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REVIEW ARTICLE

Review of the role of cigarette smoking in diabetic foot

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ABSTRACT

Diabetic foot ulceration has been a serious issue over the past decades in Asia, causing economic and social problems. Therefore, it is important to identify and reduce the risk factors of diabetic foot. Cigarette smoking has been reported to be associated with diabetes and its macrovascular complications, but the relationship between smoking and diabetic foot ulcers is still unclear. In the present review, we summarize the effects of cigarette smoking on diabetic foot ulcers with respect to peripheral neuropathy, vascular alterations and wound healing. One underlying mechanism of these impacts might be the smoking-induced oxidative stress inside the cells. At the end of this review, the current mainstream therapies for smoking cessation are also outlined. We believe that it is urgent for all diabetic patients to quit smoking so as to reduce their chances of developing foot ulcers and to improve the prognosis of diabetic foot ulcers.

INTRODUCTION

As the global prevalence of diabetes is increasing, diabetic foot ulcers have become one common complication of diabetes, with a lifetime incidence 25% in diabetes patients[1], posing enormous medical, social and economic burden. The situation of diabetic foot ulcerations in Asia remains severe. Amputations are common and specialist foot-care clinics are rare[2]. As a result, the diabetes foot epidemic is rapidly emerging, and the prevalence of diabetic foot is reported to increase to approximately 5.5%[3]. It is urgent for clinical practitioners to use systemic methods, including identification and reduction of risk factors, optimization of metabolic control (e.g., blood glucose, blood pressure and cholesterol), patient podiatric education and so on, to avoid the onset of foot ulcerations, and reduce limb amputation rate and related mortality. As is reported, the risk factors for diabetic foot include foot insensitivity to the monofilament, past history of amputation or foot ulcer, insulin use, Charcot deformity, reduced skin oxygenation and foot perfusion, increased bodyweight, poor vision, hammer/claw toe deformity, cigarette smoking and so on[4]. Cigarette smoking has been decreasing, but still remains a serious global problem[5]. According to the global data, east Asian countries have accounted for the highest percentage (38%) among smokers all over the world[6]. This risk factor correlates with many chronic diseases, such as cardiovascular disease, diabetes, cancer and lung diseases. The associations between cigarette smoking and risks of pre-diabetes, gestational diabetes, type 2 diabetes, coronary artery disease or even mortality in diabetes patients have been confirmed by many studies[7–12]. Active smokers had a much lower mean age at amputation compared with non-smokers[13], and smoking cessation improved amputation-free survival in diabetes patients[14]. Although secondhand smoke was not significantly associated with peripheral artery disease, exposure to passive smoke is independently associated with the risk of type 2 diabetes[15]. The aforementioned all indicate a role of cigarette smoking in diabetic foot. However, how smoking affects the development of diabetic foot ulcers is still not fully understood. Here, we provide a review in regard to the role of cigarette smoking in the development of diabetic foot ulcers and explore to what extent smoking might affect diabetes patients with foot complications.

We declare that the protocol for the project has been approved by the ethics committee of Mingci Cardiovascular Hospital, and that it conforms to the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013).

SMOKING AND DIABETIC PERIPHERAL NEUROPATHY

Diabetic peripheral neuropathy is one of the most common complications in diabetic foot ulcers, accounting for approximately 30% in diabetes patients, and >50% in type 2 diabetes patients aged >60 years[16,17]. The presence of peripheral neuropathy is found in 78% of patients with foot ulcerations[18]. There are many types of nerve injury in diabetic patients,

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including distal symmetrical polyneuropathy, small-fiber predominant neuropathy, autonomic neuropathy, diabetic amyotrophy, mononeuritis multiplex and so on, among which distal symmetrical polyneuropathy affects the longest nerve fibers first, and small-fiber sensory neuropathy mainly affects pain and temperature sensations, both closely related to the onset of foot ulceration[19,20]. The pathology of diabetic neuropathy includes axonal degeneration, demyelination of the nerve fibers, proliferation of Schwann cells, remyelination, hypertrophy of the basal lamina and so on[20]. The distal symmetrical sensory loss is often the first component in the pathway to foot ulceration, and the inability to feel pain in the case of trauma might subsequently facilitate chronic plantar ulcers to grow[18]. In addition, diabetic autonomic neuropathy causes arteriovenous shunting, neuropathic edema and dry skin in the foot. Motor neuropathy is named "claw foot," and characterized by clawing of the toes and plantar flexion of the metatarsal heads. These autonomic and motor neural alterations are all common causes of callus and ulceration formation[18].

Mechanisms of Diabetic Peripheral Neuropathy

Oxidative stress is believed to be the ultimate mechanism of cellular damage in diabetic neuropathy. It is characterized by high levels of sustained generation of reactive oxygen species (ROS), including ozone, superoxide, hydrogen peroxide, singlet oxygen and organic peroxides in cells[21,22]. The nervous system is especially vulnerable to oxidative damage[23]. Hyperglycemia, hyperlipidemia and impaired insulin sensitivity could activate various signaling pathways leading to oxidative stress in nerve fibers. Excessive ROS then causes demyelination and axon damage[24], leading to diabetic neuropathy[19].

Effects of Cigarette Smoking on Diabetic Peripheral Neuropathy

Cigarette smoke might exacerbate diabetic neuropathy partly through the mechanism of oxidative stress. Cigarette smoking has been confirmed an independent risk factor for diabetic neuropathy[25]. As a source of free radicals and oxidants, cigarette smoke could induce cellular oxidative stress in many organs, including the nervous system and blood vessels, leading to cellular damage and even apoptosis (Figure 1)[26,27].

In vitro and *in vivo* evidence shows that cigarette smoke contains "glycotoxins." These glycotoxins are highly reactive glycation products that can rapidly induce advanced glycation end-products (AGE) formation outside the cells[28–30]. The increased modified proteins and lipids in the circulation of smokers bind to the receptor for AGE, which activates nicotinamide adenine dinucleotide phosphate oxidase and expression of pro-inflammatory cytokines and chemokines, inducing oxidative stress. The excessive ROS caused by cigarette smoking results in the production of nitric oxide synthase and an overload of glutamate in the synapses, and the consequent influx of Ca^{2+} leads to mitochondrial dysfunction, deoxyribonucleic acid damage, inflammation and even apoptosis[31–33].

In addition, cigarette smoking also worsens neuropathy by inducing insulin resistance. Smoking is a risk factor for impaired insulin secretion, and chronic cigarette smokers are insulin resistant and hyperinsulinemic[34]. The increased insulin receptor substrate-1^{ser636} phosphorylation in smokers could return to normal after smoking cessation. This effect might partly come from nicotine through the mechanistic target of rapamycin pathway in skeletal muscle cells[35]. In adipocytes, another important cell type in insulin resistance, nicotine was proved to activate adenosine monophosphate-activated protein kinase α2, increasing circulating free fatty acid and inducing insulin resistance[36]. In neurons, nicotine-derived nitrosamine ketone could inhibit the insulin receptor and Akt pathway, leading to loss of insulin-mediated neurotropism and neuronal dysfunction[37].

Cigarette smoking also inhibits the NF-E2-related factor 2–anti-oxidant responsive element (Nrf2-ARE) pathway[38,39]. Nrf2 is a transcription factor recognized as the master regulator of the cellular response to oxidants, and upregulates the expression of the ARE-regulated genes in various cell types. When smoking occurs, the anti-oxidative effects exerted by the Nrf2-ARE pathway are weakened, exposing astrocytes and neurons to more damage, including oxidative glutamate toxicity and calcium disturbance[40].

SMOKING AND DIABETIC VASCULAR DISEASE

Diabetic vascular disease has been found in approximately 30% of patients with foot ulcers, and includes macrovascular and microvascular disease.

In peripheral arterial disease, mechanisms of atherosclerosis formation have been reported by numerous studies[41–44]. Severe atherosclerotic plaques in peripheral arteries result in ischemia in the foot tissues, resulting in tissue loss and slowness of the wound healing process[18,45]. Smoking, as a very important risk factor, is closely related to the development of vascular plaques and mortality[46,47]. A recent review has elaborated the roles of smoking on all stages of atherogenesis, as well as pathological atherothrombosis formation[48].

Microvascular Mechanisms of Diabetic Foot Ulcers

Some researchers say that diabetic foot ulcers are more of a "small-vessel disease"[49]. As an important component of diabetic neuropathy, the microcirculatory changes seem to play a more crucial role in the pathogenesis of foot ulcers. Microvascular structure in the skin consists of capillaries and thermoregulatory arteriovenous shunt flow. Although occlusive lesions are not found in diabetic microcirculation, other structural abnormalities could be detected, including thickening of the capillary basement membrane[50], decrease in luminal and capillary size[51], and reduction in capillary density[52], resulting in reduction of the vascular elasticity and impairment of normal transport through the capillary walls. Apart from the structural changes, functional ischemia also exists, as a result of maldistribution of blood flow between the capillaries and the arteriovenous shunts.

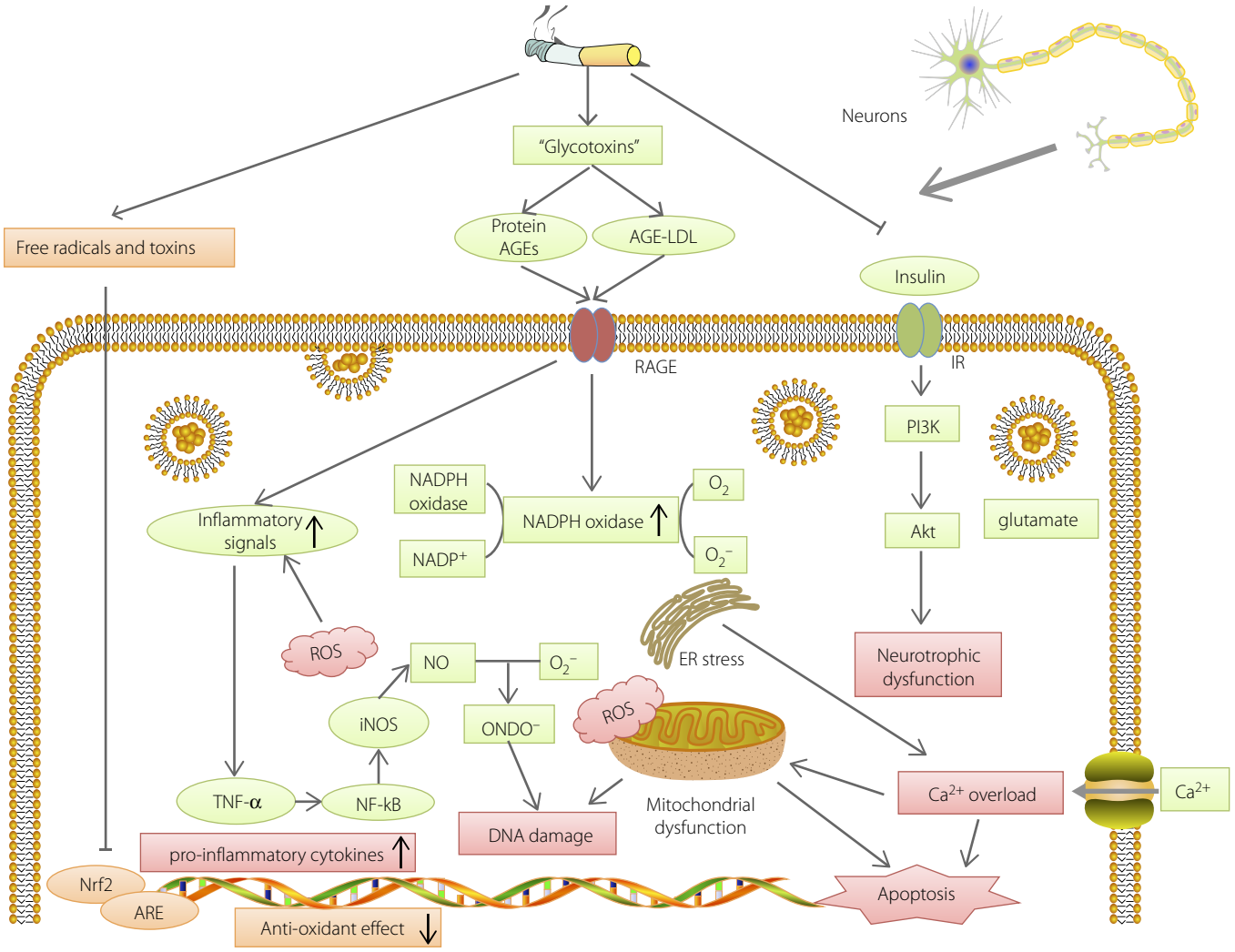

Figure 1 | Mechanisms of cell damage in peripheral neurons caused by cigarette smoking. Cigarette smoking induces formation of advanced glycation end-products (AGEs) and inhibits insulin signaling and the NF-E2-related factor 2 (Nrf2)–anti-oxidant responsive element (ARE) pathway, causing oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction, deoxyribonucleic acid (DNA) damage and apoptosis in peripheral neurons. ER, endoplasmic reticulum; iNOS, nitric oxide synthase; LDL, low-density lipoprotein; NADPH, nicotinamide adenine dinucleotide phosphate; NO, nitric oxide; RAGE, receptor for advanced glycation end-products; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α.

Both the structural and functional deficiencies lead to compromised vasorelaxation in case of stress, reduced blood flow in nutrient capillaries and lower tissue PO_2[53].

Effects of Cigarette Smoking on Diabetic Microangiopathy

Cigarette smoking exerts effects on diabetic microangiopathy. Due to the high requirement of experimental techniques in studying microcirculation, studies in this field are relatively few. It is reported that chronic smokers have a weakened vasodilation in response to different stimuli in skin microvasculature, mainly endothelium-dependent, further decreasing the already reduced blood flow in diabetic microcirculation. This impaired vasoreactivity is associated with the duration and intensity of smoking[54–56]. A recent *in vivo* study showed that this diminished acetylcholine-induced vasodilation in skin caused by cigarette smoking is a result of reduced nitric oxide- and cyclooxygenase-dependent vasodilation[57].

In addition, smoking also causes ROS generation in the leukocytes. The activated leukocytes and/or platelets aggregate in the circulation and adhere to the microcirculation endothelium[58,59], implicating the presence of local inflammation as well.

In addition, acute smoking also activates the adrenergic system and causes vasoconstriction, further decreasing blood flow and tissue oxygen tension[60–62]. The reduction of blood flow is rather substantial: by approximately 50% in healthy people and

by >10% in people with diabetes[63]. Even passive inhalation of cigarette smoke could cause an immediate and prolonged reduction in capillary blood flow velocity in healthy people[64]. However, this acute reduction could be recovered by stopping smoking[61]. Anti-oxidant vitamin C is shown to improve impaired endothelium-dependent responses in chronic smokers[65], indicating the important role of oxidative stress caused by cigarette smoking.

SMOKING AND WOUND HEALING

Normal Wound Healing Process

Normal wound healing can be divided into four phases: coagulation, inflammation, migration-proliferation and remodeling. Vascular injury in the wound triggers the formation of blood clots, and then induces the inflammatory cells including neutrophils and monocytes to migrate into the wound. These immune cells produce a large amount of pro-inflammatory cytokines, such as interleukin (IL)-1, IL-8 and tumor necrosis factor-α, and proteolytic enzymes. Monocytes then differentiate into macrophages, and remove the microorganisms (if infected), the debris and necrotic cells together with neutrophils. After this, the proliferative phase starts with the migration and proliferation of fibroblasts in the wound, and formation of the extracellular matrix and granulation tissue. At day 4–5 after wounding begin the proliferative and remodeling phases. In the normal proliferative process, fibroblasts migrate and proliferate in the wound area by the induction of platelet-derived growth factor and transforming growth factor-β, producing a great number of matrix proteins, forming the extracellular matrix[66]. Collagen is a very important type of protein, and provides strength and support for the whole extracellular matrix. Ultimately, the healing process is ended by the remodeling of the extracellular matrix and the maturation of the scar[66].

Wound Healing in Diabetic Foot Ulcers

Wound healing is already impaired in diabetic foot ulcers, and the risk of amputation is higher than for healthy people. In diabetic patients, the sensory, motor and autonomic neuropathies combined with aforementioned microcirculatory and macrovascular deficiencies are believed to be the intrinsic factors for the wound healing process being impaired, whereas infection, callus formation and high plantar pressure are the extrinsic factors, though the extrinsic factors are partly attributable to the intrinsic factors[67]. Diabetes could also cause impaired angiogenesis in the wound, probably as a result of the diabetes-induced overproduction of ROS[68], despite the fact that low levels of ROS, such as H_2O_2, actually promote angiogenesis[69,70].

Effects of Cigarette Smoking on Wound Healing in Diabetic Foot Ulcers

How cigarette smoking affects the wound healing process has always been a strong research hot spot. It is reported that smoking is associated with a higher incidence of serious postoperative complications[71], and preoperative smoking cessation of >3 weeks decreases the occurrence of impaired wound healing[72] and reduces postoperative morbidity from 52% to 18%[73], implicating the important role of smoking cessation on improving cutaneous wound healing. In fact, the effects of smoking on wound healing have been found in each phase of wound healing (Figure 2)[74,75].

Coagulation and Inflammation Phases

In the coagulation phase, smoking promotes hemostatic clot formation by activating platelets and fibrinogen release[76]. In the inflammatory phase, inflammation and proliferation of wound healing are delayed in smokers[77], and the immune system is impaired[78]. Smoking could increase the infiltration of neutrophils, but reduce the chemotaxis of monocyte-macrophages into the wound area[79]. Increased levels of protease were also observed in smokers, leading to connective tissue degradation[80,81]. In addition, ROS production and release exist in the normal healing process. A transient oxidative burst by neutrophils and monocyte macrophages in the wound has the function of attacking microorganisms[82,83], and might be involved in promoting migration of polymorphonuclear leukocytes to the wound area[22], angiogenesis[69] and intracellular signaling pathways[22]. Cigarette smoking could reduce the oxidative burst of inflammatory cells and weaken the ability of neutrophils to phagocytize the pathogens[79]. This is due to the cytotoxic effects of cigarette smoking, partly through suppression of caspase-3 activity and the modification of membrane receptors (L-selectin and CD18)[84,85].

Systemically, smoking causes chronic inflammation and increases serum polymorphonuclear leukocytes by 20–30% by stimulating the hematopoietic system in the bone marrow[86]. Chronic smoking could lead to increased products of lipid peroxidation, decreased anti-oxidants and increased inflammatory mediators, including C-reactive protein and cytokines in the circulation[87], exacerbating the systemic inflammatory responses caused by the wound.

Migration–Proliferation and Remodeling Phases

In vitro studies show that cigarette smoke extracts inhibit migration and proliferation of fibroblasts[88,89], and reduce the synthesis of collagen[89,90]. In addition, the balance of proteinase is also disrupted in smokers. Increased levels of matrix metalloproteinase (MMP)-8[90] and MMP-1 messenger ribonucleic acid[91]in skin tissues, and higher circulating MMP-9 levels[81,92] are found in smokers, resulting in enhanced extracellular matrix degradation, which could also be part of the mechanisms for the decrease of collagen.

Solid evidence shows that low levels of nicotine could enhance angiogenesis in the setting of inflammation, ischemia, atherosclerosis and neoplasia[93,94]. However, the effect of nicotine alone could not be generalized to the effects of cigarette smoking. As a matter of fact, *in vitro*, cigarette smoking inhibits endothelial migration and capillary-like tube formation[95], and

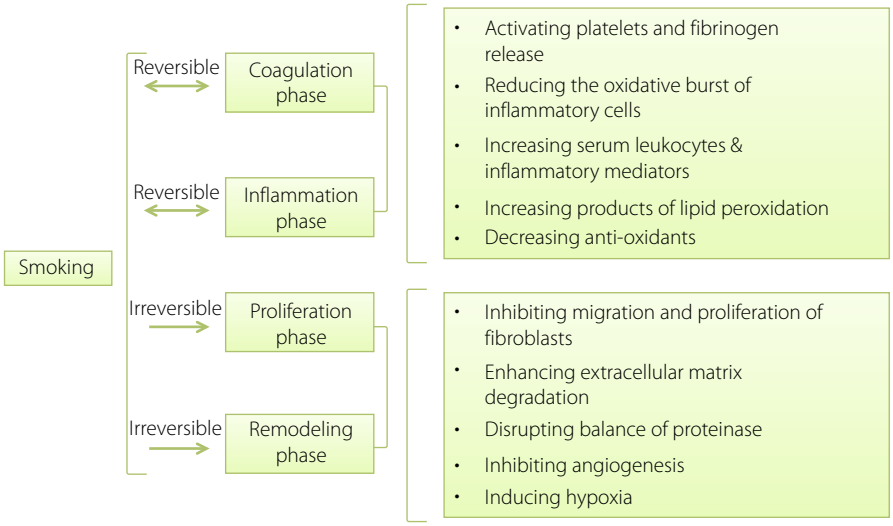

Figure 2 | Effects of cigarette smoking on wound healing. The effects of smoking on wound healing have been found in each phase of wound healing, further worsening the impaired wound healing in diabetic patients.

in vivo, smoking caused a reduction of capillary density in ischemic muscles by inhibiting vascular endothelial growth factor through decreased expression of hypoxia-inducible factor-1α[96], both showing the detrimental influence of cigarette smoking on angiogenesis and granulation tissue formation. In addition, bone marrow-derived circulating endothelial progenitor cells (EPCs) could be isolated from the blood and play crucial roles by differentiating into mature endothelial cells in areas of neovascularization[97]. A reduction of circulating EPC numbers and functions was observed in diabetes[98,99], and one study showed that decreased expression of an anti-oxidant enzyme, MnSOD, was responsible for the EPC dysfunction in diabetic mice[100], showing a role of ROS overproduction by mitochondria in this disorder. Studies showed that smokers demonstrated a decreased number of EPCs, impaired differentiation and function of EPCs, and an increase of ROS production in EPCs[101]. Smoking cessation could also upregulate the circulating EPC levels in chronic smokers[102]. This evidence shows the adverse impacts of smoking on the already impaired angiogenesis in diabetic ulcers.

Finally, as mentioned above, smoking reduces tissue blood flow and oxygen supply[18,60,75,103]. Smoking leads to microvascular alterations, such as impaired vasodilation, stimulation of sympathetic nervous activity by nicotine and atherosclerosis of the blood vessels in the lower extremities, but other possible mechanisms might be carbon monoxide, another component of cigarette smoking, could bind to hemoglobin with a much higher affinity and cyanide interferes with cellular oxygen metabolism[104]. Although acute hypoxia might initiate the healing, promote fibroblast proliferation and stimulate collagen synthesis, chronic hypoxic conditions caused by smoking exert the opposite effects by diminishing fibroblast activity, inhibiting collagen synthesis and interfering with angiogenesis[105,106]. Neutrophils were also shown *in vitro* to lose their bacterial killing capacity at a pO2 level <40 mmHg[107]. During the re-epithelialization phase, a proliferative burst of keratinocytes occurs in an oxygen-dependent manner, stimulated by various cytokines and chemokines (e.g., epidermal growth factor, transforming growth factor-α, keratinocyte growth factor, hepatocyte growth factor, insulin-like growth factor-1, IL-1 and IL-6). Hypoxia induced by smoking also inhibits this process and leads to delayed closure of the wound[108].

SMOKING CESSATION

Smoking Cessation and Diabetic Foot Ulcers

Smoking appears to increase the risk of diabetic foot amputation[109]. However, direct evidence is very limited for the effect of smoking cessation on lower leg lesions and amputation in diabetes. It is reported that effective smoking intervention programs before surgery showed a significant reduction of postoperative morbidity[73,110], indicating a beneficial effect of smoking cessation in promoting postoperative wound healing. Transient hypoxia and oxidative stress seem to be reversed by smoking abstinence, though the detrimental effects of smoking on proliferation and remodeling in the diabetic wound might be prolonged and irreversible[75]. As is known, smoking cessation is also a very cost-effective intervention for patients with atherosclerosis[111,112], slowing the progression into ischemia of the lower extremities.

Clinically, several therapies have already been adopted to increase the success rate of smoking cessation. These include behavioral interventions, nicotine replacement therapy (NRT), bupropion, electronic cigarettes and varenicline (Table 1).

Table 1 | Recommended cessation treatments for smokers

	Mode of action	Efficacy (vs placebo)	Recommended dosage	Duration of therapy	Major side-effects	Cautions
Behavior interventions	Psychotherapy	Increasing quit rate by 40–60%	–	–	None	–
NRT	Desensitizing the nicotinic acetylcholine receptors and preventing them to resensitize	Increasing quit rate by 50–70%	• (Gum) 4 mg about 8–12 times per day • (Patch) 22 mg per day • (Lozenges) at least 9 lozenges per day for the first 6 weeks	• (Gum) at least 12 weeks • (Patch) 8 weeks • (Lozenges) no more than 12 weeks	• Headache • Nausea • Vomiting • Sore throat • Hives • Mouth ulcers.	Not recommended for: • Pregnant smokers • Smokers aged <18 years old.
Bupropion	• Norepinephrine dopamine reuptake inhibitor • A nicotinic receptor antagonist	Increasing quit rate by >80%	150 mg twice a day	12 weeks	• Epileptic seizures • Hypertension • Increased risk of suicidal risk in smokers aged <25 years	Cautions for smokers with: • Liver damage • Severe kidney disease • Severe hypertension.
Varenicline	Selective $\alpha 4\beta 2$ nicotinic receptor partial agonist	More than double the quit rate	1.0 mg twice a day	12 weeks and may be continued for another 12 weeks if cessation is achieved	• Mild nausea • Headache • Difficulty in sleeping • Nightmares	Not recommended for: • Pregnant smokers • Smokers aged <18 years
E-cigarette	Heating a liquid containing nicotine etc. to generate a vapor	No efficacy	Not recommended	–	–	–

NRT, nicotine replacement therapy; E-cigarette, electronic cigarette.

Behavioral Interventions

A recent Cochrane review showed that individual behavioral counseling of >10 min significantly increases the likelihood of cessation by 40–60% than a minimal contact control (brief advice, usual care or provision of self-help materials)[113]. Additional telephone follow-up counseling sessions are also reported to double the quit rate at 12-month follow up[114]. A specialized counseling intervention has proved more effective for helping patients cease smoking than a usual state quit-line[115]. Smoking cessation counseling is associated with a higher likelihood of attempting to quit, even for patients who are less engaged during medical encounters[116]. What is good about behavioral interventions is that they are absolutely safe and have no side-effects. They are an appropriate choice for pregnant smokers to improve maternal and child health outcomes[117,118]. Thus, individual behavioral counseling should be suggested wherever the counseling is available to all smokers.

Despite the efficacy of behavioral interventions for smokers, Tindle *et al.*[119] have recently made their comments, stressing the importance of pharmacotherapy for smoking cessation treatment, even without behavioral counseling.

Nicotine Replacement Therapy

Nicotine replacement therapies could assist quitters by alleviating the discomfort in the process of cigarette withdrawal, and have been approved by Food and Drug Administration (FDA) in the USA to treat tobacco dependence. They come in different forms: gum, inhalers, lozenges, nasal sprays and transdermal patches. The absorption time of each form is different: the inhalers are the fastest (peak concentrations usually within seconds), and the transdermal patches the slowest (peak concentrations within hours). When nicotine is released continuously and slowly in the brain, it could desensitize the nicotinic acetylcholine receptors and prevent them from resensitizing, thus reducing both the pleasurable symptoms (e.g., improved mood and enhanced vigilance) and the withdrawal symptoms (e.g., anxiety, irritability and impaired concentration). Randomized controlled trials (RCTs) show that NRTs significantly increase the quit rate by 50–70% compared with a placebo. For smokers not ready to stop, NRTs could assist twice as many quitters to achieve 6 months of abstinence as those who take a placebo. A dosage of 4-mg gum rather than 2-mg gum showed an increased quit rate in highly dependent smokers. Doses of 22-mg and 44-mg transdermal nicotine therapy produced similar effects during a 26-week follow-up period, and the 44-mg patch dose produced more adverse effects, such as vomiting, nausea and erythema with edema at the patch site[120–124]. Combined use of nicotine patches and chewing gum together has the highest quit rate (95.2%) after 4 weeks and at 12-month follow up (62.5%)[125].

Theoretically, nicotine might cause cardiovascular disease due to its hemodynamic effects of sympathetic neural stimulation and systemic catecholamine release, but it was presumed to be safe and the advantages outweigh the disadvantages[126]. However, a recent cohort study[127] suggested that treatment with NRT over 4 weeks results in an increase in cardiovascular events in a follow-up period of 52 weeks, which prompts more studies with long-term follow up to clarify this concern. Furthermore, whether the NRTs should be prescribed to the critically ill patients in the intensive care units is also still questionable and in need of further studies[128]. NRT is generally not recommended for pregnant smokers, and is classified by the FDA as category D (transdermal nicotine) and category C (shorter-acting forms). Furthermore, among smokers who are motivated to stop smoking, quitting abruptly after 2 weeks of precessation NRT is shown to be more effective than gradually reducing cigarettes per day after the same precessation NRT[129].

Bupropion

Bupropion, a dopamine-uptake inhibitor, is also a FDA-approved smoking cessation and antidepressant medication. During the search for a smoking cessation medication that does not contain nicotine, a RCT in 1997 reports that administration of a sustained-release form of bupropion for 7 weeks could increase the quit rate by >80% at 1-year follow up. The dosage of 300 mg (150 mg twice a day) was recommended due to its greatest efficacy on abstinence and less occurrence of weight gain. Use of sustained-release bupropion alone or in combination with a nicotine patch resulted in significantly higher long-term quit rates than treatment of either the nicotine patch alone or placebo, also indicating the great efficacy of bupropion[130]. Bupropion was recommended to start at least 7 days before the quitting date to achieve steady-state plasma levels, and the treatment is recommended for 7–12 weeks[131]. As for safety, no increased risks of neuropsychiatric or heart and circulatory problems have been found in the bupropion studies. As quitters with a history of depression are at higher risk of developing a new episode of major depression for at least 6 months[132], bupropion seems a better choice than NRT for smokers with a history of depression[133].

Electronic Cigarettes

An electronic cigarette, or e-cigarette, is a small electronic device that resembles the feeling of cigarette smoking. It works by heating a liquid to generate a vapor, and the liquid usually contains nicotine, propylene glycol, glycerine and flavorings. The e-cigarette products vary in engineering with regard to nicotine concentrations in the solution, volumes of solution in the product, different carrier compounds, additives and flavors, and battery voltage. A study says e-cigarettes are "modestly effective" at assisting smokers to quit[134]. However, the other evidence to date is not strong enough to prove that e-cigarettes are efficacious for smoking cessation. Therefore, no e-cigarette products are currently approved by the FDA as smoking cessation therapy. Although e-cigarettes are likely to be much less toxic than cigarette smoking, they still produce lower levels of the toxic chemicals including 1,2-propanediol, glycerin, aluminum and seven polycyclic aromatic hydrocarbons, considered

probable carcinogens. Therefore, for the protection of public health, e-cigarettes are also prohibited in some public places where cigarettes are not allowed[135]. Furthermore, a cross-sectional study reported that use of e-cigarettes is associated with increased odds of cigarette smoking and decreased odds of abstinence from conventional cigarettes among USA adolescents, showing that the use of e-cigarettes might even encourage conventional cigarette use in younger people[136]. Therefore, e-cigarette currently should not be prescribed to smokers for smoking cessation, and more randomized clinical trials were still required to clarify the effects of e-cigarettes on the smoking cessation rate.

Varenicline

Varenicline is another FDA-approved smoking cessation medication. It is a selective α4β2 nicotinic receptor partial agonist, showing approximately 30–60% of the efficacy of nicotine and at the same time blocking the nicotine response *in vivo*, which is the ideal profile for reducing nicotine dependence and minimizing the potential side-effects through activation of nicotinic receptors[137]. Many RCTs have confirmed the efficacy of varenicline in smoking cessation. A review concludes that varenicline more than doubles the smoking cessation success compared with a placebo[138]. Furthermore, varenicline shows its superiority over any form of NRT monotherapy and bupropion, and is as effective as combination NRT[138,139]. For every 100 patients treated with varenicline, compared with NRT, approximately additional five patients would be abstinent from cigarettes 2 years after treatment[140]. However, other recent clinical trials comparing varenicline with combination NRT and NRT monotherapy showed no significant difference in the long-term quit rates, although varenicline might enhance the success rate in the short and medium term[141,142]. The efficacy of varenicline increases as the dose is higher, and the dosage of 1.0 mg twice daily provides the highest continuous quit rates, and shows a good safety and tolerability profile[143]. However, long-term surveillance for the safety of varenicline is still required in the aspect of adverse neuropsychiatric and cardiac events.

Combination Therapies

Some researchers advocate combination therapy for the purpose of maximizing the efficacy, which includes the pharmacotherapy plus behavioral interventions and the combination drug therapies.

A Cochrane review in 2012 concludes that combining behavioral support with medication might increase the chances of smoking cessation success by 70–100% compared with the chance of success when receiving advice only[144]. A recent RCT also showed that adopting nicotine lozenges plus phone counseling significantly increased tobacco abstinence rates compared with either intervention alone[145]. Other studies also showed the efficacy of NRT plus behavior therapy among smokers with a psychotic disorder[146] and among pregnant women[147].

Combination NRT is also recommended by many guidelines, and usually consists of the use of long-lasting nicotine transdermal patch and short-acting forms including an inhaler, gum, lozenges or nasal sprays. The combination could be sequential

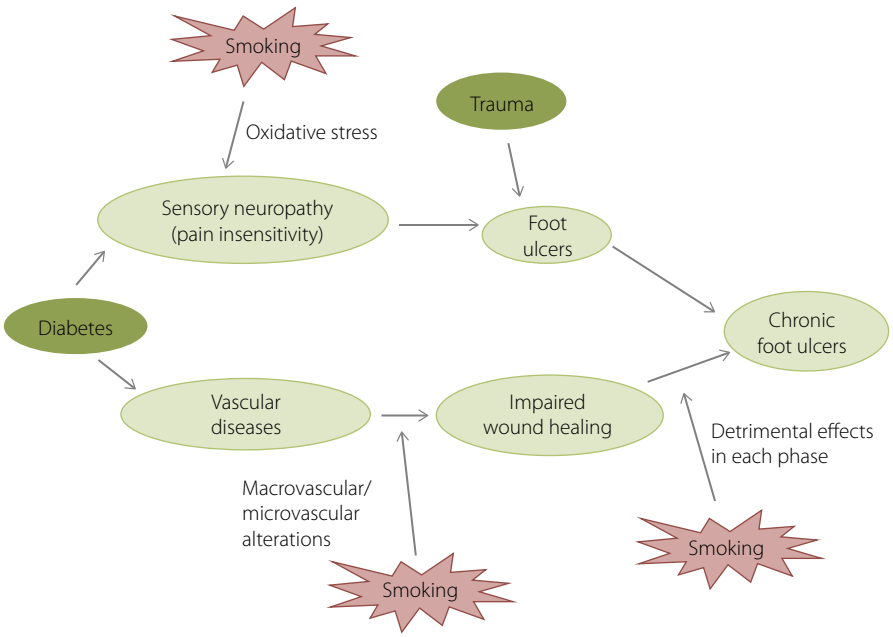

Figure 3 | Effects of cigarette smoking on formation of diabetic foot ulcers. The effects of smoking on the onset of chronic diabetic foot ulcers have been shown, from worsening neuropathy and vascular alterations to slowing wound healing.

or concurrent. The rationale for the sequential therapy is that the patch could provide a stable level of nicotine to achieve and remain cessation, and the after use of short-acting forms is expected to deal with the emergent craving. Furthermore, the rationale for concurrent combination therapy is that the sensory stimulation and acute nicotine delivery might provide a higher level of craving relief[148]. Clinical studies have shown that concurrent combination NRT significantly increased sustained abstinence rates[149,150] and is as effective as using varenicline alone[138]. In addition, the combination use of nicotine drugs is generally considered safe and no significant adverse effects have occurred, but the safety of the combined use of drugs on pregnant smokers is still unclear and caution should be taken[148].

Besides NRT, combination use of other medications might also yield great efficacy. For instance, combined use of varenicline and bupropion, compared with monotherapy, might increase prolonged abstinence[151,152]. Bupropion plus nicotine patch has also been shown to be well tolerated and significantly improve the short-term quit rate in smokers with schizophrenia[153]. However, another clinical trial reported that NRT plus bupropion was not more effective than NRT alone[133]. More relevant clinical trials are still required to clarify the efficacy of combined use of NRT and bupropion.

CONCLUSIONS

Cigarette smoking has been known to correlate with diabetes. The present review shows that smoking has extensive effects on all stages of diabetic foot ulcerations, both the onset and healing processes (Figure 3). Smoking can exacerbate diabetic peripheral sensory, autonomic and motor neuropathy, which are important reasons for the occurrence of foot ulcerations. Microvascular alterations, such as impaired vasodilation and increased[3] vasoconstriction, could also be detected in smokers, leading to tissue hypoxia and interfering with the healing process. Smoking also has negative impacts on wound healing in almost all phases through very complex mechanisms. The effects are not separate, but interact with each other. For instance, axonal degeneration and demyelination of the nerve fibers could be partly due to ischemia of the microvasculature[20] caused by smoking, and in turn, autonomous nerve dysfunctions regarding several nerve reflexes could also regulate skin blood flow through opening arteriovenous shunts and blunting vasodilation, leading to hypoxia of the skin tissue[53], forming a vicious cycle. All the effects of cigarette smoking together further jeopardize the already impaired capacity of diabetes patients to maintain skin integrity and repair the wound. One of the most important mechanisms underlying these effects is the cellular oxidative stress, as cigarette smoking is known to be a source of oxidants and increases the production of ROS inside cells from almost all tissues. Although there might still be many unknown mechanisms, quitting smoking has been confirmed to be effective in reducing mortality and increasing amputation-free survival. The current effective therapies for smoking cessation include behavioral interventions and pharmacological options, such as NRT, bupropion, varenicline or the combination use of them. In order to achieve long-term smoking abstinence success, the therapy should be individualized according to the will of the smokers, and behavioral support should always be recommended if possible. Successful smoking cessation would make the situation of diabetic foot ulcers better and lead to a better prognosis.

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DISCLOSURE

The authors declare no conflict of interest.

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