The Effects of Tobacco Smoking on Healing of Foot Ulcers and Lower Limb Amputation: A Systematic Review

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Abstract

Cigarette smoking is well known to increase the risk of peripheral arterial disease (PAD). Whether current smoking

of smoking and reported outcomes of foot ulceration or LLA were included.

Results: Fourteen studies met the inclusion criteria and were included in this review. Overall, there is a surprising lack of outcome data for the association between active tobacco use and healing of foot ulceration or LLA.

Conclusion: Further research should speciýcally look healing and LLA in those who are current smokers compared to non-current smokers. If current smoking increases risk of new ulcers, impairs healing or increases LLA this may enhance e orts by clinicians to assist patients to cease, and may encourage patients to stop.

K w : Foot ulcer; Diabetic foot ulcer (DFU); Smoking; Amputation; Lower limb amputation (LLA); Wound healing

A : ABI, Ankle brachial index; CLI, Critical limb ischaemia; DFD, Diabetic foot disease; DFU, Diabetic foot ulcer; LLA, Lower limb amputation; NDSHS, National Drug Strategy Household

Peripheral neuropathy is the most common risk factor for diabetic foot ulceration (DFU); it is found in approximately 78% of patients with foot ulcers 8. e human nervous system is vulnerable to oxidative damage which is believed to be the ultimate mechanism of cell damage leading to diabetic peripheral neuropathy [12]. Tobacco smoking may exacerbate peripheral neuropathy due to the additional oxidative stress, with previous research con rming that tobacco smoking is an independent risk factor for peripheral neuropathy [8,13]. Cigarette smoke also contains glycotoxins which promotes formation of advanced glycated end-products (AGE). Elevated AGE increases risk of peripheral neuropathy [8]. Tobacco smoking may also promote peripheral neuropathy by inducing insulin resistance, hyperinsulinemia [14], and as mentioned above, increased HbA1c

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PAD is narrowing of the arteries in the limbs due to atherosclerosis and most commonly a ects the lower limbs [15]. It is much more common in the lower limb vessels than in the upper limbs. PAD impairs blood ow, which impairs wound healing, and increases the risk of infection. Patients with PAD are more likely to develop critical limb ischaemia (CLI), which may be diagnosed in the presence of ischaemic foot ulcers, gangrene or ischaemic rest-pain [16]. In 2007, the TransAtlantic Inter-Society Consensus (TASC II) de ned ankle pressure <50mmHg, or toe pressure <30mmHg, or transcutaneous oxygen tension (TcPO2) <30mmHg, as diagnostic measures for CLI [17]. When combined with peripheral neuropathy, many people with PAD develop neuro-ischaemic foot ulcers, especially those with CLI.

found. Of these, 3074 papers were excluded a er screening, leaving 45 articles for abstract review. Twenty-three of these were excluded as not relevant. Twenty-two articles were obtained for full text review. Of these, fourteen studies were suitable for inclusion in our systematic review. e eight studies which were excluded were for lack of reported outcomes (n = 3) or because they did not assess for association between tobacco smoking and foot ulceration or LLA (n = 5).

Both reviewers (N.B. and J.G.) independently reviewed the data from the included studies. One study was cross sectional in design 1. e remainder were cohort studies; six retrospective [21-26], and seven prospective [27-33].

Four studies were undertaken in the United States of America [22, 25, 28, 32], two in the United Kingdom [24, 31], and one in each of the following; Australia [26], China [33], Denmark [23], India [27], Nigeria [29], Pakistan [1], Saudi Arabia [21] and Sweden [30].

Characteristics of the studies are described in Table 1.

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e studies had a combined total of 103,316 participants. Of these, 92,731 were in the control groups and 10,585 were in the case groups.

Of those in the control groups, 92,261 had diabetes with no diabetic foot disease (DFD), 25 had DFU but were ulcer free for 2 years prior, 223 were non-smokers who underwent a lower limb endovascular treatment and the remaining 222 had not undergone a lower limb amputation (LLA) in comparison to the case group.

All studies included both male and female participants. In most studies, consistent with the usual foot ulcer population, there were more males than females.

e characteristics of participants are summarised below in Table 1.

Populations evaluated were as follows:

(i) Al-Rubeaan et al. included those with DFU, gangrene, or LLA, and a control group with diabetes but no foot disease [21]

(ii) Five studies included those with DFU, and control groups with diabetes but no DFU [1, 24, 28, 29, 33]

(iii) Two studies only included participants with DFU [23, 27]

(iv) Kokkinidis et al. included people who underwent lower limb endovascular treatment with a case group of current smokers, and a control group of non-smokers [25]

(v) Liedberg et al. included those who had undergone a LLA, and a control group who had not [30]

(vi) Mantey et al. examined those with diabetes who had at least two recurrences of DFU within 2 years, and a control group with previous ulceration who remained DFU free for at least 2 years [31]

(vii) Anderson et al. included participants with diabetes who had undergone a LLA, with a smoking compared to a non-smoking group [22]

(viii) Moss et al. looked at those with diabetes who had undergone LLA; one group who were diagnosed with diabetes before the age of 30 and the other group a er the age of 30 [32]

(ix) Zaine et al. included participants with non-diabetes related foot ulcers [26]

Author	Exclusion criteria	Smoking results	Other results	Limitations
Al- Rubeaan et al.	<25 years old	Smoking commoner in DFD (10.1% smokers vs 6.7%), DFU and gangrene (p = <0.0001)	DFD assoc DM duration (p = <0.0001). ŷHbA1c and micro-vasc Cx ŷin DFD. ŷ DFD in males, 68.6% (p = <0.0001)	Primary DM clinics not foot ulcer clinics
Anderson et al.	Death <3 months of FU	Smokers ŷ LLA and higher amputation level (p = 0.031). Of 11 BKA, 10 smokers	NR	PAD, neuropathy, diabetes duration, HbA1c and age NR. No tests to assess smoking cessation
Bajaj et al.	Previous LLA or non-DM related foot ulceration	67% with NIU and 17% with neuropathic ulcers active smokers. Smoking assoc with NIU (p <0.0001)	DFU assoc with poor glycaemia. NIU assoc with DM duration (p = 0.015) and HT (p =0.0008) vs neuropathic ulcers	Only compared neuropathic to NIU. Small sample size. Other DFU risk factors NR. Duration of ulcer NR
Boyko et al.	Current DFU, not able to walk, too ill, unable to consent	19% of those who developed DFU were smokers vs 24% who did not develop an ulcer (p = 0.46)	ŷ DM duration, insulin-treatment, poor vision, ŷ HbA1c, claudication, past DFU, LLA and foot oedema assoc with DFU (all p = <0.01)	Mostly older, male and T2D. Change in Cx or HbA1c NR. High loss-to-FU
Engberg et al.	No prior or current ulceration	Smoking sig risk factor for recurrence or new DFU (univariate analysis)	Critical ischaemia older, ŷDM duration, ŹDiaBP, ŹHbA1c and ŷ creatinine. Ischaemic DFU ŷpast LLAs. Smokers and men ŷrisk of DFU. Past NIU + HbA1c Ó7.6% ŷ risk of DFU	Information on orthopaedic surgery, re-vascularisation, compliance with footwear and o oading NR
Heald et al.	Previous history of DFU. No diabetes	No di erences between cases vs controls for smoking (p = 0.42)	DFU older, higher HbA1c and creatinine (p < 0.0001). Peripheral neuropathy and absent foot pulses more common in DFU (p < 0.0001)	Other macro- or microvasc Cx NR. Footwear or o oading NR
Ikem et al.	NR	ŷ smoking DFU (p = 0.044). ABI <0.9 correlated with tobacco use (p= 0.044)	DFU assoc DM duration, tobacco use and SysBP. Claudication assoc age, DM duration and neuropathy. PVD in 41.9% with DFU vs 13.4%	Reported outcomes in relation to PVD not overall foot ulceration or LLA
Kokkinidis et al.	Acute ischaemia or IC	Incomplete healing at 6 months 91.1% smokers vs 66%. At 9 months 74.8% in smokers vs 54%	Not studied	Loss to FU was high
Liedberg et al.	NR	Smokers with LLA but no diabetes. Increased smoking assoc with lower age at LLA (p < 0.001)	Those with diabetes more likely to undergo amputation (p = 0.001)	Results reported unclearly. Length of diabetes and other risk factors assoc with diabetes NR
Mantey et al.	Medial wall sclerosis	No sig di erences between groups	Glycaemia poorer, and macrovasc Cx and alcohol consumption sig more common with recurrent ulceration	Detailed results for risk factors NR. Small sample size
Moss et al.	NR	In younger onset patients pack- years also assoc with LLA	LLA ŷmales, with past DFU, ŷretinopathy and ŷHbA1c. LLA in young group assoc with ŷ DiaBP, and Źdaily aspirin	Did not deýne ex-smokers. Loss to follow-up rate NR
Riaz et al.	NR	Smoking sig assoc with foot ulcer (p < 0.0001)	DFU were older, male, had ŷ DM duration and more HT (p < 0.0001 ¥	cr Ã ¥ ' % 1 "

studied 264 patients who all had endovascular interventions in the lower leg for chronic limb ischaemia. Of the 264 patients, 41(15.5%) were current smokers. In this study incomplete wound healing was high in both groups. However, it was further increased in current smokers at 6 months (91.1% versus 66% in non-smokers, p = 0.012) [25]. Incomplete wound healing at 9 months was also higher in smokers (74.8% compared to non-smokers 54%, p = 0.026).

w : In the studies that assessed LLA, there was a signi cant association between smoking and the rates of amputation. Anderson et al. studied 112 participants who had LLA and they were very likely to be smokers (59% smokers) [22]. Of the 11 participants who underwent a below knee amputation, 10 were current smokers (p = 0.031).

Moss et al. reported an association between pack-years smoked in their younger participants and LLA [32], however they did not examine whether current smoking a ected LLA. Another study found that increased smoking was associated with reduced age at LLA (p < 0.001) [30]. In contrast, Al-Rubeaan et al. reported that there was no signi cant di erence between smokers and non-smokers and the rates of LLA [21]. However, in that study DFD was more common in smokers, and there was a 25% rate of smoking in those who underwent LLA versus 6.84% in the background population. It is possible that lack of statistical di erence in LLA is due to small numbers for this outcome.

Two of the fourteen studies found no signi cant di erences between the case and control groups for amputations [24, 31]. One is a large retrospective registry study of 49 GP-practices. e second is a small study (51 patients) comparing people who had attended a diabetes service and had relapsing DFU versus those whose ulcer did not relapse within the 2 year study period.

Absence of foot pulses was more common in those with DFU (p <0.0001), and it is well known that smoking leads to the development of PAD, the clinical ndings of which are the absence of pedal pulses [8,24]

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Smoking is a major risk factor for the development and progression of cardiovascular disease and also peripheral arterial disease [34]. ere is a signi cant e ect of smoking on large artery function. Research has reported that tobacco smoking increased the pulse wave velocity suggesting an increase in arterial sti ness [35]. ese investigators also suggested that smoking decreases elasticity in both large and medium sized arteries in acute and chronic smokers.

Acute smoking causes signi cant increases in systolic and diastolic blood pressure and heart rate which usually return to baseline within 15 minutes [35]. ese e ects are also seen in the blood pressure of the aorta following only 1 cigarette in chronic smokers and non-smokers. e greatest changes were seen in the rst 5 minutes a er a cigarette. ese results suggest that acute smoking has important potential for e ects on blood ow to the lower limbs.

In addition, acute smoking causes vasoconstriction which can further decrease blood ow and oxygen delivery [36, 37]. In healthy people, there was a 50% reduction in blood ow in nger circulation, and an over 10% reduction in people with diabetes [38].

Importantly, this impairment recovers when smoking is ceased [37]. is suggests that similar e ects may be present in toes although we did not identify any studies in this area. If there was a 10-50% reduction in toe blood ow with smoking, that would be very likely to impair wound healing and may increase eventual amputation risk.

Among studies that review this area, Zhang et al. reported that there was a higher percentage of smokers with DFU (29.1%) vs a control group with diabetes (17.4%) [39]. Another meta-analysis reports that smoking history is an in uencing factor in amputation rates in DFU patients [40]. Sayiner et al. also indicated that smoking had a negative e ect in those with DFU with amputees having signi cantly longer histories of smoking (p < 0.001) [41].

Two other meta-analyses reported smoking history is a signi cant risk factor for LLA in those with DFU, one of these studies reporting that smokers had a 2 fold higher risk of amputation than non-smokers [42, 43].

A study by Markuson et al. reported a signi cant correlation between smoking history and increased HbA1c levels [44]. Other authors have also reported that smoking is associated with worsened glycaemia in diabetes [10, 11]. is increase in HbA1c with smoking may contribute to any e ects of smoking on DFU healing as increased HbA1c is associated with delayed healing of ulcers.

Camilleri et al. studied the relationship between toe brachial indices and smoking history. e authors reported that the mean toe brachial index of non-smokers (0.781) was superior to the mean scores of past smokers (0.649) and current smokers (0.544). Low toe brachial indices are a reliable method to detect PAD, and predict delayed healing in foot ulceration [45]. eir study did not assess ulcer healing or amputation.

It is widely acknowledged that tobacco smoking is a major risk factor for development of PAD. e data in this study describe signi cant associations between smoking and risk of developing DFD, and DFU. In relation to the known association between smoking and PAD, a history of smoking is associated with increased risk of LLA.

However, probably because of the limited, heterogeneous studies, we conclude that an association between smoking and poor healing or DFU is likely but not proven. e data shows that a history of smoking is associated with risk of LLA, as expected.

However, whether current smoking provides a further increase in risk is not conclusively proven. is, and data on wound healing, if proven to be worsened by current smoking, would be important for the

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ere are no con icts of interest to declare.

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