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Review

Lower-extremity arterial revascularization: Is there any evidence for diabetic foot ulcer-healing?

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Abstract

The presence of peripheral arterial disease (PAD) is an important consideration in the management of diabetic foot ulcers. Indeed, arteriopathy is a major factor in delayed healing and the increased risk of amputation. Revascularization is commonly performed in patients with critical limb ischaemia (CLI) and diabetic foot ulcer (DFU), but also in patients with less severe arteriopathy. The ulcer-healing rate obtained after revascularization ranges from 46% to 91% at 1 year and appears to be improved compared to patients without revascularization. However, in those studies, healing was often a secondary criterion, and there was no description of the initial wound or its management. Furthermore, specific alterations associated with diabetes, such as microcirculation disorders, abnormal angiogenesis and glycation of proteins, can alter healing and the benefits of revascularization. In this review, critical assessment of data from the literature was performed on the relationship between PAD, revascularization and healing of DFUs. Also, the impact of diabetes on the effectiveness of revascularization was analyzed and potential new therapeutic targets described.

Keywords: Arterial; Diabetes; Healing; Revascularization; Ulcer

1. Introduction

Diabetic foot ulcer (DFU) is a worldwide problem associated with high morbidity and mortality. While the main risk factor for DFU is the presence of peripheral sensitive neuropathy, occlusive peripheral arterial disease (PAD) is also frequently associated. Indeed, the risk of PAD is clearly associated with the presence of diabetes, with a 28% risk increase for every 1% increase in glycosylated haemoglobin (HbA_{1c}) [1]. The multicentre EURODIALE (European Study Group on Diabetes and the Lower Extremity) trial, which included 1229 patients with a new foot ulcer, showed that nearly 50% of patients present with PAD, defined as an ankle–brachial pressure index (ABI) < 0.9 and/or two absent foot pulses [2]. Moreover, critical limb ischaemia (CLI), defined as an ABI < 0.5, was also present in 12% of all patients. This high prevalence of PAD in patients with DFU should be taken into account to optimize patient management for three main reasons. First, PAD dramatically increases the risk of amputation. Armstrong et al. [3] found that the risk of amputation at 6 months ranged from 25% in cases

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with PAD alone to 100% if PAD was associated with a severe infectious disease. Second, PAD impairs healing ability [4] and, third, the presence of PAD is a strong predictor of death and cardiovascular events, and reinforces the need for optimal medical cardiovascular prevention [5].

This is why clear and systematic assessment of PAD and its severity in patients with DFU is essential. To make this assessment in the face of a paucity of typical symptoms of PAD in diabetic patients due to neuropathy and frequent underestimation of PAD by ankle pressure (AP) and ABI due to medial artery calcification (mediacalcosis), the use of other vascular parameters, such as toe systolic pressure (TP), toe–brachial pressure index (TBI) and transcutaneous partial pressure of oxygen ($TcPO_2$), is recommended [5–9].

Revascularization in patients with diabetes has long had a negative image. The distal nature of atherosclerotic lesions, their extensive distribution, the lack of a good collateral network, mediacalcosis, an association with microangiopathy and comorbid conditions are frequently present and associated with revascularization failure. However, technical progress in endovascular treatment and extensive use of distal bypass have greatly improved the effectiveness of revascularization in diabetic patients, although diabetes is still associated with a lower patency rate than in people without diabetes and the need for multiple procedures [10–16].

Nevertheless, over the past few years and due to a clear improvement in medical cardiovascular prevention, there are now data challenging the clear benefits of wider use of revascularization strategies for asymptomatic vascular lesions. This is true for coronary artery disease [17], but also for renal artery stenosis [18] and carotid stenosis [19]. In the same way, after a trend towards a consensus to revascularize patients with intermittent claudication, conflicting data have recently emerged from randomized controlled studies [20].

The problem with diabetic patients who have DFU is to assess the role of PAD in healing the wound to determine whether revascularization will be beneficial or not, although many other important factors must also be taken into account (for example, offloading of the wound, infection and nutritional status of the patient). In the presence of DFU, avoiding amputation is clearly essential, yet the issue of healing should not be minimized. Indeed, the persistence of such wounds leads to significant financial costs (home care, sick leave, medical care) and significantly reduces the patient's quality of life (bed rest, offloading). Previous reports have underlined the weakness of data in the literature concerning the assessment of healing in revascularization studies [21,22]. In one study assessing two medical strategies without revascularization for the management of CLI, the rate of limb salvage was 83% at 6 months, but the healing rate was clearly low at 24% at 6 months, highlighting the importance of having a specific concern for healing in revascularization studies [23]. Moreover, in diabetic patients, alterations due to microangiopathy, impairment of angiogenesis as well as metabolic memory resulting from glycation phenomena can all affect the benefits of any revascularization strategy.

These data highlight the need for a more critical approach to the management of PAD from a healing perspective in patients with DFU, and reasonably raise the following question: Why, how and when should we revascularize diabetic patients with DFU and occlusive PAD? The present review addresses these issues and also describes some of the factors that can limit the effectiveness of revascularization procedures in patients with diabetes.

2. Why revascularize patients with DFU and occlusive PAD?

As mentioned above, the presence of PAD leads to a considerable slowing of DFU healing as a direct consequence of the limited supply of oxygen, nutrients and topical factors essential to the healing process. The aim of the revascularization procedure is to restore sufficient blood flow to improve healing ability. There is a clear trend towards better healing in studies with revascularization than in those without revascularization, although the data should be carefully analyzed (Tables 1–4).

However, only two studies involving non-revascularizable diabetic patients are available (Table 1). Kalani et al. [24] analyzed healing rates in 50 patients with chronic DFUs not available for revascularization. They found that 40% of the patients healed with intact skin after a follow-up of 12 months; healing time was 6.6 ± 3.1 months and 30% showed improved ulcer-healing. In that study, $TcPO_2$ was a better predictor for ulcer-healing, with the probability of ulcer-healing severely decreased if $TcPO_2$ was < 25 mmHg. In 2013, Elgzyri et al. [25] did a prospective study that aimed to assess outcomes and healing factors in 602 diabetic patients who presented with DFU and PAD (defined as a systolic TP < 45 mmHg or AP < 80 mmHg) not available for revascularization. It is noteworthy that 33% of these patients died without healing, whereas 74% of the surviving patients healed without major amputation within a median period of 27 weeks. An AP < 50 mmHg was associated with a poor healing outcome and the patients' general condition was another important factor to consider. Indeed, in patients presenting with non-revascularized arterial lesions on angiography, 43% healed without major amputation, whereas the rate was only 22% in patients whose general condition had deteriorated.

In another study with a sample population that was 70% diabetic patients, 52% of foot ulcers were healed at 12 months and 23% required amputation. In this study, only 15% of patients healed at 12 months when TP was < 30 mmHg [26]. A further study assessed a revascularization strategy based on baseline $TcPO_2$ levels in 55 diabetic patients with foot ischaemia [27]. Revascularization was done only in patients with a baseline $TcPO_2 < 30$ mmHg. The healing rate was similar between the non-revascularized group, with a $TcPO_2 > 30$ mmHg, and the revascularized group, with a $TcPO_2 < 30$ mmHg, thus highlighting the usefulness of $TcPO_2$ in determining the need for revascularization.

In summary, a trend towards a better healing rate was observed in studies analyzing revascularization compared with those without revascularization, although no randomized trials have directly compared the two strategies. However, it must be borne in mind that most of the patients in observational studies were not eligible for revascularization due to severity of PAD