Journal of Diabetes and Its Complications xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Post-occlusive reactive hyperaemia of skin microvasculature and foot complications in type 2 diabetes

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ARTICLE INFO

Article history:
Received 12 February 2017
Received in revised form 8 May 2017
Accepted 9 May 2017
Available online xxxx

Keywords:
Post-occlusive reactive hyperaemia
Diabetes
Foot complication
Cutaneous reactivity
Microvascular disease

ABSTRACT

Aims: Diabetes-related microvascular disease has been implicated in the development of foot ulceration and amputation. Assessment of microvascular function may be effective in identifying those at risk of diabetic foot complications. We investigated the relationship between active or previous foot complication and post-occlusive reactive hyperaemia (PORH) measured by laser-Doppler fluxmetry (LDF) in people with type 2 diabetes.

Methods: PORH measures were obtained from the hallux apex in 105 people with type 2 diabetes. Associations were investigated between active or previous foot complication and PORH measures: time to peak (TtPeak) and peak as a percentage of baseline (P%BL). Multinomial logistic regression was used to determine the association of PORH with the likelihood of active foot ulcer or previous foot complication.

Results: For each second increase in TtPeak, the likelihood of a participant having a history of foot complication is increased by 2% (OR = 1.019, p = 0.01). This association was not reflected in people with an active foot ulcer (OR = 1.003, p = 0.832). P%BL was not found to be significantly different between those with a current or previous foot complication and those without (p = 0.404).

Conclusions: This investigation in a cohort with type 2 diabetes has demonstrated that longer TtPeak is associated with history of diabetic foot complications.

1. Introduction

Microvascular disease in people with diabetes is associated with longer duration of diabetes and chronic hyperglycaemia and is widely recognized to cause kidney, retinal and neurological pathology.[1] In the lower limb microvascular dysfunction has been implicated in the development of foot complications and poor wound healing.[1,2] Endothelial dysfunction related to the synthesis and function of nitric oxide is also considered characteristic of diabetes, even in its early stages[3,4] and is central to the development of neuropathy. In addition, both sensory and autonomic neuropathies are proposed to contribute to a reduction in functional capacity of the microvasculature. This includes the presence of Capillary Steal Syndrome which results in reduced flow in the capillary beds through dysfunction of arteriovenous shunts,[5] and structurally and neurologically driven impairment to microvascular reactivity [6] and capacity for tissue response to injury.[7,8] Recent research has also highlighted histological changes to capillary structure in the foot occurring in association with neuro-ischaemic and neuropathic foot ulcers in an older type 2 diabetes cohort.[9] There is a reduction in capillary lumen diameter, basement membrane thickening and a reduction in capillary density. The increasing evidence of the contribution of microvascular dysfunction to foot complications supports a role for assessment of microvascular function in clinical practice to assist in determining those patients at risk.

Post occlusive reactive hyperaemia (PORH) is a measure of microvascular function performed by a period of proximal arterial occlusion with subsequent release and quantification of the following rapid rise in blood flow.[10] It is proposed that shear stress associated with vessel occlusion stimulates release of vasodilators from the endothelium, although other factors such as those of myogenic, sensory nervous and metabolic origin also appear to be involved.[10,11] Overall, the measurement is said to provide a combined assessment of

Conflicts of Interest: All authors declare that there are no conflicts of interests.

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http://dx.doi.org/10.1016/j.jdiacomp.2017.05.005
1056-8727/

endothelial dependent and independent function[10] which may be of advantage when assessing global changes to microvascular function in those with diabetes.

PORH has been shown to be diminished in people with peripheral arterial disease (PAD), most likely as a result of maldistribution of blood flow,[12] and has been associated with increased cardiovascular risk in healthy females[13] and with presence of coronary artery disease.[14] In a study involving 305 adults (aged 40–65), Strain et al., determined that a rapid peak flux post-occlusion was associated with increased albumin excretion rate and cardiovascular risk.[15] In type 2 diabetes, microvascular dysfunction determined by PORH index has been demonstrated to be an independent predictor of cardiovascular disease (CVD)[16] and associated with the presence of overt peripheral neuropathy.[6] When compared to a healthy control group and a non-neuropathic diabetes group, the reactive hyperaemia in response to heat and acetylcholine (ACh) iontophoresis has also been shown to be reduced.[17] However, the relationship between the PORH response and active, or previous, history of diabetic foot complications including foot ulceration and amputation, has not been established.

The aim of this study was to investigate the relationship between presence of active or previous diabetic foot complications, including foot ulceration and amputation, and PORH performed using laser-Doppler Fluxmetry (LDF) in people with type 2 diabetes.

2. Subjects

Participants were recruited from two community Podiatry clinics in New South Wales with informed written consent obtained prior to their involvement in the study. Ethical approval for the study was granted from the University of Newcastle Human Research Ethics Committee. To be included in the study participants required a diagnosis of type 2 diabetes confirmed by medical records. Patients were excluded ($n = 5$) where there existed contraindications to PORH and toe pressure measurement including injury, ulceration or amputation of both halluces, the inability to remain in a supine position for 20 min or history of vasospastic disorder. No exclusions in relation to current pharmacotherapy were applied. At the commencement of the testing session demographic data were documented including age, sex, height, weight and smoking history. Pertinent medical history (duration of diabetes, measures of glucose control including most recent fasting plasma glucose and hemoglobin A1c [HbA1c], as well as history of hypertension, CVD, cerebrovascular disease and microvascular disease [nephropathy and retinopathy]) were confirmed from medical records. Diagnosis of nephropathy was made with an estimated glomerular filtration rate < 60 mL/min/1.73m^2, and a urinary albumin-to-creatinine ratio > 25 mg/mmol for men and >35 mg/mmol for women.[18] Retinopathy was considered to be present if proliferative or non-proliferative changes were recognized at screening.[18] Medical records and clinical examination were used to establish presence of active or previous foot ulceration or amputation and the specific location. Amputations of the lower limb were classified as per Nather and Wong.[19] Significant PAD was defined by a systolic toe pressure of less than 55 mmHg.[20]

3. Materials and methods

3.1. Equipment

A biothesiometer (Briggate Medical Company) and 10 g 5.07 Semmes-Weinstein monofilament (North Coast Medical, California) were used to determine peripheral neuropathy status. LDF was used to determine PORH parameters. Specifically, a moorVMS-LDF2 laser Doppler in combination with a VHP2 skin heater probe (Moor Instruments Ltd., Axminster, United Kingdom) were used to measure cutaneous flux at the distal plantar aspect of the right hallux. A MoorVMS-PRES automated pressure unit with toe cuff (Moor Instruments Ltd) was used to allow for calculation of toe pressure and PORH. MoorVMS analysis software Version 3.1 (Moor Instruments Ltd) was used for PORH data analysis.

3.2. Procedure

Eligible participants were advised to refrain from caffeine, alcohol, smoking, and strenuous exercise for two hours prior to the testing session. Demographic data collection and lower limb measurements were performed by one of two Podiatrists in a temperature controlled room (22–24 °C). Following a 10-min period of horizontal supine rest and acclimatization, participants underwent screening for peripheral neuropathy using VPT and loss of protective sensation (LOPS) to determine neuropathy status. Loss of perception of VPT less than 25 mV and inability to identify the 10 g monofilament at four of four sites were considered a deficit. Neuropathic status was classified as abnormal if deficits were observed in both neurological tests.[21] For LDF, the laser probe was embedded in the heat probe with the temperature set at 33 °C to maintain consistent thermo-neutral skin temperature at the site being measured. The toe cuff was applied over the proximal phalanx of the hallux avoiding contact with the laser/heat probe unit. The automated recorded sequence adhered to was: baseline flux for three minutes, cuff inflation and occlusion to 220 mmHg for three minutes followed by four minutes of post-occlusive flux, where flux is an arbitrary perfusion unit.

PORH measures used for analysis included peak flux as a percentage of baseline flux (P%BL) and the time to peak (TtPeak), measured in seconds' post-occlusion. These variables were chosen due to their ability to depict the extent of response and response over time in the context of their previously demonstrated acceptable reliability by the authors.[22] A typical PORH response is depicted in Fig. 1.

3.3. Statistical analysis

Statistical analysis was undertaken using R version 3.1.1. Data from one limb per person were used in the analysis to satisfy the assumption of independence of data.[23] For participants with an active foot ulceration or previous foot complication, data from the affected limb were used. Where amputation was present, data for that limb were used if possible. Where both limbs had been affected by foot ulceration ($n = 6$), only one leg was randomly selected and the data for that leg used. Where one limb had an active foot ulceration and the other had a previous foot complication, the limb with the active ulceration was used ($n = 1$). For those without history of foot complication, data from the right lower limb were used.

Between group comparisons (history of foot complication, no history of foot complication/no current foot ulcer, active foot ulcer) for demographic, relevant diabetes and PORH variables were determined using an ANOVA to compare the means between the comparison groups for continuous variables. The Fischer exact test was used to compare proportions for categorical data due to the low numbers of participants with active ulcers. For the purposes of this analysis, retinopathy and nephropathy were collapsed into a single variable (microvascular complications [MC]). From these results, variables demonstrating significant differences to the reference group (no history of ulcer) were identified (TtPeak, diabetes duration, HbA1c, MC and neuropathy). Multinomial logistic regression (MLR) was used to compare the associations between significantly different variables and outcome variables between those with a history of foot complication versus an active ulcer compared to the reference category of no foot complication history/no current ulcer.

Binomial logistic regression was also used as part of the sensitivity analysis, where the categories were collapsed by considering “history of foot complication” and “active foot ulcer” as the same category and included each of the variables identified as significant in the MLR. This

Please cite this article as: Lanting SM, et al. Post-occlusive reactive hyperaemia of skin microvasculature and foot complications in type 2 diabetes. *Journal of Diabetes and Its Complications* (2017), http://dx.doi.org/10.1016/j.jdiacomp.2017.05.005