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Effect of Diabetes on the Cutaneous Microcirculation of the Feet in Patients with Intermittent Claudication

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Running head: Diabetes and the Microcirculation in PAD

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Abstract

Aims: To evaluate endothelial-dependent and –independent cutaneous vasodilator responses in the feet of patients with peripheral arterial disease (PAD) with or without Type 2 diabetes.

Methods: Cutaneous microvascular responses in the dorsum of both lower limbs were measured in the supine position using Laser Doppler Fluximetry combined with iontophoretic administration of endothelial-dependent (acetylcholine, Ach) and -independent (sodium nitroprusside, SNP) vasodilators in diabetic (n=19) and non diabetic (n=17) patients with PAD (presenting as unilateral calf intermittent claudication (IC).

Results: In patients with diabetes and IC, endothelial-dependent vasodilation was significantly impaired in the symptomatic limb [74 (57,105) vs 68 (24,81) PU, Z= -2.79, p=0.005] compared to the asymptomatic limb. Patients without diabetes showed no impairment of vasodilation. Resting ankle-brachial pressure index did not identify the presence of abnormalities in microvascular function.

Conclusions: The combination of diabetes and PAD is associated with a reduction in endothelial-dependent cutaneous vasodilation in the feet without an associated reduction in endothelial independent vasodilation.

Introduction

Diabetes (Type 1 and 2) affects almost 3% of the global population (estimated to rise up to 4% by 2030) [1] and consumes more than 10% of the healthcare budget in the U.K (equating to an amount greater than £12 billion in 2012) [2]. Peripheral Arterial Disease (PAD) is 2-5 fold more common in patients with diabetes [3, 4], and the combination of diabetes and PAD is more likely to result in critical ischaemia [5], tissue necrosis and/or amputation [6], making diabetic patients with PAD at high risk of a negative clinical outcome [6] including adversely affecting their quality of life [social activities, mobility, sexual life; 2]. Given the prognosis for patients with diabetes and PAD there is a paucity of non-invasive tools to accurately identify those patients with diabetes who are at higher risk of developing complications including both cardiovascular and peripheral vascular disease. The 2012 NICE guidelines recommend the measurement of Ankle Brachial Pressure Index at rest (ABPI), but the value of ABPI in diabetic populations has been questioned [7].

There is evidence that microvascular reactivity may be impaired in patients with stable PAD both at rest and during exercise [8, 9], but few, if any, previous studies have evaluated the effects of co-existent diabetes or assessed cutaneous microvascular responses in the feet of this group of patients. Technological developments in Laser Doppler fluximetry (LDF) permit accurate non-invasive measurements of cutaneous microvascular reactivity, including vasodilator responses to iontophoretic administration of endothelial-dependent and –independent vasodilators [10,11], suggesting that this technique may be used in conjunction with ABPI, in evaluating the this vulnerable patient population. Therefore the aim of this study was to assess the cutaneous microvascular responses in diabetic patients with PAD, compare symptomatic with asymptomatic limbs and propose a measure that could potentially be used to identify patients at particular risk of impending tissue breakdown.

Patients and Methods

Thirty-eight patients with unilateral symptoms of peripheral arterial disease (presented in the form of intermittent calf claudication) (19 with Type 2 diabetes [T2D] and 19 non-diabetic) provided written informed consent to participate in this study which was approved by the Southern Derbyshire Local Research Ethics committee and was carried out in accordance with the Declaration of Helsinki of the World Medical Association. Two of them, belonging to the non-diabetic group, withdrew prior to the assessments, due to a change in their personal circumstances. Patients with signs of peripheral neuropathy, any concomitant vascular disease (eg. Raynaud's, connective tissue disease or vasculitis), venous insufficiency, taking vasoactive medication and those in atrial fibrillation and/or with heart failure or peripheral oedema were excluded. No Coronary Artery Disease (CAD) or lung disease were reported on any of the participants, and no significant differences existed in medication between groups. Demographic data collected, included age, gender, resting blood pressure (average of 3 measurements), ABPI, smoking status, total cholesterol and HbA1c (Table 1).

Assessment of Microvascular Function

After 30 minutes of quiet supine rest in a temperature-controlled room, baseline cutaneous blood flux was first measured on the dorsum of the foot of the symptomatic leg) using LDF (Moor Instruments Ltd, Axminster, UK). Endothelial-dependent and independent vasodilators, ACh (1%) and SNP (1%) respectively, were administered transcutaneously by iontophoresis (0-2000μC), as described previously [10, 11]. Incremental vasodilator responses were measured by LDF and automatically captured using the Moorsoft for windows DRT4 software program (V1.2, Moor Instruments, UK). Microvascular responses using the same protocol were then repeated in the contralateral foot (asymptomatic leg). The differences between Maximum Perfusion and mean baseline Perfusion to both ACH/SNP were analysed.

Statistical Analysis

Data are presented as the mean ±S.D, and the median and interquartile ranges (25% and 75%). Significant differences were accepted at the 5% level and non-parametric tests (Wilcoxon Signed Ranks Test) were used to compare differences between groups.

Results

Patient Characteristics

Thirty-six patients with PAD (unilateral calf claudication) completed the study: nineteen T2D (11M, aged 64±9 years) and seventeen non-diabetic patients (17M, aged 65±8 years) (Table 1). There were no statistically significant differences in the baseline demographic data (including drug prescription and smoking status). ABPI was significantly lower in the symptomatic compared with the asymptomatic limbs in both groups (0.59 [0.47, 0.75] vs 0.88 [0.70, 0.97], Z= -3.30, p=0.001, in non-diabetic patients; and 0.66 [0.50, 0.82] vs 0.84 [0.79, 1.10], Z= -2.31 p=0.02, in diabetic patients).

Microvascular Function

There were no significant differences in baseline cutaneous flux between symptomatic and asymptomatic legs, or between diabetic and non-diabetic patients. All participants had a corresponding dose response in both legs. In patients with PAD and T2D, ACh mediated Endothelial-dependent vasodilation in the foot was significantly reduced in the symptomatic compared with the asymptomatic leg (74 [57, 105] vs 68 [24, 81] PU, Z= -2.79, p=0.005; Figure 1]. There was no corresponding difference in SNP mediated endothelial independent between the two limbs (101 [77, 137] vs 78 [57, 109] PU, Z= -1.51, p=0.07; Figure 2].

Discussion

With the year by year increase in the prevalence of diabetes (estimated to reach 4% of the global population by 2030) [1] it is no surprise that the prevention and treatment of diabetes is high on the public health agenda. The heavy economic burden on health systems in the order of £12 billion per annum [2] is accompanied by a major impact on the patients' quality of life [2]. Furthermore, the rate of amputation ranges currently from 5.5% (major amputations) to 22.6% (minor amputations) in the diabetic population [12], with the presence of PAD being identified as a key risk factor for amputation in this patient group [13]. Given that the prevalence of PAD in patients with diabetes may reach up to 20.6% [3] it is important to identify those patients who are at greater risk of a negative clinical outcome. Hodges et al. [8] and Rossi et al. [9] have demonstrated that microvascular reactivity is impaired, both at rest and during exercise, in patients with stable PAD. The present study has, for the first time, identified an impairment of microvascular endothelial-dependent vasodilatory function in the symptomatic limbs of patients with IC and T2D but no difference in endothelium-independent function. We postulate that the cumulative effect of T2D (e.g. a reduction in the capillary size and thickening of basement membranes; [14]) and PAD (e.g. chronic generalized pro-inflammatory state associated with the development of atherosclerosis; [15]) in the symptomatic limb leads to a net impairment of endothelium-dependent vasodilation: if these findings were purely due to T2D, ACh-mediated vasodilation would also be impaired in the asymptomatic leg.

Abnormalities within the cutaneous circulation are not considered in IC, as by definition, there are no skin changes linked with this condition. However, our work, highlighting the differences between the symptomatic and asymptomatic leg, suggest an interaction between the development of peripheral arterial disease and T2D, with respect to microvascular dysfunction in general and endothelial dysfunction in specific. These effects may be additive and therefore, as the diabetic population is prone to rapid disease progression, microcirculatory findings may be useful for risk

stratification. Although, the complex structure of the dermal vascular bed offers limited possibilities for studying the skin microcirculation in everyday practice, the use of non-invasive, relatively-inexpensive methods such as Laser Doppler Fluximetry and Imaging, can provide monitoring of microcirculatory parameters as a part of integrated diagnostic approach that could evaluate the risk and the effectiveness of the diagnostic approaches used, as it has been suggested for other conditions within the same population [16].

In this study demographic and biochemical data were equally matched within the subject groups (Table 1). However, they were not a homogenous group with respect to claudication severity, even though they presented with calf claudication. Follow up studies could consider using maximum walking distance, treadmill studies and Duplex ultrasound assessments to provide detailed information with respect to the identification and assessment of the degree of arterial disease.

For both diabetic and non-diabetic groups, there was a significantly higher ABPI in the asymptomatic legs. However, there must be cautious interpretation of the ABPI values within the diabetic subjects as these readings may be falsely raised due to calcification, especially those with long standing diabetes [17]. It is recommended that future studies include the measurement of toe pressures.

In summary, we have presented data documenting microvascular dysfunction in the symptomatic limbs of diabetic patients with peripheral arterial disease. Although a larger number of participants may have added further significance to our findings (e.g. additional statistically-significant differences between groups as far endothelial-independent vasodilation is concerned), our current findings show that microvascular dysfunction may contribute to the development of arterial complications in patients with diabetes. Further studies are needed in larger patient groups to investigate the longer term prognostic information in patients with diabetes and PAD to identify

patients at high risk of developing ulcers and PAD leading to amputation. At present we have validated techniques including ultrasound and Doppler for the assessment of macro vascular structural and flow abnormalities which contribute to symptoms of claudication. However, it has remained a challenge for clinicians to be able to risk stratify patients who are more likely to deteriorate and develop cutaneous abnormalities including skin ulceration. We have shown that the microvascular function in symptomatic legs of diabetic claudicants to have evidence of dysfunction which may contribute to the future development of skin ulceration. This is a new finding deserving further research.

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Table 1 Patient Clinical Characteristics

Clinical Characteristics	**Non Diabetic** N=17	**T2D** N=19	**p Value**
Age (years)	65.2 ±8.1	64.5 ±9.1	0.86
BMI	26.1 ±3.6	27.4 ±4.5	0.43
Systolic BP (mmHg)	151.1 ±24.5	159.3 ±26.6	0.55
Diastolic BP (mmHg)	82.1 ±10.2	80.1 ±9.4	0.78
Total Cholesterol (mmol/L)	4.8± 1.0	5.2 ±1.0	0.65
ABPI (symptomatic)	0.59± 0.28	0.66± 0.32	0.41
ABPI (asymptomatic)	0.88± 0.27	0.84± 0.31	0.83
HbA1c (%)		8.4 ±1.6	

Figure 1: ACh response (PU) in Asymptomatic and Symptomatic T2D legs.

Figure 2: SNP response (PU) in Asymptomatic and Symptomatic T2D legs.

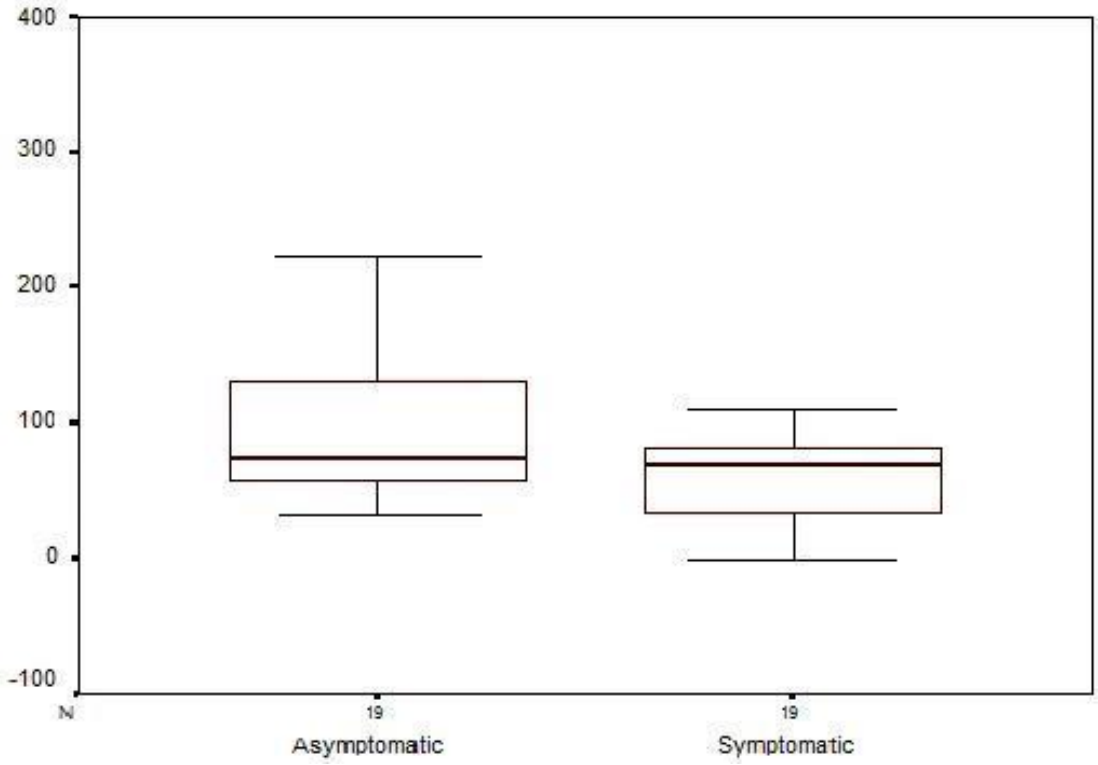

Figure 1

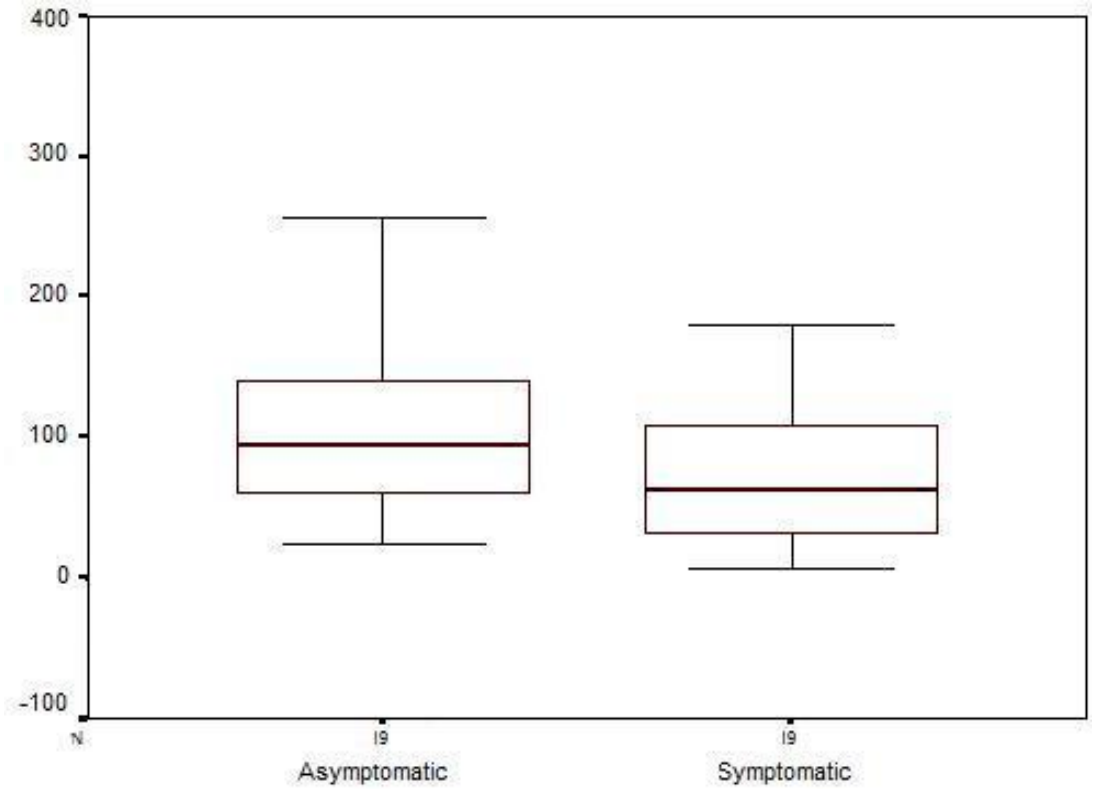

Figure 2