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Psychosocial research in the diabetic foot: are we making progress?

Running title: Psychology of the diabetic foot

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Abstract

This review summarizes recent advances regarding the role of psychological factors in people with a diabetic foot ulcer (DFU). It describes the detrimental effects of diabetic foot complications and in particular, Charcot Neuroarthropathy (CN), on health status and quality of life (QoL) and emphasizes the importance of utilizing DFU-specific assessment tools. The review highlights the significance of diabetic neuropathy (DN)-related postural instability in generating depression in high DFU risk patients and in predicting offloading non-adherence in individuals with active DFUs. The review also explains that patients' views of their own DFU risk are largely inconsistent with biomedical models, resulting in a lack of preventive foot self-care. Furthermore, it indicates that DFUs are a source of specific emotional responses, with fear of amputation predominant. While fear of amputation is associated with better preventive foot self-care, especially in those with previous DFUs, it appears to be linked to DFU non-healing, though mechanisms are yet to be elucidated. Until now, systemically released stress hormones were recognized as the only biological mechanism through which psychological stress influences healing. Recently, the skin has been found to be an extra-adrenal site for glucocorticoid synthesis with local, tissue-specific cortisol implicated in DFU non-healing. These observations could potentially lead to future targets for therapeutic and psychological interventions.
could potentially serve as a future target for therapeutic interventions.

**Keywords:** depression, fear of amputation, preventive foot self-care, offloading adherence, postural instability

**Introduction**

While research into biology of the diabetic foot is making great strides, the psychology of patient experience with DFUs remains a somewhat underappreciated topic. Nonetheless, progress have been made in two broad areas: the impact of DFUs on patient physical and mental functioning, and quality of life, and the role of psychological factors, and in particular depression, in DFU development and healing.

**The impact of DFUs on patient health status and QoL**

Research indicates that DFUs have detrimental effects on health status and QoL [1]. The loss of mobility caused by non-weight-bearing treatment is central to patients’ experience with DFU, leading to restrictions in activities of daily living [2]. Furthermore, DFUs limit performance of important social and family roles [3]. Studies have demonstrated that patient health status improves significantly with DFU healing, and deteriorates when DFUs recur/do not heal [4,5] Moreover, persistent DFUs have a negative effect on QoL not only in DFU sufferers but also in their
Persons with DFUs have worse QoL than patients who either healed primarily without amputation or underwent minor amputation. The Eurodiale study showed no QoL differences between minor amputation and conservative DFU treatment. Even a major, transtibial amputation does not necessarily compromise QoL in patients with preserved mobility. A systematic review of twelve studies aiming to identify the factors influencing QoL after lower limb amputation for peripheral arterial disease showed that ability to walk successfully with a prosthesis had the strongest positive impact on QoL. Thus, at least in terms of this important patient reported outcome, amputation may not be considered as a treatment failure but rather as a viable treatment option.

Most recent publications conducted by Wukich et al extended this area of enquiry to patients with Charcot Neuroarthropathy (CN). When comparing CN patients to diabetic patients without CN, the Short Form(SF)-36 physical component scores in patients with CN were notably lower than in the control group. However, there was no significant difference between the SF-36 mental component scores. Another study compared health status of patients with midfoot CN and no DFUs with a group with midfoot CN and concurrent DFUs. Both groups demonstrated impaired physical health status and lower extremity function to a greater degree than mental health status. The impact of CN with or without DFUs on mental health was nonsignificant.
These studies employed generic QoL assessments, revealing a common pattern, that DFUs are associated predominantly with decrements in the domain of physical and not mental health. This is in contrast to findings from other studies that showed that depression is common in this population, with over a third of patients suffering from clinical depression [13] Moreover, DFUs are a source of specific emotional distress including fear of amputation and interpersonal-emotional burden [3, 14, 15] It is therefore conceivable that the generic scales of mental functioning are not sensitive to DFU-related emotional disturbance. Indeed, a study demonstrated that while the generic SF-12 mental functioning scale was not associated with DFU presence, the Neuropathy and Foot-Ulcer-Specific Quality of Life instrument (NeuroQoL)-emotional burden scale showed a strong association with DFUs [3] A systematic review of instruments assessing QoL in DFU patients demonstrated that DFU-specific tools quantify better than generic measures the temporal changes in QoL and show greater sensitivity to DFU severity [16] It was therefore suggested that DFU-specific surveys may improve the evaluation of QoL(16).

The role of psychological factors in DFU development

Depression and DFU: is there a link?

A large epidemiological study showed that elevations in self-reported depression symptoms were associated with a 2-fold increase in the risk of incident DFUs among
adults with type 2 diabetes and no previous DFU or amputation [17]. These observations were complimented by an epidemiological investigation demonstrating a dose-response relationship between depression symptoms and increased DFU risk [18]. Another prospective study of a well-defined diabetic neuropathy (DN) population showed that both foot self-care and depression, while having no relation to the development of recurrent DFUs, significantly predicted increased risk for first DFUs [19]. These observations suggest that addressing depression and foot self-care in patients with previous DFU may be “too little, too late.”

Somewhat unexpectedly, neither prior nor active DFUs were independently associated with depression in studies that examined predictors of depression in patients at high DFU risk [20,21]. These observations mirror the findings from a recent systematic review and meta-analysis of the relationship between depression and diabetes complications [22]. While this relationship appears bi-directional, the risk of developing diabetes complications in depressed people is higher than the risk of developing depression in people with diabetes complications. The underlying mechanisms warrant further research.

**Depression and DFU-specific emotions in preventive foot self-care**

Remarkably, depression, while predictive of DFU incidence, was not associated with preventive foot self-care in the aforementioned studies [17-19]. This challenges the assumption that preventive foot self-care is the mechanism linking depression to
DFU incidence. We found that adding preventive foot self-care to the model increased rather than reduced the strength of the unique association between depression and DFU risk [19] Whether depression represents an indicator of biological risk that was not captured by the risk factors measured in our study or whether it truly is a causal agent in DFU development, acting via mechanisms other than preventive foot self-care, is an important question that deserves further investigation. It is also possible that current measures of preventive foot self-care do not capture the full impact of foot self-care on DFU risk, so that a more comprehensive measure might more fully mediate the relationship between depression and DFUs.

**Fear of Amputation: Friend or Foe?**

While the relationship between depression and preventive foot self-care requires further clarification, research evidence indicates that illness-specific emotional responses are more powerful predictors of self-care behaviours than the measures of generalized distress. Fear of amputation is emerging as a predominant emotion in DFU sufferers. A study by Wukich and colleagues identified fear of amputation as the most dreaded diabetes complication in those with active DFUs [15] Earlier reports have demonstrated that fear of amputation promotes preventive foot self-care, while anger at practitioners stemming from a perceived lack of compassion hinders foot self-care [14,23] In a recent study of persons with active DFUs, fear of
amputation at baseline was the only psychological variable associated with DFU non-healing over the six-week follow-up, although the mechanism accounting for this relationship is yet to be established [24] It is important to note that although patients at high DFU risk experience elevated depression symptoms, these are largely determined by foot problem-related physical dysfunction and interpersonal-emotional burden [20,21] Addressing causes of DFU-specific emotional distress may, therefore, be more meaningful and effective than initiating treatments specifically directed at depression.

**Patient Cognitive Representations of DFU Risk and PFSC**

Most of research to date examining the role of psychological factors in shaping preventive foot self-care was guided by the Common Sense Model (CSM) of illness behaviour [25] The CSM postulates that patients actively engage in interpreting medical diagnoses or symptom experience thereby constructing their own, common sense understanding about illness in terms of symptoms and diagnostic labels, antecedent conditions believed to cause illness, expected duration, possibility of cure or prevention and anticipated impact of illness. Two approaches have emerged to the way the CSM constructs were conceptualized and measured in DFU studies. Vedhara and colleagues adapted a generic instrument of CSM constructs, the Brief Illness Perception Questionnaire, simply by replacing the generic term “illness” with “ulceration” which allowed to examine DFU
beliefs at an abstract level [26] This study demonstrated that patients with more DFU symptoms and poorer DFU understanding reported better preventive foot self-care. This left researchers to speculate as to what patients were considering when responding to this questionnaire. As pointed out by Leventhal and colleagues, the inherent limitation of a generic instrument is that it ignores the unique biomedical processes and experiences associated with specific chronic conditions [27] Another research group employed a DFU-specific approach to CSM constructs to develop the Patient Interpretation of Neuropathy (PIN) questionnaire, an instrument capturing patients’ misconceptions about DFU risks, their level of understanding of practitioner information, and DFU–specific emotions [14] Using the PIN, they demonstrated both cross-sectionally and prospectively that accurate interpretation of medical information about the nature of DFU risks and the causal pathways to DFU predicted better preventive foot self-care, while characteristic misconceptions about DFU risk predicted potentially foot-damaging behaviours. Subsequently, a cross-sectional study of patients at high DFU risk employed the PIN and hierarchical cluster analyses to identify distinct illness schemata related to neuropathy [28] The cluster of patients with high misperceptions of DN undertook more potentially damaging foot-care behaviours than those with generally realistic beliefs about the nature of DFU risks.

The role of psychological and behavioural factors in DFU healing

The Impact of Depression on DFU Healing
Exploring the role of depression in DFU healing represents the most recent application of psychosocial research to this field, emerging from studies that examined the relationship between psychological stress and the healing of acute experimentally-induced wounds [29]. The first study examined the role of geriatric depression in DFU healing over a six-month follow-up and demonstrated that patients who healed had significantly lower scores on the geriatric depression scale [30]. A subsequent investigation considered the role of depression and coping styles in the healing of DFUs over six months. Additionally, explored were salivary cortisol and matrix metalloproteinases (MMPs) as potential mechanisms linking depression to DFU healing [31]. After controlling for clinical and demographic variables, DFU healing was predicted by higher confrontation coping scores and not depression. Furthermore, healed DFUs were associated with lower levels of inactive MMP2 and a greater cortisol awakening response. While an interesting undertaking, it provided no mechanistic evidence, but merely demonstrated that indicators of cortisol and MMPs are associated with DFU healing. It is not reported whether these potential mediators were associated with psychological variables or whether controlling for purported mechanisms attenuated the relationship between the predictors and outcome. Recently, a small study examined the effects of physiological stress (heart rate variability) on DFU healing defined as a percentage change in wound size between the two consecutive visits [32]. While there was a correlation between depression and physiological stress, no significant association between depression
and DFU healing was observed. In contrast, lower heart rate variability showed a significant correlation with less DFU healing. The authors therefore concluded that subjective stress assessments may not capture adequately the level of physiological stress. However, the study population was not sufficiently clinically defined. For instance, subjects might have had cardiac autonomic neuropathy in which case the heart rate variability may not have been the best measure of physiological stress response. As a result, definitive conclusions regarding the role of depression in DFU healing cannot be drawn from these reports.

Until recently, systemically released stress hormones were recognized as the only mechanism by which psychological stress induces dysregulation of cytokine production. However, the skin has been found to synthesize cortisol de novo at quantities comparable to free levels in plasma. Therefore, endocrine responses to psychological stress are likely to occur not only systemically, under control of the CNS, but also locally as tissue-specific responses [33]. A novel finding that local, tissue-specific cortisol is implicated in DFU non-healing could potentially serve as a future target for therapeutic interventions [24].

**Determinants of Offloading Adherence in DFU Healing**

A recent prospective study provided evidence for a relationship between varying levels of offloading adherence and DFU healing [34]. Interestingly, there were no significant associations between offloading adherence and depression or DFU-
specific beliefs and emotions. Perhaps beliefs that are more closely focused on an offloading device, such as expected efficacy or convenience might be more powerful predictors than patient perceptions of their DFUs. The emergence of DN-unsteadiness as the symptom that was most strongly associated with nonadherence to offloading merits attention, especially, as studies indicate that DN-unsteadiness is an important determinant of depression in patients at high risk for developing DFUs [20,21] Unfortunately, balance deficits may be overlooked by clinicians, as patients often do not report balance concerns during medical consultations owing to the perception that these are an indicator of diminishing self-resources—a sign of premature aging rather than illness-related disability [3] In view of these findings, clinicians should take this neuropathic symptom into consideration when selecting an off-loading device, as offloading–induced postural instability may further contribute to nonadherence.

Conclusions
DFUs are a source of physical dysfunction, emotional distress and diminished QoL. Patient misconceptions about their DFU risk and specific emotional responses have important relationships to preventive foot self-care in high-risk patients. DFU-specific scales capture more adequately than generic measures the patient models of their DFU risk and the impact of DFUs on QoL. An illness-specific approach is therefore recommended when studying the psychology of DFU development and healing. While depression is a risk factor for incident DFUs, this link that does not appear to be accounted for by preventive foot self-care. Thus, the pathways linking depression
to an increased DFU risk are yet to be established. While an understanding of the ways psychological stress affects DFU healing is still in its infancy, ongoing studies aim to identify the relative importance of physiological and behavioural pathways that might explain such a relationship. Interventions that target psychological problems in people with a DFU are currently lacking. However, meta-analyses of randomized controlled trials in people with diabetes showed that different psychological interventions can reduce diabetes-distress and depression (35) There is therefore an urgent need for high quality trials testing psychological interventions in people with a diabetic foot ulcer and a co-morbid psychological problem.

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Author Contributions

LV has drafted the manuscript; FP and JSG have contributed to specific sections and edited the manuscript. All authors have read and approved the final manuscript.

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