

A REVIEW ON DETERMINING FACTORS FOR WOUND HEALING IN DIABETIC FOOT ULCERS

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ABSTRACT

Diabetic Foot Ulcers (DFU) are significant complications of diabetes mellitus. DFU will often heal in a shorter period if factors that inhibit wound healing are identified and managed. This review was to identify determining factors that are associated with wound healing in DFU patients. Glycaemic control, adequate nutrition, presence of infection, the use of modern dressing approach, provide sufficient off-loading and avoid unhealthy lifestyle like smoking are the highlighted determining factors discussed in this review and found to have an association towards a timely manner of wound healing in diabetic foot ulcers.

Keywords: determining factors, diabetic foot ulcer, wound healing, review.

Introduction

Diabetic Foot Ulcers (DFUs) are significant complications of diabetes mellitus, which are linked with increase mortality, and reduce the quality of life which potentially life-threatening amputations (Sørensen, Jansen, Wilbek Fabricius, Jørgensen, & Svendsen, 2019). For a lifetime prevalence of up to 25% in diabetes patients, foot ulcers are common and severe diabetes complications (Walsh, Hoffstad, Sullivan, & Margolis, 2016). Because of the growing burden of diabetes ulcers, both to the patient and society, it is paramount to find relevant determining factors concerning diabetic foot ulcer wound healing. (Jeffcoate, Chipchase, Ince, & Game, 2006)

About 2.7% of all hospitalized patients with diabetes mellitus have DFUs (Nussbaum et al., 2018; Zimny, Schatz, & Pfohl, 2002). Although a lot of these patients might still have inadequate arterial blood flow to their limbs, it is at least in part caused by a loss of cutaneous sensation (peripheral insensitive neuropathy) (Walsh et al., 2016). Diabetes patients are unable to perceive sensations because of peripheral neuropathy which makes them vulnerable to trauma. (Grennan, 2019).

For wound healing of Diabetic Foot Ulcers with minimal to no complications, wound care management is essential (Broughton, Janis, & Attinger, 2006). In four distinct and overlapping stages, wound healing is a complex sequence of interactions and reactions between cells and mediators, namely haemostasis, inflammation, fibroplasia, and maturation (AWC, MR, Helmy, & Ramdhan, 2014). Diabetic Foot Ulcer involves several modes and multidisciplinary teamwork (Greenwell et al., 2018). Wound infection and non-healing Diabetic Foot Ulcers represent a hidden epidemic that affects a large fraction of the world's population and poses a huge and increasing challenge to public health and the economy (Ministry of Health Malaysia, 2018). Roughly 200,000 patients in the United Kingdom have infection-related non healing Diabetic Foot Ulcers. Treatment is estimated in the sum of 2.3 billion to 3.1 billion per year for patient with infected wound. (Harries, Bosanquet, & Harding, 2016). This review aimed to highlight the determining factors of wound healing in diabetic foot ulcers and what impaired wound healing.

Methods

This narrative review included articles searched through PubMed and Google Scholar as a search engine to look for articles related to keywords of "determining factors", "wound healing" and "diabetic foot ulcers". Articles in these databases were from the year 2000 to 2019. A total of 50 eligible studies identified but only through the search. However, only 10 studies have met the inclusion criteria, whereas the other 35 studies were excluded in regard to duplicated and unrelated to the study criteria.

Determining factors of wound healing in diabetic foot ulcers

Haemoglobin A1c level in wound healing

Haemoglobin A1c (HbA1c) is a reliable marker to monitor blood glucose in diabetic patients. HbA1c levels were associated with the process as well as the duration of wound healing in DFUs (Christman, Selvin, Margolis, Lazarus, & Garza, 2011). Controlled HbA1c level of less than 6.5mmol/L is linked to the acceleration of the duration of DFUs wound healing within three months (Li, Chen, & Kirsner, 2007). However, an elevated HbA1c level (> 6.5 mmol/L) new cut off point for HbA1c is 5.7mmol/L is associated with poor prognosis and significantly delayed in wound healing of more than six months (Hasan et al., 2016). This is due to the inability of nutrients and oxygen to energize the cells. An uncontrolled level of sugar also prevents the immune system from functioning efficiently, which resulted in inflammation in the body cell, thus delayed in wound healing (Christman et al., 2011).

Nutrition in Wound Healing

The provision of nutritional care is proven to accelerate wound healing. Malnutrition or nutrient deficiencies can impair the maturation phase such as collagen synthesis prolong inflammation, dysfunction of B and T cells due to decrease in phagocytosis, as well as reduce in mechanical strength of the skin (Sajid, Miyan, Zaidi, Jaffri, & Abdeali, 2018; Vas, Edmonds, & Papanas, 2017). Optimal wound healing requires adequate nutrition as the process of healing demands increased consumption of energy to replace the injured tissue with new tissues (Guo & DiPietro, 2010). However, ongoing monitoring is necessary to evaluate the outcome of nutrition intervention. The recommended intake for wound healing is as shown in table 1

Table 1: Recommended nutrients intake for wound healing in Diabetic Foot Ulcers patient

Nutrients	Recommended Intake
Energy	30-45kcal/kg/day
Carbohydrate	50-60% of energy
Fat	0.8 – 1.5g/kg/day
Protein	1.25g – 1.5g /kg/ day
Pharma co-nutrients	Omega-3 Fatty acid, Linoleic acid, L-Glutamine (0.2-0.5g/kg/day), Arginine 30-60g/day
Vitamins	Vitamin A, Vitamin B complex, Vitamin C, Vitamin E, Vitamin K, Zinc, Selenium, Manganese, Copper

Source: Ministry of Health Malaysia (2014)

Modern Dressing

Wound care management using a modern dressing approach showed a significant change in wound healing of DFUs (BaMohammed et al., 2012). Selecting the appropriate wound care products on DFUs based on TIMES concept assessment (Tissue, Infection, Moisture Balance, Epithelialisation, and Skin Surrounding) by providing a well-vascularized, stable wound bed that is conducive to normal and timely healing (Dowsett, 2009; Finlayson et al., 2017). Modern dressing includes a selection of an appropriate solution, products, and technique of wound closure on the safety, preservation of function, and aesthetically pleasing outcome (Ministry of Health Malaysia, 2018).

Diabetic Foot Infection

Wound infection is found to hinder the wound contraction for both acute and chronic wounds (Gubara Musa & Ahmed, 2012). The mechanism of which this occurs is assumed to be the release of bacterial enzymes and degrading of metalloproteinase fibrin and wound growth factors (Everett & Mathioudakis, 2018). Aerobic gram-positive cocci, mainly Staphylococcus, are the most common pathogens that impair wound healing and increase the risk of gangrene, sepsis and bone infection like osteomyelitis. Early identification of the local and systemic infection is essential to prevent the worsening of the wound (Boulton, Kirsner, & Vileikyte, 2004). The infection could be treated either with oral antibiotics, topical microbial agents, and parenteral antibiotics or surgical considerations (Raja, 2007). The selection of antibiotics is also paramount, especially patients with multidrug-resistant organisms, renal impairment, allergies, and immunosuppression (Zimny et al., 2002).

Wound Size and Grading

Wound size and grade impaired wound healing (Tsang et al., 2003). Various wound classification systems are used to describe the wound size and grade (S. Oyibo et al., 2001; Wong et al., 2015). The Wagner system is the one that commonly used to assess ulcer depth and the presence of osteomyelitis or gangrene by using the following grades; Grade 0, grade 1 (partial/full-thickness ulcer), grade 2 (probing to tendon or capsule), grade 3 (deep with osteitis), grade 4 (partial foot gangrene), and grade 5 (whole foot gangrene) (S. Oyibo et al., 2001). Wound healing of DFU depends on the classifications, delayed wound healing is associated with the depth, size, and grade of the DFUs (Dinh, Elder, & Veves, 2011).

Smoking

Smoking has been related to slow wound healing (Guo & DiPietro, 2010) and insulin resistance (Gubara Musa & Ahmed, 2012), especially in those smoking more than 10 packs/year (Guo & DiPietro, 2010). Smoking is harmful and is associated with delaying the healing of diabetic foot ulcers (Gubara Musa & Ahmed, 2012) and may help reduce the medical and economic burden on poor healing of diabetic foot (Guest, Fuller, & Vowden, 2018).

Off-loading

Off-loading is the most important healing factor in wound healing for diabetic foot ulcers (Boulton et al., 2004). The central goal of any treatment program designed to heal these wounds is effective off-loading (Guest et al., 2018). Structural abnormalities in a diabetic foot such as claw toe deformity and Charcot's neuroarthropathy are among the abnormalities that lead to significant disruption and elevate local foot pressures which resulted in the delay in wound healing (Bharat Kotru, 2015). Common off-loading methods include bed rest, wheelchair, crutch-assisted gait, total contact casts, felted foam and removable cast walkers (Cavanagh, Lipsky, Bradbury, & Botek, 2005; Margolis, Kantor, Santanna, Strom, & Berlin, 2000). Therapeutic shoes are designed to reduce the risk of skin breakdown (Walsh et al., 2016). Selection of shoes depends on numerous factors; how long someone has had diabetes, the presence of normal sensation on the feet, and if there are any abnormalities or deformities on the feet (O'Brien et al., 2003).

Discussion

There are numerous determining factors in the literature reviews associated with wound healing in DFUs. Despite, there was no standard criterion yet established to predict the prognosis of diabetic foot ulcer healing; however, this review revealed several determining factors that help influence the healing rate of diabetic foot ulcer. This review found that glycaemic control, such as HbA1c in the body shows the significant healing rate of DFUs (Gubara Musa & E. Ahmed, 2012). Elevated glucose level due to compromised glycaemic control in the body results in impaired oxygen and nutrient supply (Falanga et al., 2017; Xiang et al., 2019) to the ulcer area and delayed the duration of healing (Finlayson et al., 2017). HbA1c is a reliable marker of glycaemic control to diagnosis diabetes as recommended by the American Diabetes Association and by the World Health Organisation (WHO) (Manjunath & Kumar, 2018).

Nutrition plays an essential role in the prevention and treatment of DFU, where an inadequate nutrient can result in altered immune function, malnutrition, and poor glycaemic control (Sajid et al., 2018). Nutrition is essential in healing which is also a substantial determining factor for accelerated healing rate (Vas et al., 2017). all repeated (Falanga et al., 2017; Rohmayanti & Handayani, 2017). Patients with adequate nutrition and healthy body weight can help maximize wound healing due to obesity harms glycaemic control (Falanga et al., 2017).

Modern dressing plays a pivotal role in the management of diabetic foot ulcers, which comprises cleaning techniques and selection of the proper wound care products to provide a moist healing environment (Lindholm & Searle, 2016). The modern dressing also comprises of topical treatment as well as bedside surgical management (debridement) and callous removal (Rohmayanti & Handayani, 2017). In the advanced wound care management uses of vacuum aided devices, hyperbaric oxygen, and maggots help in accelerating wound healing (Margolis et al., 2000).

The local ulcer characteristic, that is, depth and presence of skin callous had a significant effect on delayed wound healing (Oyibo et al., 2001). Serial debridement may increase the healing rate (Kavitha, 2014). A study by previously (Chaby et al., 2007) found that grade 4 and above classifications may impair speedy healing and often lead to amputation if not treated effectively. The presence of infection as such *Staphylococcus Aureus* may also delay the healing rate as compared to those non-infected DFU (Gubara Musa & Ahmed, 2012).

Similarly, smoking is related to slow wound healing (Gubara Musa & Ahmed, 2012) and insulin resistance. An accelerated wound healing can also be seen in non-smoker patients compared to a smoker (Guo & DiPietro, 2010). Meanwhile, offloading is commonly recognized as a tremendous off-loading modality in healing DFU (Cavanagh et al., 2005) and a substantial healing factor in DFU (Gubara Musa & Ahmed, 2012). Around 75% of DFU patients using off-loading had accelerated healing within six months to 1 year, while 25% did not heal for more than one year (Dinh et al., 2011).

Despite all the highlighted determining factors discussed in this study, a few other factors could influence the delay in wound healing of DFU. These are the factors that suggested to be explored in future research; the role of growth factors in wound healing wound debridement, ischaemia and distal sensory neuropathy, delays in seeking treatment, systemic medication, antineoplastic chemotherapy, tumours and environmental factors. The failure of these wounds to heal is also multifactorial. Therefore, treatment of DFU needs to be directed against main etiological factors responsible for the wound.

Conclusion

Diabetic foot ulcers remain a compelling burden despite the number of currently available treatment modalities. Numerous determining factors could influence the healing rate of DFU in a timely manner such as haemoglobin, nutrition, modern, presence of infection, classifications of DFU, smoking, and off-loading. This review revealed that these factors should be taken into considerations when managing DFU. As a result, future wound care management should be aimed at addressing these challenging deficiencies in the hope to accelerate the healing rate of DFU. However, this review did not further investigate the other confounding or determining factors that impair wound healing at every wound healing stage.

Conflicts of Interest:

The authors declare no conflicts of interest.

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