,63</sup>

**Flaps for covering open fractures have a higher risk of necrosis.** Due to the risks of delayed wound healing, open fractures in smokers should be treated with external fixation.<sup>64</sup> Complications associated with smoking are particularly problematic after flaps performed for fractures in orthopaedic surgery. Hwang et al<sup>65</sup> analyzed the association between smoking and flap survival in 113 papers. They found that postoperative complications such as flap necrosis, haematoma, and fat necrosis occurred significantly more frequently in smokers than in nonsmokers. The flap loss rate was higher in smokers who were abstinent for 24 hours postoperatively than in nonsmokers. The flap loss rate was significantly lower in smokers who were abstinent for one week postoperatively than in those who were abstinent for 24 hours postoperatively. Thus, it is suggested that a postoperative abstinence period of at least one week is necessary for smokers who undergo a flap operation.

**Risk of infection is higher in smokers.** Inhalation of the mixture of combustion components of tobacco has adverse consequences on the immune system,<sup>66</sup> both at a local site and throughout the entire body. As a consequence, smokers are at an increased risk of infections.<sup>67,68</sup> Smoking promotes infection of surgical wounds. Tobacco smoke contains more than 4000 active components. Nicotine and CO are the principal substances predisposing to wound infection. CO restricts the flow of oxygen to the tissues by the inhibition of binding sites for Hb. Nicotine causes vasoconstriction by increasing the production of thromboxane A2 and catecholamines, and by decreasing the secretion of prostaglandin I2. Other components of cigarettes induce a reduced deformability of erythrocyte, which is associated with lesions of the endothelium that block repair processes. As a result, this maintains hypoxia and bacterial growth at the surgical site.<sup>69</sup>

## Medical and surgical complications of fractures in smokers

**Risk of delayed union.** There is increasing evidence from both observational and experimental studies that smoking delays bone healing (union) after fracture or surgery.<sup>70-72</sup> This risk could be related to the risk of each of the complications described previously in smokers. Therefore, at present there is no causal demonstration that delayed union is directly linked to smoking, but there is strength of association in clinical reports and biological plausibility in animal studies.<sup>73</sup>

**Clinical reports:** the effect of smoking is more apparent in open fractures. Adams et al<sup>74</sup> remarked that patients with open and high-grade open fractures needed significantly more time to heal if they were smokers (32.3 weeks for smokers vs 27.8 weeks for nonsmokers). Harvey et al<sup>75</sup> confirmed these observations in a report concerning 105 patients with 110 open tibial fractures. In a study of 114 diaphyseal long bone fractures, Hernigou and Schuind<sup>70</sup> demonstrated that smoking was a risk factor of nonunion regardless of the open or closed nature of the fracture. When risks factors were cumulated, the nonunion rate increased. A key difference was also observed for infection: a study of 118 patients presenting open tibial fractures showed a high incidence of osteitis if the patient was a smoker (27% vs 9% for nonsmokers).<sup>76</sup> Nicotine hinders blood flow by increasing the release of catecholamines from the central nervous system, which activates vasoconstriction.<sup>77</sup>

**Animal studies:** CO impairs the oxygenation of tissues by binding Hb and displacing molecules of oxygen. As a result, smoking one pack of cigarettes per day might cause a permanent tissue hypoxia.<sup>76</sup> Nicotine is also known to affect angiogenesis of bone grafts in animals.<sup>78</sup> Microvascularization, on the other hand, increased with the administration of nicotine in a model of rabbit osteogenesis. However, this phenomenon occurred without any increase in blood flow.<sup>79</sup> Another important growth factor for revascularization, the vascular endothelial growth factor (VEGF), decreases when rabbits are administered parenteral nicotine.<sup>57</sup> The expression of transforming growth factor  $\beta$  (TGF- $\beta$ ) may detect downregulation of this process, shown by significantly reduced TGF- $\beta$  serum levels during the fourth week after injury in patients with impaired fracture healing.<sup>80</sup> This may be due to hypoxia associated with cigarette smoke, but it may also be related to nicotine, by decrease of TGF- $\beta$  mRNA in rabbits.<sup>81</sup>

**Smoking increases the risk of nonunion and subsequent bone grafting.** Most studies concerning the effect of smoking on fracture healing involve tibial fractures. Researchers generally agree that smoking is associated with higher rates of nonunion both for the upper and lower limb, regardless of the method of treatment (plaster, plate and screws, nail, or external fixation).<sup>70,82-88</sup>

Interestingly, there is no recommendation for the treatment of nonunion in smokers, except cessation of smoking before surgery. However, given the fact that smokers have an increased risk of infection<sup>67,68</sup> and a decreased number of MSCs,<sup>89-91</sup> new technologies should be discussed in these patients for the treatment of nonunion. Local transplantation of bone marrow concentrated granulocyte precursors<sup>92,93</sup> can be used to protect the bone graft in case of infection. Autologous transplantation of MSCs has become an important strategy in nonunion therapy and concentrated bone marrow allows a high number of stem cells to be percutaneously injected.<sup>94,95</sup> Autologous, expanded, and bone marrow-derived mesenchymal stromal cells associated with biphasic calcium phosphate biomaterials<sup>96,97</sup> can be used with success when a large defect requires open surgery.

**Drug interactions in smokers.** Smoking modifies the action of various drugs. Practitioners should know about these interactions when medications are prescribed and also when patients stop using cigarettes, as dosages may need to be revised.<sup>98</sup> Drug interactions are divided into two groups: 1) pharmacokinetic interactions (PKIs) occur when cigarette smoke impairs a drug's metabolism; and 2) pharmacodynamic interactions (PDIs) occur when the physiological effects of cigarette smoke change the physiological effects of the drug.<sup>99,100</sup> The PKIs include augmentation of metabolism of caffeine, heparin, warfarin, theophylline, antipsychotic drugs, and benzodiazepines. A review of the interaction between smoking and anti-vitamin K (AVK) found that smoking increased AVK dosage requirements by 12%.<sup>101</sup> Although it is hard to know which of the estimated 4800 compounds in cigarette smoke is responsible for these interactions, polycyclic aromatic hydrocarbons are suspected. These hydrocarbons activate liver cytochromes and thereby hasten the clearance of any drugs for which their metabolism requires these enzymes.<sup>99,100</sup> The PDIs also produce a reduced response to corticosteroids in asthmatic smokers,<sup>102</sup> a decreased effect of benzodiazepines (possibly due to the stimulant effects of nicotine), and a slowed absorption of subcutaneous insulin (possibly due to decreased blood flow to the skin, mediated by nicotine).

**Is vitamin D supplementation useful in smokers?** Hypovitaminosis D is globally prevalent in smokers and is probably due to skin ageing, which is affected by smoking, regardless of sun exposure or age. Alteration in skin colour and increased wrinkling have also been connected to the use of cigarettes,<sup>103-107</sup> as has loss of elasticity (elastosis) in the skin with degeneration of the connective tissue.<sup>108</sup> Smokers appear to be up to 4.7 years older than nonsmokers of the same age.<sup>109</sup> Studies of twins have confirmed this observation.<sup>110,111</sup> As production of vitamin D is correlated with skin function, smokers have hypovitaminosis D.<sup>112,113</sup> Although it is well established that vitamin D plays an important role in bone

metabolism, its role in acute fracture healing is less clear. Experimental studies in animals<sup>114,115</sup> have suggested that vitamin D may have a positive impact on fracture healing. Regardless of these experimental data, there is controversy over the significance of hypovitaminosis D and how to detect and treat this deficiency in the fracture population.<sup>116</sup>

**A low-risk, high-gain therapy to prevent delayed union.** Vitamin D has been found to influence fracture healing positively<sup>117</sup> and to reduce the risk of stress fractures.<sup>118</sup> Therefore, given the high prevalence of hypovitaminosis D in fracture populations of smokers, and considering the risk of delayed union and nonunion, the assessment of hypovitaminosis D and the prescription of vitamin D in fracture smoker patients should be discussed. In a survey of practitioners,<sup>119</sup> approximately two-thirds of all respondents indicated that they routinely prescribe vitamin D for ‘fragility’ fracture patients (including smokers with fractures). This suggests that some surgeons believe it is more cost-effective to treat all patients rather than test and treat those with a vitamin D deficiency. This could be the case for smokers.

**A low-cost, high-reward therapy to prevent infection in smokers.** Fractures in smokers can be compromised by infection. Could infection prevention be as simple as taking a vitamin D supplement? There is no clinical evidence of the efficiency of vitamin D in preventing infection in smokers, but there is a biological plausibility that it could be efficient at a low cost. The study by Hegde et al<sup>120</sup> suggests that it might help. The authors investigated vitamin D supplementation by using a model of infection in which mice received a stainless-steel implant followed by inoculation with *Staphylococcus aureus*. The results essentially showed that vitamin D rescue treatment reduced bacterial burden and neutrophil infiltration by increasing the macrophage activity. The epidemiological observations may be directly linked to the well-established fact that vitamin D is necessary for normal macrophage activity and inflammatory responses.<sup>121</sup> It remains to be seen whether the beneficial effects of vitamin D are translatable to smokers. Since vitamin D is relatively harmless, this strategy could be considered ‘low risk and high reward’.<sup>122</sup>

## Discrimination against patients who smoke

**Impact of smoking cessation on fracture healing after treatment of acute fracture.** Cessation of smoking is often difficult to implement in the postoperative period after treatment of acute fractures. Even with cessation, some of the consequences appear to continue for decades afterwards.

After cessation, CO and nicotine levels decline rapidly in the body. Nicotine drops to a low level within a few hours, and most of the metabolites of nicotine are eliminated after one week.<sup>123,124</sup> Within two days, the CO level

in the blood decreases. After two months, blood viscosity and blood flow are improved in the limbs. After six months, improvement of the immune system occurs.<sup>125</sup> Therefore, the bone biology alteration that impairs fracture healing can persist in smokers a long time after they have stopped smoking. It should be noted that investigations into the effectiveness of fracture healing after smoking cessation are based on patient reports and thus may be biased. Therefore, there is no scientific evidence that stopping smoking after a fracture can improve healing.

However, it is necessary to explain to the patient that quitting smoking can lead to immediate benefits. There are also long-term health benefits for women and men, whatever their age; the risk of diseases related to cigarette smoking is reduced, with an overall improvement in health. There was strong evidence for this benefit outcome when a 50-year follow-up study of 34 000 British male doctors (started in 1951) reported the severe impact of the number of years when smoking on health and eventual mortality.<sup>4,126,127</sup> Quitting cigarette smoking at the age of 50 years decreased the risk of smoking-related death two-fold, and cessation by the age of 30 years avoided all the risks. Stopping at the ages of 60 years, 50 years, 40 years, or 30 years resulted in gains of approximately three years, six years, nine years, or ten years of life survival, respectively.

The patient should be made aware that there is a biologically plausible relationship between tobacco smoke and delayed healing, as well as a decrease in the number or functional activity of MSCs. Recent studies investigating the impact of nicotine on human adult stem cells found a reduced proliferation of cultured human MSCs in the presence of nicotine.<sup>90,91</sup> van Adrichem et al<sup>128</sup> measured blood flow in the thumb with laser Doppler in smokers and non-smokers. After smoking a single cigarette, vasoconstriction occurred for 90 minutes, decreasing the blood flow by 24%. Smoking a second cigarette had an additive effect, decreasing the flow by a further 29%, while a smoking habit of one pack per day induced a hypoxic state for a 24-hour period.<sup>129</sup> In addition, the blood that reaches the tissues is less effective, as CO from smoking reduces the oxygen-carrying capacity of red blood cells, while hydrogen cyanide impedes cellular oxidative metabolism.<sup>130</sup>

Molecular pathways have also been examined in smokers. In patients with compromised bone healing, Chassanidis et al<sup>131</sup> carried out a retrospective study and reported that overall bone morphogenetic protein (BMP) expression decreased in smokers with fractures; specifically, BMP-2 and BMP-6 expression was lower in smokers. Moghaddam et al<sup>132</sup> demonstrated that TGF- $\beta$ 1 levels, a possible marker of fracture healing, were decreased in patients who smoked, at four weeks following long bone injuries compared with nonsmokers.

The dose-response gradient is complex. All the improvements in health outcomes related to cigarette

smoking have demonstrated a dose-response relationship. However, it is not certain whether decreasing the number of cigarettes smoked per day is sufficient to improve bone healing. An improvement in health or lifespan does not appear noticeable among smokers who cut down on a long-term basis.<sup>133</sup> This is perhaps because smokers continue to seek the same level of nicotine by inhaling more deeply. Thus, the reduction in the number of cigarettes smoked may not lead to a reduction of toxins.

The effect of transdermal nicotine, as a replacement for smoking, on fracture healing is unknown. Donigan et al<sup>134</sup> undertook an animal study on the effects of transdermal nicotine on fracture healing as an initial step in determining whether nicotine replacement therapy would be helpful in lowering the risk of delayed union or nonunion in smokers with fractures. Some *in vivo* animal studies<sup>58,135-138</sup> have indicated that nicotine alone may not inhibit fracture healing. However, nicotine in humans induces vasoconstriction by the production of catecholamines, which may have an adverse effect on healing.

**Impact of smoking cessation on fracture healing before treatment of nonunion.** In cases of nonunion, the problem is different, since the surgeon has the option of not performing elective surgery until the patient stops smoking. Several studies have shown that the failure rate of treatment of nonunion is greater in patients who smoke.<sup>139-141</sup> Many hospitals, communities, and even health insurance companies sponsor smoking cessation programmes that educate the patient in the many adverse risks of smoking. Such programmes should include a discussion of the risks of surgery associated with smoking. Currently, there are no specific criteria to suggest how long the surgeon should wait after smoking cessation before performing surgery. A minimum of 24 hours is recommended, based on the time it takes to clear CO from the blood and return the carboxyhaemoglobin to normal. The surgeon could opt to wait one week, based on the half-life of free radicals and thrombotic components in tobacco, as well as the fact that nicotine can impair the wound healing of incisions for up to ten days. A meta-analysis by Mills et al<sup>142</sup> reviewed data from randomized trials and observational studies that had compared postoperative complications in smokers and patients who quit smoking before surgery. The analysis found that smoking cessation decreases postoperative complications. In randomized trials, complications were reduced by about 40%. The review found that the longer the period of preoperative smoking cessation, the greater the reduction in complications. Encouraging patients to quit smoking several weeks prior to surgery would therefore be another possibility. While acute fracture itself is not predictable, the modification of risk factors arguably is beneficial.

**Associated negative effect as part of nicotine withdrawal.** While the long-term benefits of cessation are

not discussed, stopping smoking is linked with a number of troublesome short-term complications. Smokers with a history of depression tend to have higher levels of nicotine reliance and have more serious and prolonged withdrawal episodes, with a more negative mood. Additionally, smoking cessation tends to result in increased weight but the extent and duration of this effect are uncertain.<sup>143</sup> The mean weight is about 3 kg to 4 kg less in smokers compared with nonsmokers. The weight difference, however, is further complicated by the finding that despite their lower weight and body mass index (BMI), smokers have a greater waist-to-hip ratio than nonsmokers.<sup>143</sup> The medical advantages of smoking cessation far exceed the health risk from extra body weight, unless the weight gain is substantial. Despite this, fear of weight gain is a significant cause preventing quitting and provoking recidivism in smokers.

## Discussion

**Delivery of lower levels of nicotine, CO, and tar: efficient or not?** Following evidence linking smoking with cancer, tobacco companies have experimented with changes to their products. These have included the addition of filters and ventilation holes with tiny perforations placed around the mouth piece, in the hope of decreasing the delivery of nicotine, CO, and tar to the smoker. However, such 'lower-delivery' cigarettes do not seem to be a less dangerous form of tobacco.<sup>144</sup> Since addicted smokers have to maintain a level of nicotine, they compensate for the delivery of low levels by altering their pattern of inhalation; they also increase the number of cigarettes per day, and may block the perforation holes around the filter.<sup>145</sup>

**Smoking other substances.** Even cigarettes without tobacco or nicotine may produce other toxic substances, such as carcinogens.<sup>144</sup> For example, exposure of human lung cells to the smoke of tobacco- and nicotine-free cigarettes (lettuce and herbal extracts) causes DNA damage, as demonstrated in recent research.<sup>144</sup> Smoking tobacco-free and nicotine-free cigarettes has been shown to be as hazardous as smoking cigarettes that do include these substances. In a study by Gan et al,<sup>146</sup> biomarkers were analyzed from urine samples provided by 135 herbal smokers and 143 regular smokers. No difference was detected and herbal cigarettes did not deliver fewer carcinogens than regular cigarettes.<sup>146</sup> If these cigarettes are not better for lung cells, the biological plausibility that these cigarettes might be better for bone cells is very low.

Bidi cigarettes<sup>147</sup> are hand-rolled cigarettes made with sundried tobacco flakes rolled up in a dried tendu or temburni leaf (from plants of Asia). They are unflavoured or flavoured with a sweet or fruit essence (e.g. mango, chocolate, and cherry). Bidi use is prevalent in Bangladesh, India, Nepal, Pakistan, and the Maldives. A bidi contains

three to five times the nicotine of a regular cigarette, with the same risk for nicotine addiction as standard cigarettes.

**E-cigarette use does not change blood nicotine level.** In this review, we have used the term ‘e-cigarette’ for a range of products, which includes ‘e-cigarettes’, ‘e-cigs’, ‘cigalikes’, ‘e-hookahs’, ‘mods’, ‘vape pens’, ‘vapes’, and ‘tank systems’. Their health effects can be considered under those due to aerosolized nicotine and those due to the potentially harmful doses of heated and aerosolized constituents of e-cigarette liquids, including solvents, flavourants, and toxicants. These are not completely understood and there is a paucity of evidence of their effect on bone.

For nicotine, the risk of using e-cigarettes is the same as that of using tobacco; blood nicotine levels in e-cigarette users are comparable to, or higher than, levels in smokers of conventional cigarettes.<sup>148</sup> The concentration of liquid nicotine in the e-cigarette is only one factor that influences the plasma nicotine levels. When the device type and liquid dose were held constant in a controlled session, plasma nicotine concentrations in different people varied considerably (0.8 ng/ml to 8.5 ng/ml). This variation was most likely due to the manner in which the users inhaled when using e-cigarettes.<sup>149</sup> Adult cigarette smokers given an e-cigarette appeared to show a greater ability to extract nicotine from their device after four weeks of use.<sup>150</sup>

In conclusion, the deleterious effects of smoking on bone are now well known (decreased BMD, increased rate of fracture and nonunion, and increased perioperative complications). After a fracture, the patient should stop smoking even if there is a lack of scientific evidence about the benefits to bone union. However, alternatives to smoking, such as nicotine patches and e-cigarettes, seem to be a safer option after a fracture.

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