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Pain management of chronic wounds: Diabetic ulcers and beyond

Stavroula A. Paschou[a], Maria Stamou[b,c], Hubert Vuagnat[d], Nicholas Tentolouris[e], Edward Jude[f,g,*]

[a] Division of Endocrinology and Diabetes, "Aghia Sophia" Hospital, Medical School, National and Kapodistrian University of Athens, Athens, Greece
[b] Harvard Reproductive Sciences Center, Massachusetts General Hospital, Boston, MA, USA
[c] Mount Auburn Hospital, Harvard Medical School Teaching Hospital, Cambridge, MA, USA
[d] Woundhealing Centre, Medical Directorate, Geneva University Hospitals, Geneva, Switzerland
[e] Diabetes Center, First Department of Propaedeutic Internal Medicine, Laiko General Hospital, Medical School, National and Kapodistrian University of Athens, Greece
[f] Diabetes Centre, Tameside Hospital NHS Foundation Trust, Ashton-under-Lyne, UK
[g] Manchester University and Manchester Metropolitan University, Manchester, M13 9PL, UK

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ABSTRACT

Patients who suffer from ulcers often experience pain of sufficient severity to reduce their quality of life. The aim of this review article is to collect, analyze and qualitatively resynthesize information regarding the definition and prevalence of ulcer pain, the pathophysiology of such pain, its assessment, and the optimal systemic and topical treatments. Early identification and prompt treatment are key to pain management. Further management should focus on appropriate dressing as much as on pain medication. The goal is to provide maximum relief with minimum side-effects.

1. Introduction

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. Pain perception is generally subjective and an observer cannot really judge the level of pain reported by an individual. In this context, the use of one of the many validated tools developed can help in measuring the individual's pain. Patients suffering from ulcers very often experience pain and for some this is lived as their main problem, disrupting their quality of life [1,2]. The aim of this review is to present the reader with updated information regarding the definition of ulcer pain, to discuss the pathophysiology of such pain and to provide an individualized guide for the optimal diagnostic and treatment approach.

2. Methods

In order to identify relevant publications for this review, a search with combinations of terms "pain", "wound", "ulcers", "diabetic foot" in English language was conducted in PubMed until June 2018. Special attention was paid to guidelines or original papers focusing on the management of patients with ulcers. This review collected, analyzed and qualitatively resynthesized information regarding: (1) the definition and prevalence of ulcer pain, (2) the pathophysiology of such pain, (3) the appropriate diagnostic assessment and (4) the appropriate medical treatment.

3. Results and discussion

3.1. Definition and prevalence

Wound pain is defined as an unpleasant sensation deriving from ongoing inflammatory or other tissue damage. Pain manifestations can vary and are broadly divided into the following categories: (i) The background pain that is a continuous or intermittent pain that is felt even at rest, (ii) the incident pain that occurs during day-to-day activities such as mobilisation, (iii) the procedural pain that results from routine procedures such as dressing change or wound cleansing, and finally (iv) the operative pain that is associated with significant wound intervention, such as debridement or biopsy [1]. The severity of pain experienced by an individual is usually related to the type and extent of the physical trigger, which can be affected by psychosocial factors, such as age, gender, culture, education, mental status, anxiety, depression and also different environmental factors such as timing of procedure, setting and resources, all which can increase the pain sensation of the patient.

The patients' pain can either be nociceptive, which usually is an appropriate physiological response to a painful stimulus, occurring during acute or chronic inflammation, secondary to tissue damage and

* Corresponding author at: Diabetes Centre, Tameside Hospital NHS Foundation Trust, Ashton-under-Lyne OL6 9RW, UK.
E-mail address: edward.jude@tgh.nhs.uk (E. Jude).

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is usually time limited, or neuropathic that is an “inappropriate” response caused by primary lesions or dysfunction in the nervous system. The latter is frequently linked to nerve damage and is perceived as altered or unpleasant sensations [1,2].

Diabetic neuropathy and diabetic foot ulcers are truly debilitating conditions for patients and contribute to 50% of all chronic wounds in industrialized countries with a prevalence of 5–7% (1–1.4 million people in Europe) and incidence of 2–3% (with 400–600,000 new cases per year in Europe) [2,3]. Apart from the major debilitating consequences in patients' health and everyday life, the financial burden of managing such ulcers can also be devastating. The chronic nature of such ulcers generates medical cost of 7,700–25,000 Euros per patient with global annual health cost reaching 10 billion Euros [4]. Apart from diabetic foot ulcers, 30% of chronic wounds consist of venous leg ulcers with an annual incidence of 1–1.5%, requiring 4% of the total health care budget in UK [5]. Pressure ulcers, contributing to 20% of all chronic wounds, have a prevalence of more than 0.5 million people in the UK, with the majority of these patients requiring hospitalization, and 1 out of 5 in hospital patients will develop a pressure ulcer. The cost for managing pressure ulcers can reach up to £4,300-6,400 per patient in the UK [3,4]. Although other causes of ulcer exist, these 3 main ones, by their number and the morbidity they bear are largely on top of our preoccupations. Their incidence is directly or indirectly linked to aging, with special characteristics for each category. Risk and therefore incidence for venous leg ulcers is more tightly linked to the evolution of venous deficiency, mobility, and obesity, resulting in fluid overload. Risk for pressure ulcers is affected by a decrease in mobility and being ‘bed-bound’, and/or sensitivity which happens more in the elderly. Diabetic foot ulcers are more commonly seen in patients with impaired sensation and are linked to aging both by the later onset of type 2 diabetes and to the years needed to develop peripheral neuropathy. Thus, it is clear that the medical diagnoses, prevention, timely treatment of such conditions are crucial not only for better management of the patients, but also for decreasing the related health care cost [3–5].

3.2. Pathophysiology

Pathophysiology is highly different in various ulcers. Neuropathy is an important risk factor for the development of diabetic foot ulcers, while peripheral vascular disease and poor glycemic control increase the risk for delayed healing. Patients, who suffer from peripheral neuropathy can experience diminished perception of pain and temperature. This can delay the recognition of an injury to their feet compared to other patients. Poor perfusion in diabetic patients' lower extremities can also delay the process of healing and make the inflammation increase rapidly. Additional factors such as dry skin (and fissuring), often due to autonomic neuropathy but also aging, can also facilitate the entry of microorganisms to the deeper skin structures, increasing the risk of infection. Diabetic foot infections are associated with substantial morbidity and mortality [6]. In addition, secondary trauma can prevent wound healing and increase the risk for secondary infections. Poor glycemic control can also impair the host immune response, making wound healing and recovery from the infection a more difficult task [7]. Diabetic neuropathy and pain related to the diabetic foot ulcer itself are distinct entities. In case of a diabetic foot ulcer, there usually is lack of wound sensation and pain experienced by the patient, which by no way means that all diabetic foot ulcers are painless. Also and interestingly, ischemic pain in diabetic patients can be often confused for neuropathic pain. Classically, ischemic aching is aggravated by elevation, while shooting pains are associated with neuropathic pain.

When such wounds get infected, it is most likely due to polymicrobial organisms [6,8–10]. Diabetic foot infections can either be superficial (such as cellulitis), usually secondary to aerobic gram positive cocci (including Staphylococcus aureus, Streptococcus agalactiae, Streptococcus pyogenes, and coagulase-negative staphylococci) or deep, which may involve multiple organisms such as enterococci, *Enterobacteriaceae,* Pseudomonas aeruginosa, and anaerobes. Anaerobic infections should also be considered if the patient demonstrates any of the following signs: necrosis, malodorous drainage, or gangrene with signs of systemic involvement [11–15]. Increased pain is now being recognized as an early marker for infection. Infected ulcers are painful due to wound breakdown and nerves damage [16].

Venous leg ulcers (VLU) occur on a terrain of chronic venous insufficiency (CVI) which is linked to the leg muscular pump dysfunction leading to venous hypertension. During calf muscles contraction, valvulae normally prevents blood reflux from the deep venous system to the superficial one. Out of the many causes of CVI, two main one arise: primary varicose diseases and late effects of deep venous thrombosis. This reflux will lead to an increase of pressure in the skin, which will trigger processes that, although not entirely identified, will end up in skin breakdown [5,17].

Pressure-induced ulcers (PU), similarly to diabetic foot ulcers, can derive from multiple injuries, triggered by a complex process that requires the application of external pressure to an area of the skin usually facing a bony prominence [18]. However, not all patients who undergo such external pressure will develop PU. The factors that predispose some patients to develop PU are multifactorial: (i) The characteristics of the pressure: pressure applied to the skin in excess decreases the delivery of oxygen and nutrients to tissues, resulting in tissue hypoxia, microthrombosis, accumulation of metabolic waste products, and free radical generation. The higher the pressure, the faster and more devastating is the formation of the ulcer. Of course, the longer the pressure is applied, the worse the lesion will be [19,20]. (ii) The tissue susceptibility and the nature of the underlying structures: muscle tissue can be very susceptible to pressure, followed by subcutaneous fat and then dermis. A high-stage pressure injury usually commences as a deep tissue injury that may then progress to the surface. There is little evidence to suggest that high-stage pressure injuries develop as a gradual progression from stage 1 through stage 4 [21,22]. (iii) Body position and supporting material: immobility is one of the major risk factors for pressure ulceration and air-mattresses have proven to provide some support and relief in chronically immobilized patients. Pressure over bony surfaces can be high and body position can play a role. For example, sitting position generates higher pressures compared to lying position and finally (iv) compression and reperfusion injury: reduced skin perfusion can be associated with pressure induced ulcers. Even though hypoxia can play a major role in the development of ulcers, it is the compression induced ischemia compared to any other type of ischemia that is responsible for worsening of PU [23,24].

3.3. Diagnostic assessment

The diagnosis of chronic wounds, which can be either diabetic, VLU or PU is mainly clinical [25]. The diagnosis of infection of these ulcers is more certain in presence of cumulated classical features of inflammation, such as erythema, warmth, tenderness, swelling, induration and purulent secretions [26]. However, signs specific to secondary wounds, such as increased pain, serous exudate, delayed healing, discoloration of granulation tissue, friable granulation tissue, pocketing at the base of the wound, foul odor and wound breakdown have been proved to be better indicators of chronic wound infection than the above-mentioned classic signs [16,27]. The presence of microbial growth alone in wound cultures is not sufficient to make a diagnosis of infection [28]. Pain is particularly common in patients having ischemic and neuroischemic ulcers, as well as infected ulcers, where the inflammatory response, stimulated by the infecting microorganisms, causes the release of inflammatory mediators and stimulates the production of enzymes and free radicals, which can cause tissue damage. Pain may result from direct stimulation of peripheral pain receptors by the mediators, from tissue damage, and from the swelling that occurs as part of the inflammatory response. The inflammation and cell damage