THE IMPACT OF PATIENT HEALTH AND LIFESTYLE FACTORS ON WOUND HEALING, PART 1:

STRESS, SLEEP, SMOKING, ALCOHOL, COMMON MEDICATIONS AND ILLICIT DRUG USE

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The impact of patient health and lifestyle factors on wound healing, Part 1:

Stress, sleep, smoking, alcohol, common medications and illicit drug use

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This article should be referenced as:
Gethin G, Touriany E, van Netten JJ, Sobotka L, Probst S; The impact of patient health and lifestyle factors on wound healing, Part 1: Stress, sleep, smoking, alcohol, common medications and illicit drug use; J Wound Management, 2022; DOI: 10.35279/jowm2022.23.01.sup01.01

The document is supported by an unrestricted educational grant from BBraun, Nestlé Health Science and Urgo Medical.

Published by the European Wound Management Association, Nordre Fasanvej 113, 2, 2000 Frederiksberg, Denmark
Web: www.ewma.org. Email: ewma@ewma.org

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1. Abbreviations

ARNTL: Aryl hydrocarbon receptor nuclear translocator-like protein 1
BMAL1: Brain and Muscle ARNT-Like 1
CA: Cannabis arteritis
CI: Confidence interval
CO: Carbon monoxide
CVI: Chronic venous insufficiency
DFU: Diabetic foot ulcer
ECM: Extracellular matrix
EU: European Union
IL: Interleukins
HIF-1: Hypoxia-inducible factor 1
LD: Light-dark
MMPs: Matrix metalloproteases
mRNA: Messenger RNA
PDGF: Platelet-derived growth factor
TGF-ß1: Transforming growth factor B1
NHS: National Health Service
NSAID: Non-steroidal anti-inflammatory drug
OECD: Organisation for Economic Co-operation and Development
PAI 1: Plasminogen Activator Inhibitor 1
PBMC: Peripheral blood mononuclear cell
PER2: Period circadian regulator 2
PGE2: Prostaglandin E2
PWIDs: Persons who inject drugs
RA: Rheumatoid arthritis
RCT: Randomised controlled trial
SCN: Suprachiasmatic nucleus
SR: Systematic review
TAO: Thromboangiitis obliterans
THIN: The Health Improvement Network
TIMPs: Tissue inhibitors of metalloproteases
UK: United Kingdom
VEGF: Vascular endothelial growth factor
VLU: Venous leg ulcer
WHO: World Health Organization

2. Introduction

Health and a healthy lifestyle are the aspirations of many, but achieving such goals is influenced by a complex interplay of individual choices, intrinsic factors, external influences and context. In 1948, the World Health Organization (WHO) defined health as a 'state of complete physical, mental and social well-being and not merely the absence of disease or infirmity', and this definition has not changed since.[1] The definition is equally applicable to people with chronic wounds as it is to the general population. The health of those with chronic wounds or at risk of a wound is important to understand so that interventions for prevention and management can be developed with the goal of improving the lives of those impacted by wounds.

This document sets out to understand the prevalence of various health and chronic illness risk factors among those with chronic wounds and how those factors influence healing. The work is organised in two parts. Part 1 provides background information on population health and identifies the risk factors for chronic illnesses that are the focus of this document. Factors including stress, sleep, smoking, medication, illicit drug use and alcohol consumption are explored, all commencing with an understanding of pathophysiology as it relates to wound healing, followed by a review of the literature as it applies to chronic wounds. Evidence of interventions at the level of randomised controlled trials (RCTs) to manage these factors and their impact on wound prevention or treatment is limited and thus we will refer to systematic reviews, observational studies and in vitro studies as appropriate. Part 2[2] follows a similar format and will focus on physical activity and nutrition. Figure 1 provides an overview of these factors and their interrelationships. Finally, we provide recommendations for clinicians and future research. We believe this document will constitute an up-to-date resource for clinicians, policymakers and researchers alike.

Background

Globally, the burden of chronic disease is increasing, with significant variations between countries, age groups and socio-economic status. The health status of European Union (EU) citizens was summarised by the Organisation for Economic Co-operation and Development (OECD) in their latest report, Health at a Glance: Europe 2020 State of Health in the EU Cycle.[3] The report outlines trends in mortality, life expectancy, chronic disease and risk factors for chronic illness, among other factors affecting health. The picture is one of overall increasing health status in the EU, although significant differences remain between and within countries.

Across EU countries, about 37% of people aged 65 and over reported having at least two chronic conditions in 2017 and about 30% of the same cohort reported at least one limitation in (instrumental) activities of daily living that may require some long-term care assistance.[3] In contrast, 90–95% of people with chronic wounds reported having at least one chronic condition[4, 5], with an average of 4.1 conditions.

The Global Burden of Disease study has shown a wide variation in patterns of age-related disease burden in 2017: the highest estimated rate of age-standardised age-related disease burden is more than four times higher than the lowest rate.[6]. For example, 76-year-olds in Japan have the same level of age-related disease burden as 69-year-olds in the USA.[6] This is of direct relevance to

Figure 1: The interrelationships between health and lifestyle factors in wound care

the population with chronic wounds who have an average age of 65–69 years.

Large inequalities in life expectancy exist not only by gender, but also by socio-economic status, no matter how they are measured—by education level, income or occupational group.[3] In every EU country, women live longer than men by an average of 6 years.[3]

As people get older, the share of the remaining years of life that they can expect to live free of disability falls. While women across EU countries can expect to live almost 22 more years when they reach the age of 65, only 10 of these years can be expected to be free of activity limitations. For men, the remaining life expectancy at age 65 years is almost 4 years shorter across EU countries (18 years); they can also expect to live only about 10 years free of disability.[3]

Modifiable risk factors for health include smoking, alcohol consumption, illicit drug use, unhealthy nutrition, lack of physical activity and obesity.[3] It is important to understand how modifiable risk factors and other factors that influence health, such as stress and sleep, affect individuals with wounds or at risk of wounds. It is these factors that are the focus of this paper.

A meta-analysis of 11 studies in the general population of 13 countries (65% of which were European countries) estimated a total prevalence of chronic wounds of 1.67 per 1,000 population (CI: 0.83–2.8).[7] A subgroup analysis based on the type of wound, revealed a combined prevalence of 2.21 per 1,000 population (CI: 0.56–4.94) for studies reporting more than one aetiology.[7] Given that all included studies presented a prevalence of wounds detected within health-care systems, self-treated cases were not reported.[7] In the UK, a recent analysis of the electronic records of 3,000 adult patients from The Health Improvement Network (THIN) database for 2017/2018 reported an estimated 3.8 million patients (7% of the adult population) with a wound managed by the National Health Service (NHS).[5]

Over 4.6 million people died in EU countries in 2017, with the main cause of death being

circulatory diseases (37% of all deaths) and various types of cancer (26% of all deaths), followed by respiratory disease (8% of all deaths) and external causes of death.[3] Diabetes represented 2% of all deaths across EU countries.[3] Deaths from ischaemic heart disease (IHD) are over 80% higher for men than for women across EU countries because of a greater prevalence of risk factors among men, such as smoking, hypertension and high cholesterol. While smoking rates overall have fallen, cholesterol, blood pressure, low physical activity, obesity and diabetes are on the rise in many EU countries.[8] A systematic review of 20 venous leg ulcer (VLU) studies showed a lack of comprehensive reporting of comorbidities or modifiable risk factors for health; however, when reported, hypertension was documented in 53% of the studies (4 studies) and type 1 and 2 diabetes accounted for 17% of the studies (seven EU studies).[9]

On average, about one in four men and one in six women smoke daily in EU countries, and tobacco consumption remains more common among men than women in all EU countries.[3] In the UK, this rate is lower among those with a wound, as an estimated 17% currently smoke and 30% are ex-smokers.[5] Measured using sales data, overall alcohol consumption stood at 10 litres of pure alcohol per adult on average across EU countries in 2018, down from 11 litres in 2008.[3]

Almost a third of all adults in the European Union aged 15–64, or around 97 million people, have used illicit drugs at some point in their lives, with the experience of drug use being more frequently reported by men than women.[3] Data on usage among those with chronic wounds is very limited.

In 2018, on average, one in nine adults (11%) across EU countries had symptoms of psychological distress. While rates varied between countries, these self-reported numbers can be influenced by cultural differences and different levels of stigma and literacy around mental health.[3] A systematic review of patients with chronic wounds reported poorer health-related quality of life and reduced mobility as the main problem areas for patients with chronic wounds with pain.[10]

In the USA, health-care spending attributable to modifiable risk factors for 2016 was US$730.4 billion, corresponding to 27% of total health-care spending.[11] This spending was largely due to five risk factors: high body-mass index, high systolic blood pressure, high fasting plasma glucose, dietary risk and tobacco smoke, with the fraction of attributable spending largest for those aged 65 years and older.[11] The health conditions with the most attributable spending were cardiovascular disease and diabetes.[11] What is apparent globally is that the cost associated with health is enormous and accounts for a significant proportion of national health spending. However, health spending is not limited to the government provision of services but also includes personal spending, insurance costs and lifestyle choices that can contribute to improved health.

The annual cost of wound care supported by the NHS in the UK was estimated at £8.3 billion in 2017/2018, with 81% of costs incurred in the community and the remainder within secondary care.[5] In Ireland, the total annual wound-related health-care cost has been estimated at €629,064,198, accounting for 5% of the total public health-care expenditure in 2013.[12]

Chronic wounds, as with any other chronic condition, demand prolonged nursing care, significant lifestyle changes and adherence to therapeutic regimes that include the use of compression therapy, off-loading, maintenance and preventative strategies that promote healing and prevent recurrence (such as leg elevation, off-loading, weight control, physical activity, skin care, protection against injuries, emotional management and social support, among others).[13] It is therefore important to understand how risk factors for chronic illness impact on wound healing. This document will address these relationships.

Literature search strategy

For each section, a separate search strategy was employed. Keywords were identified from the literature and used to search the following databases: Cinahl, Embase, Web of Science, Cochrane Library, Medline (PubMed). No limits were applied to the date of publication, although the search was limited to the English language. The focus was on original research papers, reports or systematic reviews.

Details about the individual search strategies and a brief overview of the findings can be found in Appendix 1 . (Available at https://ewma.org/what-we-do/projects/lifestyle-factors).

3. Stress

Introduction

Stress is defined as the process through which environmental demands exceed an individual's perceived ability to cope, thereby resulting in affective, behavioural and physiological changes.[14] It is seen as a state of threatened homeostasis that mobilises a complex spectrum of adaptive physiologic and behavioural responses that aim to re-establish the challenged body homeostasis.[15]

Similar to emotions, stress consists of characteristic physiological, affective, cognitive and behavioural changes that can affect well-being whether or not successful adaption is achieved.[16] Integrated biobehavioural patterns of activation, such as stress, appear to exert fundamental effects on health.[16]

Physiology of stress

Environmental demands or stressors are assumed to impact health through two interacting routes: (a) directly, by activating the hypothalamic-pituitary-adrenal (HPA) and the sympathetic-adrenal medullary axes, and (b) indirectly, by inducing negative emotions, which in turn, impact the physiological processes and/or behavioural patterns that influence health.[17]

The stress hormone cortisol is regulated by the pituitary gland through the secretion of the adrenocorticotropic hormone (ACTH). In response to stress, the corticotropin-releasing factor, which regulates the HPA axis, initiates a cascade of reactions that result in the release of glucocorticoids from the adrenal cortex.[18] High levels of this hormone may inhibit further response to stress through a negative feedback loop.[18]

In order to re-establish the disturbed equilibrium against an intrinsic or extrinsic stressor, a range of physiologic and behavioural responses are rapidly mobilised, constituting the adaptive stress response.[15] As with other adaptive stress responses, typical inflammatory reactions are programmed to subside once the initial threat is contained. Thus, at sites of conventional inflammation (e.g. infections and injuries), cytokines are secreted by immune cells for limited periods in order to avoid prolonged macrophage activation, which has destructive effects.[15]

When the adaptive stress response is chronically stimulated, it may become maladaptive, with potentially harmful consequences. Indeed, excessive and/or chronically imposed stressors can impair a number of essential physiological functions, such as metabolism, growth, reproduction and immunocompetence, as well as personality development and behaviour.[15] Chronic hypercortisolemia is considered to play a critical role in deleterious processes as a result of the adaptive stress response.[15] In the context of a mobilised stress response, glucocorticoids exert primarily catabolic effects, recruiting all available energy resources to defend body homeostasis against the imposed stressor.[15]

Chronic stress is also characterised by increased sympathoadrenal system activity, which can contribute to impaired glucose tolerance and increased risk for acute cardiovascular events.[15] Persistent, sustained physiological stress or frequent, rapid increases in stress have a range of consequences, including wear and tear on arteries and coronary vessels, formation of thrombi, suppression of host resistance and other direct biological effects.[16] Prolonged and non-remitting stress via chronic hypercortisolemia can progressively cause visceral fat accumulation, decreased lean body mass and insulin resistance.[15]

The physiological understanding of how stress affects wound healing is based primarily on animal and experimental wound models[13] and shows that physiological stress responses can retard the initial inflammatory phase of wound healing.[19] An excessive inflammatory response contributes to increased levels of proteases, such as neutrophil elastase and matrix metalloproteases, leading to a switch from tissue synthesis to matrix degradation with downstream impaired wound healing.[17] It must be acknowledged that while these studies undoubtedly offer significant insights into the physiological response and findings can stimulate further enquiry, they do not or cannot emulate the context and experience of an individual living with a sometimes life-limiting, protracted, recurring chronic wound (characterised by odour, exudate, etc.) and who may experience social isolation, pain and fear of amputation or death.

Stressors that are perceived uncontrollable and/or unpredictable can lead to negative emotional states.[17] With continued exposure to high concentrations of neuroendocrine hormones, as observed in chronic stress, leukocytes can mount a counterregulatory response and down-regulate the expression and/or function of the receptors responsible for binding glucocorticoid hormones; in this way, the immune system's sensitivity to cortisol declines, thereby leading to excessive inflammation.[20]

Stress is a particularly important mediator of health–behaviour relationships because it is a common and seemingly inevitable aspect of life and because its broad effects can influence a range of bodily systems and behaviours.[16] Stress and its associated negative emotions can induce immunomodulatory behaviours, such as poorer sleep patterns, poorer nutrition, less physical exercise and abuse of alcohol, cigarettes and drugs.[16] The emotional, cognitive, behavioural, and physiological changes that occur as part of the stress response are the mechanisms by which stress impacts health and well-being.[16]

In addition to directly modulating the physiological response to skin damage, stress can also indirectly influence wound repair by promoting the adoption of health-damaging behaviours.[19] Individuals who experience greater levels of stress are more likely to increase their alcohol and tobacco use, decrease their participation in physical activity, experience sleep disturbances and make poorer dietary choices than individuals reporting less distress (see Figure 1). These negative health behaviours can then compound the detrimental impact of stress on physiologic healing processes.[21]

Psychoneurological symptoms associated with chronic VLU, which include pain, cognitive dysfunction, fatigue, depression and anxiety, have attracted more and more attention recently due to their impact on mental and emotional processing, which are necessary for the self-management of the illness.[13] That is, these symptoms can generate new negative emotional states or exacerbate current ones.[13]

Common definitions

Psychosocial interventions are broadly defined as non-pharmacological interventions focused on psychological or social factors that can improve symptoms, functioning, quality of life and social inclusion.

Psychological interventions are by nature complex and difficult to define.[22] However, it is known that they use 'the therapeutic alliance between the patient and the therapist to bring about change in emotional, cognitive and behavioural function'.[23] Psychological interventions are distinct from other types of interventions, such as education or medication. Their aim is to improve the psychological and physical well-being of the individual using a form of communication, often talk therapy, to foster a supportive relationship in order to promote patient autonomy and empowerment in the self-management of their chronic condition.[23] A psychological intervention includes a psychotherapeutic mechanism (improved emotional, cognitive or behavioural functioning), a psychosomatic mechanism (addressing the stress of having a chronic condition) or both.[24]

Psychological treatments may be categorised in a variety of ways, depending on current behaviour, change taxonomies or the underlying theory.[22]

Prevalence and wound healing outcomes

It has long been suspected that a bi-directional relationship exists between diabetes and chronic stress disorders, such as depression.[15] Growing evidence supports that stress and depression may, in some circumstances, precede the onset of central obesity and type 2 diabetes, potentially participating in the underlying pathophysiology.[15] People with diabetes exhibit depression rates up to twice as high compared to persons without diabetes.[15]

An observational study of 93 participants (73% male, mean age 60 years) examined the role of psychological distress and coping in the healing of diabetic foot ulcers (DFUs).[25] At 24 weeks, 60% healed. Ulcer area at baseline and confrontational coping were observed to be significant predictors of healing, with patients reporting a greater propensity for confrontational coping and exhibiting larger ulcers at study entry being less likely to have a healed ulcer by week 24. Depression was a statistically significant predictor, with patients exhibiting clinical depression having smaller changes in ulcer size over time ($p = 0.04$). Indeed, clinical depression accounted for over 30% of the variance in ulcer size over the observation period. Confrontational coping was not found to be related to the change in ulcer area over time. Instead, patients reporting clinical depression exhibited a smaller change in ulcer area. Finally, an analysis of potential mechanisms suggested that cortisol and pro-matrix metalloproteases-2 (MMP2) levels may contribute to the relationship between psychosocial factors and DFU healing.[25] However, it has been argued that the significance of physiological mechanisms may be difficult to determine without accounting for the role of behaviour.[26]

Psychological health is not well reported across VLU studies. One systematic review of 20 randomised controlled trials (RCTs) showed that only 3 studies considered factors related to mental health (e.g. body image feelings, self-esteem, depression, reasoning and cognition) using multiple assessment tools, making overall conclusions difficult.[9] Among the emotional consequences of VLUs are anxiety, depression, shame, low self-esteem, loss of control over one's own body, impotence and hopelessness; among social consequences, we can count isolation, social disconnection, loneliness and less perceived social support.[13]

Identifying factors (psychosocial ones in particular) that are present in VLU patients is difficult since such patients have been included both in studies of risk factors for developing VLU and in studies of factors that influence its recurrence.[13] Nevertheless, anxiety and depression are the most common reported factors affecting individuals.[13] People with VLU are perceived as restricted because they believe they are making other people uncomfortable—a feeling of segregation that hinders social interaction and contributes to social isolation and low self-esteem.[13]

An integrative review of 16 studies of 1,738 patients with VLUs identified 7 psychosocial factors among this population: depression, anxiety, feelings of hopelessness, subjective well-being, self-esteem, loneliness and spirituality/hope for a cure.[13] Across these studies, odour, exudate and pain were associated not only with states of depression and anxiety but also with feelings of helplessness, low subjective well-being and low spirituality.[13]

A study of 63 people >≤with VLUs (60.3% female, mean age 68.1 years) investigated the possible psychosocial predictors of healing at 24 weeks.[27] The study participants had lower physical and mental health-related quality-of-life summary scores compared with the general population of the United States. Few participants scored above the threshold (>7) suggestive of emotional disturbance for anxiety (30.2%) and depression (22.2%). More than a third had a negative emotional representation of ulcer (39%). Compared with

those with positive perceptions, the participants in the negative cluster reported a greater number of ulcer symptoms and believed the ulcer to be a chronic condition. Those with positive schema perceived the ulcer to be acute, with fewer symptoms and less serious consequences. The participants in the negative cluster of cognitive illness perception exhibited a more negative emotional representation of the ulcer (3.7 [0.9], 2.7 [0.8], t(47), $p < 0.001$).[27] Higher levels of perceived stress, holding negative perceptions about the ulcer, poorer adherence to bandaging and higher alcohol consumption were related to larger ulcer areas at baseline. Significantly slower rates of healing were observed for those with a negative cluster of illness perceptions ($ß = 1.4$, $p = 0.45$), higher perceived stress ($ß = –0.6$, $p = .008$) and depression at baseline ($ß = –0.5$, $p = .039$). No behavioural variables (adherence, alcohol consumption, diet, physical activity, smoking or sleep) were related to the healing rate.[27] The probability of healing was lower for those with a strong negative emotional representation of the ulcer at baseline. Higher levels of depression and exhibiting a negative cluster of illness perception were associated with a significantly slower rate of change in the VLU area, regardless of the sociodemographic, comorbidity and ulcer characteristics.[27]

An observational study of 53 participants with chronic VLUs assessed anxiety and depression using the hospital anxiety and depression (HAD) scale and wound healing scores.[28] Patients scoring in the top 50% on the HAD scale (more severe anxiety and/or depressive symptoms) were four times more likely to have delayed healing ($p = .015$) than those scoring in the bottom 50%. Of note in this study is that stress per se was not assessed but rather the psychological disorders of anxiety and depression.

Systematic reviews and literature reviews

Four systematic reviews (SR) have summarised the evidence for psychological interventions in the management of chronic wounds.[22, 29-31]

While there is extensive literature on the relationship between DFUs and well-being, there is a distinct lack of tools to measure well-being in this population. Well-being is a dynamic matrix of physical, social, psychological and spiritual factors, and the concept is inherently individual, varies over time, is influenced by culture and context and is independent of wound type, duration or care settings.[32,33] One by McIntosh, Ivory[32] assessed spiritual, psychological (including depression, self-esteem and powerlessness), physical (sleep) and overall well-being in patients with DFU.[32] However, as the different studies used a variety of tools, this impeded an overall comparison of study outcomes.

Another systematic review of psychological interventions in 19 RCTs on healing of all types of wounds identified only 2 RCTs on chronic wounds related to VLUs and DFUs.[30] Interventions included a social support Leg Club Model in the management of patients with VLUs[34] and biofeedback-assisted relaxation training in patients with DFUs.[35] The authors of the review concluded that psychological interventions can improve wound healing but acknowledged that more research is needed in this area.[30]

A systematic review aiming to synthesise existing knowledge about the relationship between psychological stress and wound healing identified 22 relevant studies.[31] However, although the review was limited to human studies, only one study referred to chronic wounds[28] and assessed anxiety and depression rather than stress. Additionally, the included studies used different methodologies, measurements and conceptual interpretations of stress, thus making comparisons between reports difficult.[31] The authors did suggest that a robust negative relationship, whereby stress is associated with impairment of healing and the dysregulation of biomarkers is associated with wound healing, is broadly consistent across a variety of clinical and experimental studies of acute and chronic wound types.[31] The size of the relationship between stress and wound healing estimated by this analysis was $r = 0.42$ (medium effect size).[31]

A systematic review of psychosocial interventions for the prevention and treatment of foot ulcers in people with diabetes identified 31 RCTs (4,511 participants), of which 24 focused on prevention.[29] A strong educational focus was a particular feature of prevention studies. The authors concluded that despite the relatively large numbers of studies identified, there is limited evidence for the impact of interventions aimed at either the prevention or treatment of foot ulcers: ulceration and healing outcomes were often not reported or showed no clear effects and were additionally affected by limitations in study size, design and reporting.[29] The relatively unselected populations enrolled in the included studies, the settings and personnel delivering most interventions and the fact that the results were compared with 'usual care', 'standard care' or alternative interventions meant that most of the existing studies are pragmatic in nature.[29]

Another systematic review of psychological interventions for the treatment and prevention of recurrence in DFUs identified seven trials (290 participants).[22] Three trials used a counselling-style intervention, and one assessed an intervention designed to enhance the understanding of well-being. One RCT used a biofeedback relaxation training intervention, while another used a psychosocial intervention based on cognitive behavioural therapy. A quasi-RCT assessed motivation and tailored the intervention accordingly. The authors were unable to determine whether psychological interventions are of any benefit to people with DFUs or a history of DFUs to achieve complete wound healing or prevent recurrence.[22]

The focus on prevention is very positive in these reviews, as if such strategies are effective, the impact on the individual could be quite significant. Although few would argue that healing or prevention of recurrence is not a valuable outcome to measure, this review[22], like others, seems to focus only on such 'clinically' relevant outcomes and has therefore ignored outcomes of relevance to patients. Surely, psychological interventions should also have an impact on the levels of stress, anxiety and depression reported in patients with chronic wounds.[13] Consequently, there is a need to include patients in defining the outcomes of interest, which should, in turn, contribute to shared decision-making and person-centred care approaches.[36]

Concluding remarks

Stress is a complex psychological phenomenon with physiological and behavioural impacts. It is influenced by context, individual circumstances and intrinsic and extrinsic factors. There is a bi-directional relationship between stress and wound healing. The onset of a wound may of itself cause the individual to be stressed, and chronic stress may affect the healing of the wound. Additionally, the health behaviours that may ensue due to stress can impact wound healing or wound recurrence. All of this underscores the need for the members of the multidisciplinary team to use a person-centred approach and recognise the factors beyond the wound itself that may impact healing and the individual's ability to cope with the wound. More research on employing psychological interventions to improve healing outcomes and the psychological well-being of individuals with wounds or at risk of recurrence of wounds is required.

4. Sleep

Sleep: a factor that influences wound healing

Like other animals, humans have evolved towards a division of behaviour into two fundamental behavioural states: one characterised by activity (wake) and the other by rest (sleep). The alternation of these behaviours during the daily 24 hours is punctuated by a constellation of physiological changes that play essential roles in the organism's homeostasis and growth and enhance its adaptation and anticipation to daily environment changes.[37] Sleep is considered a restoration period in which the nervous system slows its activity. While the activities of wakefulness enhance catabolic processes (degradation), sleep enhances anabolic processes (renewal). As anabolic components are required to preserve lean mass and maintain the healing process, it has been suggested that rest and sleep are factors that promote healing.[38,39]

Sleep–wake cycle and the circadian system

Sleep and wake occur in precise 24-hour cycles that have evolved as an adaptation to light-dark (LD) cycles resulting from earth's rotation around its axis. These cycles, referred to as circadian rhythms, are regulated by an internal circadian timekeeping system. This system is composed of a master pacemaker in the suprachiasmatic nucleus (SCN) neurons in the brain and subsidiary clocks in almost all peripheral cell types.[40] It governs most aspects of human physiology and behaviour, such as the sleep–wake cycle, acuity of the sensory system, body temperature, heart and respiratory rates, blood pressure, hormone secretion, renal, liver and gastro-intestinal activity, etc. At the molecular level, the two clocks are thought to consist of two coupled feedback loops in the expression of the same set of specific core-clock genes.[41] In turn, each circadian clock affects the expression of distinct gene sets and modulates physiological functions in the different cell types. The rhythmic output of the central SCN clock, whose phase is entrained by the daily LD cycle via the retina, synchronises the oscillators in the peripheral tissues by a variety of direct signalling pathways (humoral signals and the sympathetic nervous system) and indirect signalling pathways (sleep–wake cycles, body temperature and feeding–fasting cycles). The synchronisation of the multiple independent peripheral oscillators allows the generation of overt cyclic outputs in physiology and behaviour. The sleep–wake cycle is thus one signalling pathway that modulates circadian rhythmicity in the periphery. Importantly, it can also feed back into and modulate the activity and output of the central SCN clock.

The circadian oscillators in the skin

The principal function of the skin is to protect the body against different environmental aggressions, such as toxin or pathogen exposure, physical injuries, ultraviolet (UV) light, extreme temperatures or water loss. Since most of these insults vary as a function of the day/night cycle, it is therefore no wonder that the circadian system is implicated in the modulation of skin functions.[42]

The presence of circadian oscillators has been identified in most skin cell types, including epidermal and hair follicle keratinocytes, melanocytes, dermal fibroblasts and adipocytes. A growing amount of evidence is attributing diverse roles to these circadian oscillators.[42] For example, the circadian clock intrinsic to keratinocytes appears to be a key modulator of cell proliferation, as prominent diurnal rhythms in DNA replication, DNA repair mechanisms and cell division have been observed in progenitor/stem cells.[43,44] The supra-basal

epidermal layers also exhibit diurnal variations in several physiological parameters, such as skin pH, trans-epidermal water loss and stratum corneum capacitance.[45] In the hair follicle, the circadian clock seems to be involved in modulating cell proliferation at distinct stages of the hair cycle.[46] It has also been shown that the oscillators present in adipocytes are required for the fulfilment of these cells' metabolic and endocrine functions.[47] In fibroblasts, the clock has been suggested to be implicated, among other things, in the regulation of cellular senescence pathways.[48] In addition, emergent research has revealed that immune cells in the skin (resident and transient) also possess a clock, which has been suggested to play a role in these cells' ability to counter infection depending on the time of day.[49]

Importantly, these studies demonstrate that the diurnal modulations of most of these skin functions depend on the presence of an intact clock both locally (in the diverse types of skin cells) and systemically (direct and indirect coordination coming from the SCN central clocks).

Impact of sleep–wake cycle disturbances on health

An appropriate timing, duration and quality of sleep allows one to maintain the coherence of this multi-oscillator system to support optimal biological functioning. Sleep alterations can be caused by challenging work and lifestyle schedules, inappropriate exposure to light, the type of food that is imposed by modern society, an acute or chronic condition (hospitalisation, pain, noise, depression, etc.) or simply by aging.[50,51] The potential economic health burden of disrupted sleep is growing and should not be neglected. Recent analyses on both mouse (brain and liver tissues) and human (whole blood) transcriptomic data have begun to elucidate the potential molecular mechanisms and pathways that may underlie the effects of sleep disturbances on health. Chronic sleep loss or mistimed sleep have been shown to alter the expression levels and the temporal organisation of expression of circadian transcripts that are associated with key important pathways, including those implicated in glucose and lipid metabolism, immune and inflammatory responses, cell cycle regulation, hormone signalling, cellular signalling, and the regulation of transcription, translation and protein synthesis.[52]

Wound healing is a complex and multistep process, whose progression requires the engagement of many of these pathways in a finely orchestrated manner.[53] It would therefore not be surprising if chronic sleep loss or mistimed sleep also altered the expression of circadian transcripts in skin and SCN oscillators and affected tissue repair and regeneration upon physical injury to the skin. From this perspective, sleep loss has indeed been suggested to be one of the factors that can influence the wound healing process.[51,54]

Impact of sleep–wake cycle disturbances on wound healing

To achieve adequate skin closure, many factors and cell types have to interact during the sequential and sometimes overlapping stages of haemostasis, inflammation, angiogenesis, growth, re-epithelialisation and remodelling.[53] The effects of sleep alterations on many of these processes have been discussed in the literature, and it has been suggested that an appropriate timing, duration and quality of sleep are important for proper skin closure.

The first response to a wound is the constriction of the injured blood vessels and the activation of platelets to form a fibrin clot. A recent study observed the circadian variation of haemostasis, with transient hypercoagulability in the morning hours, as evidenced by the circadian circulation of a number of haemostasis parameters: increased platelet aggregation, fibrinogen, PAI-1 concentrations and thrombin generation markers (TAT complexes).[55] These results may explain the transient nature of thromboembolic events, with the most frequent cardiovascular events occurring in the morning. In the context of wound healing, these results may help in optimising the coagulation treatment in acute or chronic settings. From this

perspective, an appropriate sleeping architecture has been shown to improve the efficiency of the coagulation pathway.[56] For example, von Känel et al.[57] showed that in a sample of 135 unmedicated men and women, sleep fragmentation, sleep efficiency and sleep apnoea were associated with higher levels of the following prothrombotic factors: the von Willebrand factor, soluble tissue factor and plasminogen activator inhibitor, respectively. Another study with 190 patients found an association between increased morning fasting plasma levels of fibrinogen and insomnia symptoms.[58] However, the correlation between sleep duration and prothrombotic markers remains elusive.[59]

Once the fibrin clot ceases blood flow, neutrophils are immediately recruited to the wound in response to several signals that are released by resident cells. Monocytes, Langerhans cells, dermal dendritic cells and T-cells are subsequently involved in the clearance of cellular debris and infection resolution. Delayed wound healing can be caused by many factors that can lock the wound in a prolonged inflammatory state characterised by abundant neutrophil infiltration, with its associated reactive oxygen species and destructive enzymes.[60,61] Normal healing can proceed only when the inflammatory phase ends. Inflammatory and immune responses have been shown to oscillate over the course of the day, with peaks during the active phase, likely to provide an increased skin response during the periods of highest risk for encountering acute inflammatory insults and infections.[49,62] In line with a higher immune response during the active phase, sleep restriction has been shown to transiently activate the immune system by up-regulating many immune response-related genes in the peripheral blood mononuclear cells (PBMCs).[63] For example, in a study including 30 healthy volunteers, Irwin et al.[64] demonstrated that cytokine production and the mRNA level of interleukin-6 (IL-6) and tumour necrosis factor-*a* (TNF*a*) in PBMCs are significantly increased in the morning following partial sleep deprivation (sleep restricted between 3 AM and 7 AM) when compared to normal sleep (sleep from 11 PM to 7 AM). Similarly, Aho et al.[65] identified changes in gene expression in PBMCs in experimental conditions of sleep restriction (4 h/night for 5 nights, N = 9) vs. normal sleep conditions (8h/night in bed, N = 4) using genome-wide microarrays. Of the 25 most up-regulated transcripts, 8 were related to immune function, and accordingly, the majority of up-regulated Gene Ontology pathways were also related to immune function. Interestingly, some of the same genes that changed their expression in the sleep restriction group were also affected at the population level in individuals who reported insufficient sleep (population cohort of 472 individuals taken from the National FINRISK Study). In yet another study[66], 11 healthy women were subjected to a 42-h sleep deprivation assay. Different parameters were measured before and after the stress. Plasma interleukin-1ß (IL-1ß), TNFß, and natural killer cell activity were increased. In addition, delayed skin barrier function recovery was observed 3 hours after a tape stripping assay (67.5% recovery after sleep restriction vs. 80% before sleep restriction). A connection between immune system alteration and wound healing was also made in a study performed by Smith et al.[67] on 56 healthy unmedicated young participants in whom wounds were created by removing the top layer of eight forearm blisters induced via a suction method. The time to skin barrier restoration was significantly higher (5.0 ± 0.9 days) for participants whose sleep was restricted to 2h/night during 3 days compared with participants with adequate sleep (4.2 ± 0.9 days, p = 0.02). Concomitantly, as measured in wound fluids, the local immune response was altered. All in all, these results suggest that sleep troubles caused by a wound (pain, anxiety, depression, etc.) and its management (hospitalisation, noise, abnormal light exposure, etc.[51]) may thus have a non-negligible impact on acute or chronic wound healing progression. A better understanding of the relationship between sleep disturbances, inflammation and the risk of adverse health outcomes, such as chronic disease[68], would help advance our knowledge of specific aspects of sleep. This relationship could also be targeted to augment therapeutic control. In addition to diet and physical activity, treatment

of sleep disturbances may represent an additional aspect to consider in promoting wound healing.

As the inflammatory phase ends, angiogenesis occurs. Angiogenesis involves endothelial cell proliferation, migration, and branching to form new blood vessels. Angiogenesis plays a crucial role in wound healing to allow the delivery of nutrients and the maintenance of oxygen homeostasis required for cellular proliferation and tissue regeneration to occur.[69] The impact of sleep alterations on angiogenesis is less clear. Nevertheless, some evidence supports a circadian regulation of angiogenesis by both circulating circadian factors and cellular circadian clock machinery.[70] For example, it seems that melatonin influences the expression of the vascular endothelial growth factor (VEGF)[71] and may have a positive effect on both angiogenesis and wound healing.[72] Melatonin is produced by the pineal gland. Its secretion is regulated by the central clocks of the SCN and exhibits high blood concentrations at night and low levels during the day.[73] This pattern is significantly altered by sleep deprivation[74] and may likely influence angiogenesis progression. Furthermore, a study in mice showed that some important angiogenic factors exhibit circadian patterns of mRNA expression in skin and that the period circadian regulator 2 (PER2) core-clock gene has an influence on this pattern in both intact and wounded skin tissue, suggesting a role of the circadian system in the wound healing process.[75]

While new blood vessels are formed, fibroblasts and keratinocytes proliferate and invade the clot to form the granulation tissue. Here, some fibroblasts differentiate into myofibroblasts, which allow the drawing of wound margins together. The dividing fibroblasts deposit an extracellular matrix (ECM) and shift the wound microenvironment from the inflammatory to the growth state. As mentioned previously, skin stem cell populations exhibit prominent daily cell proliferation cycles, with higher proliferation during the day, that appear to be involved in the maintenance of epidermis homeostasis and in the restoration of its integrity following injury.[42,76,77] Cell cycle is a tightly regulated process whose progression is gated by checkpoint proteins. It seems that the circadian clock can directly time cell division by regulating checkpoint gene expression or by modulating checkpoint protein interactions and may play an important role in tissue regeneration during wound healing.[43,44,48,78,79] Janich's[80] work further showed that core-clock genes are expressed in successive waves in human epidermal stem cells and that each of these waves is associated with the expression of different groups of genes involved in differentiation (late-night to early-morning hours), DNA replication and cell division (afternoon and evening hours). In addition, a study using fibroblasts derived from mouse skin demonstrated that fibroblast mobilisation to the site of wounding appears to be directly under the control of the cell-intrinsic circadian clock that rhythmically modulates the efficiency of actin assembly in invading fibroblasts.[81] Accordingly, when the authors performed wounds by incision in living mice, fibroblast enrichment at wounds after 48 h was significantly greater when wounds were inflicted during the active phase than when they were inflicted during the rest phase ($p < 0.032$). Such high cell migration during the active phase and high cell proliferation during the afternoon and evening might have important implications for the optimisation of therapeutic approaches. Importantly, after the proliferation burst, proper skin wound healing requires myofibroblast replicative senescence and granulation tissue remodelling. A growing number of studies have revealed a link between human circadian rhythms and cancer and have suggested that the clock is involved in the regulation of tumour suppressor pathways.[82] For example, Mullenders et al.[83] showed that the suppression of the core-clock component ARNTL (BMAL1) in human cells affects the ability of p53 to induce a cell cycle arrest. Other studies found associations between irregular working hours and risks of breast cancer (odds ratio of 1.7 for night employment > 6 years vs. daytime work, n = 14,070 Danish women, 30–54 years old)[84] or prostate cancer (relative risk of 3 for rotating shift work vs. daytime work upon a 10 years follow-up, n = 14,052 Japanese men, 40–79 years old).[85]

Thus, abnormal sleeping schedules might have an impact not only on cell proliferation and cell mobilisation but also on the replicative slowdown process that is required for scar remodelling and maturation.

Circadian medicine

Although the impact of circadian rhythms on human physiology is recognised, little to no emphasis is placed on the importance of sleep architecture and the amount, quality or timing of treatment. Rather, in hospital settings, the focus is on health-care logistics and an acute care paradigm is followed—that is, treatment is administered as needed regardless of time of day.[86,87] Circadian medicine refers to the behavioural interventions that improve daily rhythms (chronotherapy), optimise the timing of treatment dispensing or drug delivery and eventually target clock components (chronotherapeutics and chronopharmacology), with the aim of preventing or treating acute or chronic diseases. The aim of this approach is to target different aspects of sleep for therapeutic optimisation, increase treatment efficiency and reduce side effects or toxicity by administrating the intervention according to the time of the day (i.e. according to the body's internal circadian rhythm).[88-91]

For example, in a study conducted on 596 patients at Lille University Hospital[92] showed that the incidence of major adverse cardiac events following aortic valve replacement was lower in patients who underwent cardiac surgery in the afternoon (9% of patients) than in those who had surgery in the morning (18% of patients) (hazard ratio 0.50; 95% CI 0.32–0.77; p = 0.0021). Another example is cancer treatment. In a multicentre RCT, Levi et al.[88] highlighted the beneficial effects of chronomodulated (administered to coincide with relevant circadian rhythms) chemotherapy (oxaliplatin, fluorouracil and folinic acid) compared with a constant-rate infusion method in metastatic colorectal cancer. In their study involving 186 patients, they observed an objective response (decrease in tumour size) in 51% of the patients in the chronotherapy group vs. 29% of the patients in the constant-rate group (21.5% difference; 95% CI 13.7–31.2; p = 0.003). Concomitantly, chronotherapy significantly reduced toxicity.[93] Similarly, the chrono-release of prednisone was shown to significantly increase the efficacy of rheumatoid arthritis (RA) treatments. In patients with RA, impaired function due to pain and joint stiffness are commonly most severe in the early morning because of the abnormal rise of pro-inflammatory cytokines during the night. Nocturnal secretion of cortisol, which can counteract the effects of these cytokines, is perturbed in patients with RA. The optimal time for the delivery of the glucocorticoid treatment is thus during the night. An RCT with 288 patients with active RA[94] demonstrated that administering programmed tablets (that release prednisone 4 hours after ingestion) at bedtime diminishes morning pain and joint stiffness by 22.7% vs. 0.4% for immediate-release tablets taken in the morning (mean relative change; 95% CI 0.49–44.30; p = 0.045).

Applied in the context of wound care, the circadian medicine approach could help to augment the therapeutic control of healing.[95] For example, favouring the administration of anti-inflammatory drugs during the active phase and limiting them during the rest phase has been shown to improve healing during postoperative recovery.[96] Alternatively, knowing when skin stem cells are more prone to proliferation and migration might have important implications for the successful integration of cutaneous substitutes. Moreover, favouring wound care and debridement when clotting is the most efficient could lower side effects. Improving sleep by modulating some of its different aspects could have a significant positive impact on the inflammatory state of wounds with delayed healing or chronic wounds. Thus, the optimisation of the timing of wound care as a function of the time of day (i.e. according to the body's internal circadian rhythm), as well as the modulation and optimisation of sleep, could enhance clinical outcomes. Nevertheless, for such knowledge to emerge, further research that integrates circadian parameters is needed.

The application of circadian timing to patient treatment is an emerging practice in clinical trials. Its implementation when designing clinical studies and evaluating trial results will without a doubt impact the quality of life of patients and the effectiveness of disease therapies. In addition, incorporation of circadian education in the curriculum of medical and nursing schools will also be important for filling this gap. Circadian medicine could represent another arm in the effort towards more person-centred and personalised medicine.[97,98]

Concluding remarks

Circadian clocks seem to be implicated in the regulation of many aspects of the wound healing process (including hemostasis, inflammation, immune function, angiogenesis, cell division and cell mobilisation), and could thus have an impact not only on skin homeostasis but also on skin restoration following injury. This regulation, which appears to involve both local skin oscillators and systemic time cues, could be disrupted by sleep–wake cycle alterations (e.g. by shift work, hospitalisation, pain, noise, depression, etc.). However, further studies are needed to better understand and characterise the consequences of disrupted circadian rhythms on skin wound healing.

5. Smoking

Definitions

Smoking or tobacco products can be divided into these primary categories:[99]

- Smoking (or traditional) tobacco products: These include cigarettes, cigars, cigarillos, or pipes.
- E-cigarettes or similar electronic devices (e-shisha, e-pipe): These are electronic devices that use e-liquids, which usually contain nicotine and produce vapour.
- Heated tobacco products: These are, for example, sticks or capsules containing tobacco which are heated by devices.

Table 1: European survey on the use of tobacco[99]

Some conclusions from the European survey (n = 28,300):

- The overall number of smokers was stable between 2014 and 2017 (26%) and has decreased since (23%).
- European smokers smoke more than 14 cigarettes a day.
- 14% of Europeans have tried e-cigarettes (of which 29% are in Ireland and 6% in Poland) and 2% currently use them (of which 7% in Ireland). The younger the smokers are, the more likely they are to have tried or used e-cigarettes.
- 48% of e-cigarette users use e-cigarettes with nicotine every day.

Note: Europe has an estimated population of 447.7 million citizens.[100]

Prevalence of tobacco use

Each year, 700,000 people in Europe die because of complications related to tobacco use.[99] 27% of all cancers can be immediately associated with smoking, and smokers have a high risk for developing cardiovascular and respiratory diseases.[99] Within the EU, smoking is the largest avoidable health risk; consequently, the EU organises and supports many initiatives to reduce tobacco consumption and to raise awareness. Since 2003, the European Commission has been conducting repeated surveys (special Eurobarometers) to estimate the use of tobacco and the attitudes of Europeans towards tobacco-related issues in the population older than 15 years. The most recent surveys were conducted in 2017 and 2020.[99]

Evidence of the harmful effects of smoking has been growing, showing an increased risk of heart, vascular and lung disease, stroke and cancers, as well as impaired wound healing and tissue repair.[101,102] Smoking also has a negative impact on skin health, wrinkling and skin aging.[103,104]

Prevalence of tobacco use in patients with wounds
Studies describing the prevalence of tobacco use in patients with wounds are very limited. Wigston[105] found that in 73 patients with healing and non-healing wounds, 11 (15%) of them were smoking. In 6 of the 11 cases, the wounds were not healing (55% of the smokers).

Walker[106] identified the number and types of wounds treated in the Gippsland area (Australia) using the Mobile Wound Care Program. In a

population of about 240,000 people, they identified 1,762 patients with wounds, among whom 261 (14.8%) were smokers. This is similar to the 2015 prevalence figures of people smoking in Australia: 13.3% (women) and 15.6% (men).[107]

How smoking affects (chronic/complex) wound healing

Extensive research has been conducted on the numerous health risks caused by smoking, in contrast to smoking as an impairing factor to wound healing, which has been inadequately documented and for which high-quality evidence is lacking.[108] As cigarette smoke contains multiple components, it is difficult to pinpoint which one plays a role in impairing the healing process.[108] There is a paucity of studies examining the effect of smoking on chronic/complex wound healing; however, there is sufficient clinical and scientific research to suggest that assessing smoking status and promoting smoking cessation in any patient with a wound should be part of their assessment and treatment.[109]

Composition of cigarette smoke

Cigarette smoke contains over 4,000 identified chemical components, of which 250 are known to be harmful. The 4 components most frequently implicated in impairing wound healing are nicotine, carbon monoxide (CO), hydrogen cyanide and nitric oxide.[101,109-111] Many other components may play a significant role but have not yet been investigated.

Nicotine

Nicotine ($C_{10}H_{14}N_2$) is found in the plants of the nightshade family and is highly concentrated in the leaves of the tobacco plant (Nicotiana Tabacum). Nicotine is part of the alkaloid family, and its toxicity protects the plant against herbivore parasites. Both the plant and the substance are named after Jean Nicot, the French ambassador to Lisbon who introduced tobacco to the French court in the 16th century.[110]

With each cigarette, 2 to 3 mg of nicotine is inhaled.[112] Nicotine causes peripheral vasoconstriction and reduces tissue blood perfusion by stimulating sympathetic nervous activity, leading to the release of epinephrine.[101,109-111] Smoking can also cause tissue ischemia due to augmented blood viscosity caused by fibrinolytic activity and increased platelet adhesiveness.[101] Nicotine reduces the proliferation of erythrocytes, macrophages and fibroblasts.[112]

Carbon monoxide

Carbon monoxide is a colourless and odourless gas.[110] With each cigarette, smokers inhale 20 to 30 ml CO;[112] thus, cigarette smoke consists of approximately 4% CO.[110] CO has a 200 times greater affinity to bind to haemoglobin than oxygen. This results in the formation of carboxyhaemoglobin, reducing the capacity of oxygen transportation in the blood. This leads to impaired tissue perfusion and cellular hypoxia as the oxygen–haemoglobin saturation curve shifts to the left.[101,109-111] This hypoxic state increases the production and aggregation of erythrocytes and increases blood viscosity.[110] Heavy smokers can reach carboxyhaemoglobin concentrations similar to those of people with CO poisoning.[111]

Hydrogen cyanide

Hydrogen cyanide (HCN) is a toxic chemical that is used as a rodenticide and in chemical weapons. Hydrogen cyanide impairs the transport of oxygen and inhibits the cellular oxygen metabolism and leukocyte function, resulting in decreased cellular repair and a decreased inflammatory response. In marihuana smoke, HCN levels are three to five times higher than in tobacco smoke.[110]

Nitric Oxide

Nitric oxide (NO) is an important biological signalling molecule which is present in cigarette smoke in high concentrations. When inhaled, it causes acute bronchodilation and the vasodilation of pulmonary capillaries, which increases the absorption of nicotine. Chronic exposure to nitric oxide in cigarette smoke is thought to inhibit endothelial nitric oxide synthase, resulting in lower circulating concentrations of nitric oxide and increased resting tone of the vascular smooth muscle[110]

Wound healing is impaired due to the suspected synergistic action of these four key components, resulting in decreased oxygen metabolism and attenuated wound healing processes.[110]

Effects of tobacco use on (chronic/complex) wound healing

Oxidative stress, hypoxia and tissue oxygen

Perfusion and oxygenation

Cigarette smoking causes peripheral vasoconstriction and reduces the blood flow in the skin by 40%.[102] This vasoactive effect of smoking on tissue oxygenation and the aerobe metabolism is temporary. Within 45 minutes after smoking, tissue blood flow and oxygen levels are completely restored.[102] Smoking just one cigarette leads to decreased tissue oxygen levels and does not depend on smoking habits. Heavy smokers experience tissue hypoxia during longer periods each day.[109]

Mosely and Finseth[113] investigated the harmful effect of smoking on the circulation of the hand and, as such, proved the link between smoking, poor oxygen supply and wound healing. Van Adrichem et al.[114] investigated the acute effect of smoking on the microcirculation in the skin of the thumb in 32 healthy volunteers (22 smokers and 10 non-smokers). Using laser Doppler, they assessed the blood flow of the smokers after smoking two cigarettes. A decrease in flow was observed after the first cigarette (23.8%) and after the second (29%). Ten minutes after smoking, half of the decrease in blood flow was restored.

Oxidative stress

Oxidative stress is caused by an exogenous and endogenous release of various reactive oxygen species. Hydrogen peroxide, superoxide, nitric oxide and hydroxyl radicals interfere with cellular functions and damage different components of cells and tissues. Antioxidants, such as vitamin C, protect these cells and tissues against harmful reactive oxygen species. Studies[115] have shown that up to 1/3 of smokers suffer from severe vitamin C deficiency. In smokers, oxidative stress is high, which means that the turnover of vitamin C is increased (see Part 2, section 'The effect of nutrition on wound healing'[2]). In addition, smokers tend to eat less fruit and vegetables, resulting in insufficient vitamin C intake.[102]

Inflammation/immune response

Smoking decreases to the risk of clot formation by increasing platelet activation and fibrinogen release, although it changes the composition of the thrombus, leading to an increased release of cytokines and growth factors, such as PDGF and TGF-ß1, resulting in an altered inflammatory response.[102] Many different pathways induced by smoking modify the function of neutrophils and macrophages, resulting in a decrease in the cell count, impairing chemotaxis, migration and phagocytosis.[102] In the inflammatory phase, smoking causes impaired white blood cell migration, resulting in lower numbers of monocytes and macrophages at the wound site, and reduces neutrophil bactericidal activity. Lymphocyte function, the cytotoxicity of natural killer cells and the production of IL-1 are all depressed, and macrophage sensing of Gram-negative bacteria is inhibited.[101,116] Smoking also compromises the normal regulation of MMPs and tissue inhibitors of metalloproteases (TIMPs), resulting in an abundant protease release and reduced protease inhibition, which in turn leads to connective tissue degeneration.[102] The early immune response after wounding is diminished, causing a decreased opportunity to control bacterial invasion to the wound bed and augmenting the risk of contamination or infection.[102,109]

Proliferation and remodelling

The proliferative and remodelling phase of wound healing by smoking is affected by a number of mechanisms.[102]

Formation of the ECM/collagen production and angiogenesis

Smoking decreases fibroblast activity (chemotaxis, migration and proliferation), leading to a diminished production of the ECM compounds,

reduced collagen synthesis and deposition and a disturbance of the protease balance.[101,102] Wong et al.[117] demonstrated that even secondary smoking can inhibit the migration of fibroblasts in wound healing. As growing vessels depend on the extracellular matrix for support, the reduced collagen deposition in smokers is likely to translate into impairment of wound angiogenesis.[102]

Epithelialisation

Nicotine stimulates the release of catecholamines and attenuates epithelialisation by impairment of keratinocyte chemotaxis and proliferation.[118] In smokers, the epidermis and especially the stratum corneum is thinner than in non-smokers.[102]

Contraction

The transformation of fibroblasts into myofibroblasts is stimulated by fibrinogen and fibronectin, of which a higher concentration is observed in smokers, leading to enhanced wound contraction. The exact mechanism remains unclear.[102]

Effect of smoking cessation on wound healing

Møller et al[119] investigated the complications after surgery in 120 patients (60 smokers vs 60 non-smokers) assigned to an intervention (counselling and replacement therapy) and a control group. The overall complication rate was 18% in the smoking intervention group and 52% in controls (p=0.0003). The most significant effects of intervention were seen for wound-related complications (5% vs 31%, p=0.001), cardiovascular complications (0% vs 10%, p=0.08), and secondary surgery (4% vs 15%, p=0.07). In an RCT among 78 people (48 smokers vs 30 non-smokers) with incisional wounds and followed for 15 weeks showed an infection rate of 12% vs 2% ($p < 0.05$) after 15 weeks.[120]

Oxygen levels restore quite fast after smoking cessation.[102] The vasoconstrictive effect of nicotine only lasts for 45 to 90 minutes[121], and blood flow, tissue oxygen and oxygen metabolism are restored. The CO levels return to normal after 12 h of abstinence.[121] The vasoconstrictive and hypoxic effect of smoking disappears 24 h to 48 h after cessation.[121] Vitamin C levels and collagen synthesis increase because of a decrease in oxidative stress, and after two weeks, the damage of this stress is reduced.[102] After about four weeks of abstinence, the inflammatory functions, such as the neutrophil count and the function of monocytes and macrophages, are restored and the oxidative killing mechanisms normalise.[102] However, the harmful effect of smoking on proliferation and remodelling is not reversed as rapidly.[102] It takes several months or longer to restore epidermal regeneration, fibroblast proliferation and collagen metabolism.[121]

Before surgery, total abstinence from smoking is recommended for at least four weeks before the intervention and should be maintained until the wound is completely healed. Of course, definitive smoking cessation or at least a prolongation of this time is more beneficial to the patient's overall health status.[121] Complications in wound healing and incisional wound infections decrease with smoking cessation.[109]

Effect of nicotine replacement therapy

The Native Americans were already aware of the habit-forming properties of tobacco. In the '70s, scientists identified nicotine as the cause of tobacco addiction by proving the withdrawal effect when suddenly putting smoking on hold after perpetual use. By the '80s, it became clear that a nicotine substitute was needed to achieve nicotine cessation.[122] Both assistance and substitute therapy are necessary to achieve successful smoking cessation.[121] Preoperative smoking cessation can be facilitated by a small counselling intervention.[121] Caregivers should not hold back to give cessation advice or to enlist the help of a tobacco treatment specialist.[121] Substitute therapy (e.g. nasal spray, chewing gum, inhaler, tablets or transdermal devices) contains a nicotine dose necessary for the withdrawal effect but does not contain any of the other toxic substances found in cigarette smoke.[121] Although nicotine has proven negative effects on the human body, it is not the main substance responsible for

the many pathologies linked to smoking.[121] By using nicotine replacement therapy, the high peaks of nicotine plasma concentrations are avoided, as, for example, patches keep these concentrations stable at less harmful levels.[121] The effect of nicotine on wound healing needs more investigation[102] and is dual: nicotine can attenuate the wound healing mechanisms[102], although some studies suggest that low doses can actually have a positive effect on healing.[123,124] The use of transdermal patches seems to have no negative or positive effects on infection rates or wound healing.[125]

E-cigarettes and wound healing

E-cigarettes are electronic devices that allow the user to inhale vapour (vaping) produced by a solution that is absorbed by a wick attached to a heating element and powered by a rechargeable lithium-ion battery. The solution contains a dose of nicotine, a flavour and a combination of glycerol and propylene glycol (solvent).[126,127] E-cigarette smoke contains nitrosamines, diethylene glycol and other potentially harmful contaminants.[128] The long-term effects and safety of the use of e-cigarettes need to be investigated.[126] The results of early studies imply that e-cigarettes may cause impairing effects on wound healing that are very similar to those related to traditional cigarettes.[129]

Smoking as a causal factor of wounds

Pressure injuries

A systematic review and meta-analysis[130] of 15 studies (11,304 patients) evaluated the relationship between smoking and pressure injuries. It was concluded that among those at risk of pressure injuries, current and past smokers have a significantly higher risk (about 1.5 times) of developing pressure injuries than non-smokers.

Thromboangiitis obliterans or Buerger's disease

Thromboangiitis obliterans (TAO) (also called Buerger's disease) is a nonatherosclerotic, segmental inflammatory disease that most commonly affects the small and medium-sized arteries and veins in the upper and lower extremities.[131,132] It is strongly associated with smoking and affects mostly men between the ages of 25 and 35 years.[133] TAO occurs more often in the Middle East (45%–63%) and Far East (16%–66%) than in Europe (0.5%–5.6%) and with a prevalence of 80% in Israel (Ashkenazi Jews).[132-134] The prevalence of the disease in women is increasing (11%–23%).[133]

Although the aetiology of Buerger's disease (See Figure 2) is unknown, a complex interaction between smoking, genetics, hypercoagulability, endothelial dysfunction, infection and immunologic mechanisms is suspected. Tobacco smoking plays a central role in the initiation and progression of the disease.[131] TAO presents in young male smokers with complaints of claudication, pain at rest, distal ischemic ulcers or gangrene.[132] The diagnosis is made by ruling out other vascular or autoimmune diseases.[133] An abnormal Allen test is highly suggestive of TAO[132] Total and immediate abstinence of all tobacco-related products results in spectacular improvement and is the cornerstone of treatment and prevention of amputation.[132,133] Revascularisation is mostly not possible, and other treatment options, such as sympathectomy, spinal cord stimulation, growth factors, and prostacyclin, need to be investigated more thoroughly.[133]

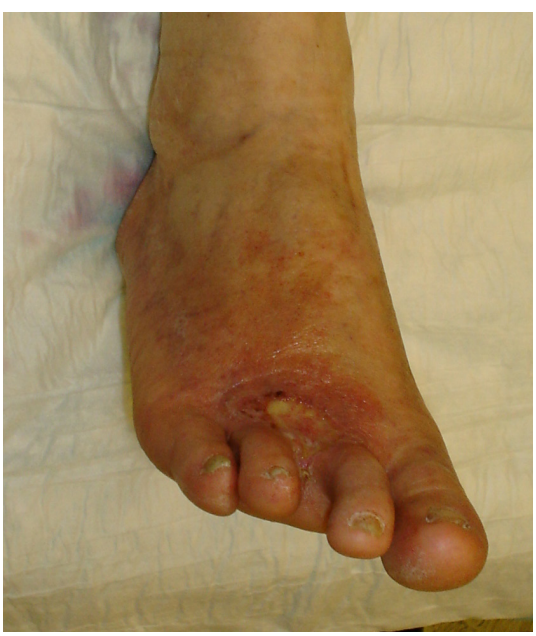

Figure 2: Buerger's disease

Cannabis arteritis or cannabis-associated arteritis

According to the European Drug Report (2020), cannabis is the most used illicit drug in Europe, especially among adolescents. Approximately 27.2% of Europeans aged 15–64 have used cannabis at least once in their lifetime. Fifteen percent of them are between 15 and 34 years old and have used cannabis within the last year. Approximately 1% of European adults use cannabis (almost) daily (20 days or more in the last month), and 75% of them are male.[135]

Cannabis is derived from the hemp plant Cannabis sativa, and the active substances are 9-tetrahydrocannabinol (THC)[136-138] and cannabidiol (CBD).[139] Cannabis smoke also contains most of the same toxic substances that are present in tobacco smoke.[137] Chronic cannabis use can set off the development of thrombosis, inflammation and atherosclerosis, leading to myocardial infarction, cardiac arrhythmias, cardiomyopathies, stroke and arteritis.[136,139,140]

Cannabis arteritis (CA) is an exceedingly rare condition caused by chronic cannabis use and comparable to Buerger's disease.[138-140] It mainly affects the lower extremities and presents as peripheral or digital necrosis.[141] The first case was reported in 1960, and since then, over 100 cases have been published. This may be an underestimation.[139] In young patients with peripheral arterial disease, CA is probably underdiagnosed[140], and due to the growing legalisation of cannabis for medicinal and recreational use, there is a need for more awareness.[136,139] In patients with a diagnosis of TAO, 40% are believed to also be cannabis smokers.[140]

The pathogenesis of CA remains unclear and debated and causes disagreement as to whether to name the condition CA or cannabis-associated arteritis.[142] It is thought to be a subtype of Buerger's disease because of the comparable clinical and arteriographic findings in both disorders.[137]

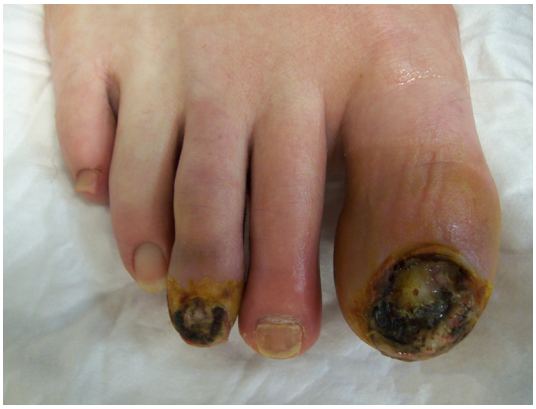

Figure 3: Cannabis arteritis

Cannabis is at least a co-factor in the development of arteriopathy because of the vasoconstrictive effects of THC. The often seen co-abuse of tobacco and cannabis raises the suspicion of a common contaminant or a synergistic effect.[138,139] The presence of arsenic is also considered a possible explanation, as arsenic inhibits the VEGF and induces endothelial cell apoptosis, leading to impaired angiogenesis.[138,139] Arsenic concentrations are high in handmade cigarettes, and Europe has controlled arsenic concentration in cigarettes since 1957. Additionally, illicit drugs may contain higher levels of arsenic.[138]

Patients with CA present with the following symptoms: claudication, painful distal ischemia, tissue necrosis and gangrene.[139] Remission of the symptoms occurs with cessation, although the symptoms reappear if the abuse is recommenced. Amputation is often needed if cannabis consumption is not stopped.[138-140] Termination of cannabis use is crucial in the treatment of CA, and vasodilator drugs and anticoagulants might be administered during the acute phase. In more severe cases, sympatholytics, hyperbaric oxygen therapy, thrombolysis or a distal rescue bypass can be considered.[138]

E-cigarette burn injuries

Over the past years, increasing numbers of burns related to the explosion of an e-cigarette or its battery, flame or contact burns from overheating or explosion of the device and chemical burns from the lithium-ion battery have been reported.[126,127,143]

Keeping e-cigarettes close to the body (e.g. in a pocket) is a risk factor, and these burns are more often seen in men, as women tend to keep their cigarettes in a purse.[126] The burned areas are related to clothes pocket location: hands, buttocks, thorax, thighs and genital areas are exposed[126] Explosions while using the device cause facial burns and/or inhalation injuries.[127] The burns may be contaminated by lithium-ion, and this must be taken into account before cooling the burns with water.[143] The use of mineral oil would be encouraged, if available, followed by early excision and debridement.[143] Users of electronic cigarettes should be warned about the risks of wearing the devices close to the body.[126]

Concluding remarks

There is a relationship between smoking and wound healing, as smoking impairs all wound healing phases. Smoking cessation should be encouraged in smokers with wounds and cessation aids like nicotine patches can be used (except in TAO). In some rare cases, smoking might cause ulcerations.

6. Alcohol misuse

Acute and chronic alcohol consumption impairs the wound healing process.[54] Alcohol intoxication at the time of injury is a risk factor for increased susceptibility to infection in the wound.[144,145] For example, Gentilello et al.[146] used data from a larger RCT to demonstrate that a blood alcohol level of > 200 mg/dl can trigger inflammation.[147] Beyond the increased incidence of infection, alcohol consumption also seems to influence the proliferative phase of healing. A one-time exposure to alcohol decreases wound angiogenesis by up to 61%. This drop in angiogenic capacity involves both a reduced expression of VEGF receptors and a decreased nuclear expression of HIF-1 alpha in endothelial cells.[148,149] Wound vascularity is reduced and causes increased wound hypoxia and oxidative stress.[148] Additionally, alcohol consumption affects connective tissue restoration, resulting in decreased collagen production and alterations in the protease balance at the wound site.[150] A trial including 16 participants (n = 9 abstinent and 7 alcohol abusers) evaluating the collagen and total protein accumulation in wound granulation tissue after 8 weeks of alcohol abstinence showed a significant increase in proline levels (median 81.3 nmol/mm vs. 69.3 nmol/mm, $p < 0.05$) and in total protein levels (median 632 nmol/mm vs. 571 nmol/mm, $p < 0.05$), respectively.[151]

Concluding remarks

Alcohol consumption can lead to impaired wound healing by decreasing the early inflammatory response and inhibiting wound closure, angiogenesis and collagen production. Additionally, an alteration of the protease balance at the wound site may occur.

7. Commonly used medication

Introduction

This section outlines the implications of drugs on the wound healing process. In order to get an overview of prescribed and non-prescribed medicine use in the European Union, a European Health Interview Survey was conducted between 2013 and 2015. Citizens of Europe, 15 years or older, were asked about their medicine use 2 weeks prior to the survey. In Europe (2014), women use more prescribed medicines than men, and this difference can be explained by the use of contraceptive pills and hormones. The use of prescribed medicines increases with age.[152]

Table 2 presents a list of some of the most common medications and the phases of wound healing they may affect.

Antibiotics should be used appropriately, and routine use should be avoided for acute and chronic wounds.[153,155,156] Tetracycline and erythromycin have an anti-inflammatory impact on wound healing[153,157], gentamycin delays re-epithelialisation[157], bacitracin and mupirocin inhibit contraction.[157]

Antiseptics are significantly cytotoxic to keratinocytes and fibroblasts, causing a delay in re-epithelialisation and an inhibition of wound contraction and tissue strength[154,156,157]

Anticoagulants, warfarin and heparin, may impair wound healing by inhibiting fibrin formation.[153,158]

Antiplatelet drugs (aspirin, clopidogrel and dipyridamole) prevent aggregation and the activation of platelets, and as such, they inhibit the early stages of wound healing.[158] Platelet aggregation is irreversibly inhibited by aspirin.

Table 2: Common medications and their possible effect on wound healing[153,154]

Wound healing phase	Interfering drugs
Coagulation phase	Anticoagulants Antiplatelet drugs NSAIDs
Inflammatory phase	Antibiotics Antiseptics Aspirin Colchicine Corticosteroids Dapsone NSAIDs
Tissue formation	Antineoplastic drugs Colchicine Corticosteroids Vasoconstrictors
Wound contraction	Corticosteroids
Tissue remodelling	Corticosteroids

Coagulation is inhibited by warfarin and heparin and increases the risk of hematoma formation.[154]

Corticosteroids affect almost every phase of the wound healing process, as they inhibit gene expression in different cell types[153,157], resulting in anti-inflammatory, antiproliferative, immunosuppressive and vasoconstrictive effects.[157,159]

Inflammation is influenced by the impediment of

the synthesis of prostaglandin and a decrease in chemotaxis and phagocytosis by the white blood cells.[153] A decreased presence of macrophages and platelets reduces cytokine stimulation; re-epithelialisation, fibroplasia and angiogenesis are decreased due to reduced mitotic activity; in addition, the synthesis of collagen, proteoglycan and glucosamine is decreased, all of which result in impaired tissue formation.[153] Tissue remodelling is decreased because of inhibition of fibroblast activity and reduced wound contraction.[153] The long-term use of corticosteroids has a negative impact, while the impact of short-term use is limited.[157]

Colchicine is used for the treatment of gout and has an anti-inflammatory effect.[160,161] It has vasoconstrictive properties and may impede the blood supply to the wound bed.[157] The formation of microtubules is inhibited, leading to an impairment of granulocyte migration, which affects the early inflammatory phase.[153,157] Colchicine has an important effect on inflammation by impairing neutrophil function, activation and migration. The activation of macrophages is prevented by a decrease in TNF-a receptor expression, and the degranulation of mast cells is interrupted.[161] The synthesis of collagen is obstructed, as in the absence of microtubules, procollagen cannot be moved extracellularly from the fibroblasts, resulting in a decreased formation of the ECM. Colchicine increases collagenase synthesis and affects collagen lysis and collagen remodelling, which leads to decreased tensile strength.[153,157]

Dapsone is an anti-inflammatory drug, and its action is mainly targeted against polymorphonuclear neutrophilic leukocyte (PMN)-mediated inflammation.[153,157] As normal wound healing does not require the presence of neutrophils, wound healing may not be impaired.[153] In conditions of PMN-mediated injury and inflammation, dapsone might be useful.[153]

Immunosuppressive agents are used to reduce rejection rates in organ transplants.[162] They have an impact on the wound healing process because of their interactions with inflammatory mediators.[162] Until complete wound healing has occurred, limitation of the dose or even termination of the therapy should be considered, particularly for the newer agents, such as everolimus.[162]

Antimalarials (chloroquine and hydroxychloro-quine) decrease inflammation without immunosuppression by interfering with the cell surface receptor complexes.[153] Hydroxychloroquine inhibits platelet adhesiveness and platelet aggregation but causes no bleeding disorders.[153] In oral lichen planus or lower limb ulceration in systemic lupus erythematosus, it enhances ulcer healing.[153]

Non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, inhibit the production of PGE2 to reduce pain.[158] The short-term use of NSAIDs has a limited impact on wound healing, although long-term use and the use of higher doses may delay the inflammatory response.[157]

Vasodilators can be administered for treating vasospasms causing necrosis and ulcerations. Using vasodilators for a long period to treat leg ulcers is not recommended.[153]

Vasoconstrictors, such as adrenaline, lead to poor wound healing or increased ulcer necrosis by impairing microcirculation and causing tissue hypoxia.[157]

Medications as a causal factor of wounds

Hydroxyurea

Hydroxyurea is used in the treatment of chronic myeloid leukaemia and myeloproliferative disorders, such as thrombocythemia, polycythaemia vera [163,164], severe psoriasis and sickle cell disease.[165] Diverse cutaneous reactions are known to be side effects of hydroxyurea treatment, including xerosis, hyperpigmentation, nail discolouration, scaling, lichen planus-like lesions, poikiloderma, skin and tissue atrophy and leg ulcers[163,164] (See Figure 4). The ulcers are very painful, localised in

the malleolar region and often non-responsive to local wound care and systemic therapy.[163-165] To achieve wound healing, cessation of the medicine is needed.[163,164] In some cases, debridement and skin grafting should be considered.[163,164]

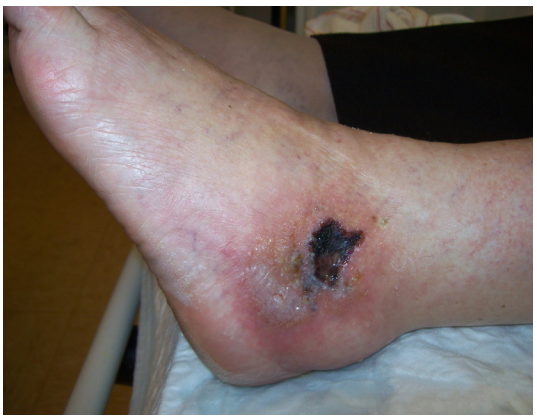

Figure 4: Example of hydroxyurea induced leg ulcer

Methotrexate

Autoimmune conditions like rheumatoid arthritis and psoriasis are often treated with methotrexate (antimitotic agent) despite of the many possible side effects. One of these side effects is the development of cutaneous ulcers. These ulcers are rarely reported in patients with psoriasis and extremely rarely reported in non-psoriatic patients. The occurrence of ulcers is dose-related and discontinuation leads to healing of the ulcers.[166]

Warfarin-induced skin necrosis

Warfarin-induced skin necrosis is a rare complication[167,168] with high morbidity and mortality.[168] Warfarin is prescribed in the primary and secondary prevention of thromboembolic disorders.[168] Warfarin-induced skin necrosis affects approximately 0.01% - 0.1% of patients receiving this anticoagulation therapy per year.[167-169] Within 24 hours of administration, petechiae and ecchymosis occur and evolve to skin necrosis between the 3rd and 10th day, primarily in multiple areas with increased subcutaneous fat, such as the abdomen, buttocks, thighs and breasts in female patients.[168,169] Risk factors are obesity, perimenopausal age, viral infections, hepatic disease and drug interactions[167] and hereditary protein C or protein S deficiency.[170] The risk of necrosis increases if the patient receives the initial dose of warfarin without simultaneous heparin administration.[167,169] Diagnostic procedures include clinical history, time of onset, location of the lesions, laboratory results and skin biopsy.[168] Discontinuation of warfarin is a crucial step in treatment to stop the progression of necrosis.[168] Intravenous heparin therapy or low molecular weight (LMW) heparin can be administered if anticoagulation is essential until the necrotic lesions heal.[167] Local treatment depends on the size of the lesions, and classic wound management, debridement or grafting should be considered.[167,168] Oral anticoagulation with vitamin K antagonists (Warfarin) is also a risk factor in the development of calciphylaxis and Martorell Hypertensive Ischemic Leg Ulcer.[171,172]

Heparin-induced skin necrosis

Heparin-induced skin necrosis is a rare complication of treatment with low molecular weight heparins (LMWHs) or unfractionated heparin (UFH)[169,173] and is probably underreported.[173] The necrosis may appear at the site of administration after subcutaneous injection[169,174] and is paradoxically associated with intravascular thrombosis caused by antibodies formed against the heparin-PF4 complex or associated with a poor injection technique.[169] Within 5 to 10 days after the beginning of the LMWH therapy, the first symptoms, painful erythematous plaques, progressing to purpuric plaques, may occur and evolve in bullae followed by necrosis.[169] Diagnosis is clinical, although heparin-PF4 antibodies can be detected in the serum[169] Cessation of the heparin and local wound treatment often leads to complete healing of the lesion.[169] Other anti-thrombin drugs should provide an alternative to heparin therapy, and warfarin should be avoided because it can worsen protein C deficiency.[169]

Extravasation injuries

The extravasation of various agents administered via intravenous infusion, such as solutions of calcium, potassium, bicarbonate, hypertonic dextrose, cardiac drugs, chemotherapeutic

drugs, cytotoxic drugs and antibiotics, may cause tissue necrosis[175] or an inflammatory reaction.[176] A combination of factors is responsible for the development of extravasation injuries: the osmolality of the solution, the toxicity to the tissue, vasoconstrictive properties, the pressure of infusion and the local anatomical characteristics.[175,176] Extravasation injuries can occur in every patient, although seriously ill patients in intensive care units, neonates and geriatric patients are at higher risk.[175] These injuries occur in the typical places used for intravenous infusion: the dorsum of the hand or foot, the forearm or the ante cubital fossa.[175,176] Local swelling, erythema, blistering and pain are the first symptoms[175,176] and are warning signs to caregivers, who should react promptly by stopping the infusion.[176] The extent of the damage may only be visible after a few days or up to three weeks in the case of the extravasation of calcium solutions.[175] Delayed diagnosis can have serious complications, including scaring, contracture, cellulitis, skin grafting, amputation and death.[176] Treatment consists of a few possible options: immobilisation, observation, antidotes, irrigation, surgical debridement or fasciotomies.[176] Iatrogenic injuries should be prevented rather than cured.

Concluding remarks

Medicines can interact with all wound healing phases and in some cases, medications can cause ulcerations. A multidisciplinary approach is necessary when withdrawal of medicines is needed to achieve wound healing

8. Illicit drug use

Prevalence of illicit drug use in Europe

Almost 29% (83 million) of Europeans aged between 15 and 64 years have used illicit drugs at least once in their lifetime. In 2019, approximately 5,141 Europeans died because of an overdose of illicit drugs. This is an increase of 3% compared to 2018. A variety of substances are being used (See Table 3), and polydrug use is not unusual. Cannabis use is common, with a prevalence five times higher than that of other drugs. Although the use of heroin and opioids is lower, it is more damaging when the substances are injected. Evidence is rising that there might be a growing number of people injecting drugs. Consumption habits are individual and go from experimenting to habitual use and dependence. Across the European countries, there is a variation in the types of drugs used and the extent of usage.[177]

Illicit drug use and wound healing

There is little evidence on the impact of illicit drug use on wound healing. The only drug that has been described is cocaine, which has strong vasoconstrictor properties[153,179] and may therefore impede the blood supply to the wound bed and affect wound healing.[153] The use of tobacco, cannabis and alcohol (see section 'Alcohol and wound healing') among drug users is higher than in the general population.[180] Illicit drug use affects the lives of many people, and users come from all ethnic, educational, religious and socio-economic backgrounds.[179] Illicit drug use may lead to other lifestyle choices that influence wound healing. Harrel et al.[181] investigated the connection between cigarette smoking and the routes of administration of illicit drugs for smoking drug users. They concluded that the use of cannabis and crack cocaine was associated with cigarette smoking (see section 'Smoking and wound healing'). Among heavy cigarette smokers, injection use was more common. Regular cigarette smokers were more likely to have a lifetime history of regularly injecting heroin.

Table 3: Classification of drugs[178]

Illegal drugs	Stimulants	Hallucinogens	Tranquillizers
Natural	Khat	Hallucinogenic mushrooms (psilocybin) Hallucinogenic cactus (mescaline, peyote) Salvia Divinorum (family of sage of the diviners) Ayahuasca Cannabis	
Semi-synthetic	Cocaine Crack	LSD	Heroin
Synthetic	Amphetamines MDMA, ecstasy	Ketamine, PCP	GHB
	NSP (e.g. PMA, PMMA, MDA, MDEA, MEA)		

To moderate withdrawal symptoms and enhance the effect of or replace heroin when not available, alcohol is consumed by drug users.[179] Cocaine users may lose their ability to function normally and, while using cocaine for days, they forget to eat and/or sleep.[179] Homeless drug users with financial problems have little possibility of cooking or storing food and are therefore at risk of malnourishment[182] (see section 'Sleep and wound healing' in this publication and Part 2, section 'Nutritional aspects of wound healing'[2]).

Illicit drug use causing wounds

Cannabis arteritis or cannabis-associated arteritis

See section on 'Smoking and wound healing'

Injection-related wounds and injuries

Injection drug use remains an important cause of drug-related harm, even though it has declined over the last 10 years. Besides heroin, amphetamines, cocaine, synthetic cathinones, opioid substitution medications and other medicines are also used for injection.[177] Drugs can be injected in three ways—intravenous, subcutaneous and intramuscular—and this type of administration is referred to as 'injection drug use'.[180] Injecting drugs is associated with an increased risk of developing wounds, such as venous ulcers, burns or abscesses[179,182,183], caused by adulterants and contaminants, repeated injury, infection and poor injection technique[179] (See Figure 5). This risk increases when drugs are combined, as this increases the level of impurities.[182] Chronic wounds may appear even years after the injection of drugs is stopped.[179]

Coull et al.[183] investigated the prevalence of skin problems and leg ulceration in a sample of young injecting drug users in Glasgow (Scotland) through face-to-face interviews. Two hundred participants aged between 21 and 44 years were recruited. 60% reported that they had skin problems at least once, such as abscesses and track marks, 15% had had a leg ulcer and 7% had an open ulcer during the interview. The authors concluded that among young injection drug users, skin problems are a significant concern and the high prevalence of leg ulceration is worrying.[183]

Existing wound beds and vascular tissue may be used as efficient drug delivery routes.[184] Persons who inject drugs (PWIDs) may maintain these wounds, as injecting drugs may have become difficult because of limited venous access.[184]

Venous ulcer

Injecting drugs damages the venous and lymphatic system, and adulterants have a sclerosing effect[179], leading to the sclerosis and thrombosis of superficial veins.[185] The risk of venous insufficiency is increased when PWIDs inject drugs into the groin, as the sclerosing substances are transported immediately into the veins of the lower limb.[179] Phlebitis may be induced by the vasoconstriction of blood vessels

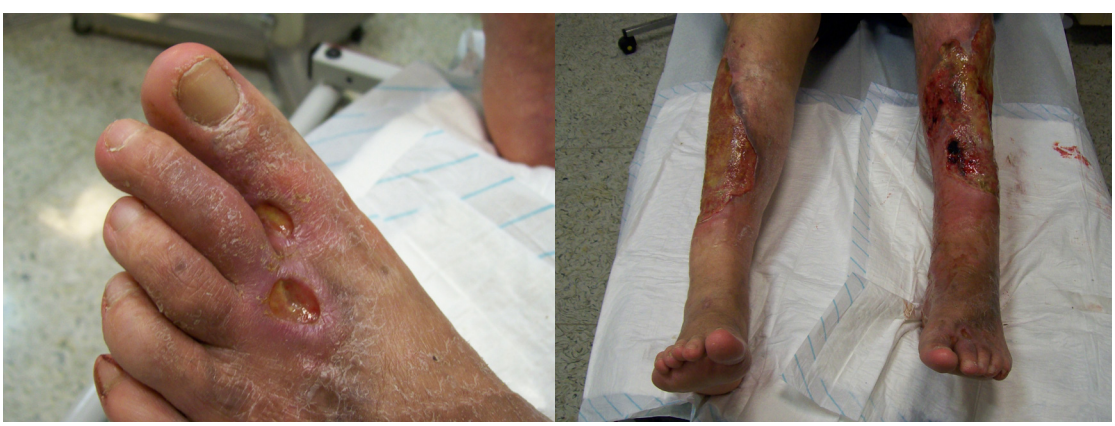

Figure 5: Examples of wounds caused by illicit drug use

caused by the injection of drugs.[185] Thrombosis and clot formation lead to deep vein thrombosis and valve damage, which can eventually cause chronic venous insufficiency (CVI) and venous ulcers.[185]

Tissue infection and abscesses

The drugs must be prepared before injection; therefore, 'special' equipment (spoons, needles, syringes, etc.) is needed. These tools are not sterile and are often (re)used by multiple PWIDs. [179,182] Infection may lead to septicaemia, necrotising fasciitis and wound botulism.[182] Abscesses are often caused by 'skin popping' and may lead to (chronic) ulcers and scars.[179]

Injuries by adulterants or excipients

Adulterants or diluents are mixed with heroin before it is sold. Quinine, mannitol, talc, baking soda, strychnine, caffeine and cocaine are used to increase the effect of heroin or as fillers, and these products can cause vasospasms, the release of norepinephrine, damage the intima, cause thrombi and embolisation.[179]

Quinine is often used to adulterate heroin because it is similar in taste and appearance. It is responsible for the development of abscesses at the injection site, the advancement of anaerobic bacteria and cardiac problems.[179]

Levamisole is an anthelmintic drug that is used to adulterate cocaine. It can cause levamisole-induced necrosis syndrome (LINES). Clinical symptoms of LINES are vasculitis, neutropenia and purpura, which evolve to skin necrosis. The diagnosis is made by physical examination and assessing the history of cocaine use[186]

Citric acid is often used to prepare drugs for injection. Users tend to use too much of it to dissolve heroin, which can lead to acid burns in the veins or in the skin tissues.[185,187]

Concluding remarks

More research is needed about the possible effects of illicit drug on wound healing. When treating illicit drug users with wounds, a multidisciplinary approach is needed and should be focused rather on harm reduction and prevention than cure.

9. Recommendations

Table 4: Recommendations for research and practice

Section	Recommendations
Stress	• Clinicians should be aware of the potential impact of psychological stress on the wound healing process among people with chronic wounds • There is a need to identify outcomes that are measurable and valid for use in research among people with chronic wounds • Research on psychological interventions that improve healing outcomes and the psychological well-being of individuals with wounds or at risk of recurrence of wounds is required.
Sleep	• Clinicians should encourage persons with wounds to sleep from 11 PM to 7 AM. • To improve healing outcomes, regular sleep is important for proper coagulation pathway efficiency and melatonin production, which may likely influence angiogenesis progression. • More research is needed to better understand and characterise the consequences of disrupted circadian rhythms on skin wound healing.
Alcohol	• Clinicians should be aware of and communicate to patients that alcohol can increase the incidence of infection and decrease collagen production. There is a need to better understand the mechanisms of light and moderate alcohol consumption in regard to wound healing.
Smoking	• Smoking cessation should be encouraged • Clinicians and patients should be aware that smoking affects all phases of wound healing

Medications	• Clinicians should be aware of all prescribed and non-prescribed medications that are in use by their patients and understand whether and how they are affecting the healing process. • Knowledge of how some medications for example warfarin therapy can cause wounds should be included in educational programmes for wound care professionals.
Illicit drug use	• Clinicians should be aware of possible use of illicit drugs among their patients • A multidisciplinary approach is needed when taking care of illicit drug users with wounds • Research is needed on the possible effects of illicit drugs on wound healing

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