

# Vascular risk profiling and exercise therapy for diabetic foot complications

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## **Statement of originality**

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. I give consent to the final version of my thesis being made available worldwide when deposited in the University's Digital Repository, subject to the provisions of the Copyright Act 1968.

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## **Statement of authorship**

I hereby certify that the work embodied in this thesis contains published papers of which I am a joint author. I have included as part of this thesis a written statement, endorsed by my supervisor, attesting to my contribution to the joint publications.

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## Synopsis

Diabetes is associated with a life-time risk of developing a foot ulcer of between 15-25% and is the leading cause of non-traumatic lower limb amputations. With prevalence of diabetes rising globally, the contribution of diabetes-related foot complications to morbidity and mortality associated with the disease is significant. This thesis considers the relationship between clinical measures of lower limb macro- and microvascular vascular function and likelihood of diabetic foot complications including foot ulcer and amputation. In addition, the role of exercise therapy for treatment of diabetes-related vascular pathology is investigated. Firstly, to explore the role of lower limb vascular assessment in establishing risk of diabetes related foot complications, two separate cohort investigations in community based populations with diabetes were conducted.

The first study investigated the relationship between measurements of large (ankle-brachial index [ABI] and continuous wave Doppler [CWD]) and small arterial function (toe-brachial index [TBI]) in the lower limb and history of diabetes-related foot complications. This study revealed that a low TBI ( $\leq 0.6$ ) was associated with an eight-fold increase in likelihood of previous foot complications. Large arterial screening measures did not demonstrate such clinical risk profiling.

The aim of the second cohort study was to investigate possible relationships between the parameters of cutaneous microvascular reactivity (CMR) at the hallux, measured via post-occlusive reactive hyperaemia using laser-Doppler, and their relationship with current or previous foot complications in people with diabetes. The results of this investigation demonstrated that for every increase in unit of the parameter of time to peak flux following occlusion (TtPeak), the likelihood of current or previous foot complication was increased by 6%. This supports an independent role of microvascular disease in development and subsequent outcomes of foot ulceration.

To investigate the impact of exercise therapy on microvascular function (with a view to it being a possible treatment for cutaneous microvascular disease) a systematic review with meta-analysis of pooled data of controlled trials investigating the effect of exercise therapy on CMR in older adults was undertaken. The review was limited by number and quality of controlled trials, though most revealed a tendency for improved CMR following the intervention. Subsequent meta-analysis of the pooled results showed a moderate significant improvement to CMR following moderate-intensity exercise training in older adults. This systematic review also revealed the lack of investigation into the effect of exercise training on CMR in diabetic populations with only two of the trials using a diabetes cohort.

As a result of the promise demonstrated by exercise training in our systematic review as a mechanism for improving CMR, coupled with the paucity of evidence in diabetes cohorts we undertook an additional investigation. This was a pilot investigation using a randomised controlled trial and was conducted to examine the effect of exercise therapy on micro and small arterial function in adults with type 2 diabetes. Eleven participants undertook 12 weeks of either a supervised continuous aerobic exercise training program (CONT) (n = 4), a supervised high-intensity, low-volume exercise program (HIIT) (n = 4) or a sham exercise placebo intervention (PLA) (n = 3). The results of this pilot trial demonstrated a significant increase in TBI following both exercise interventions suggesting a positive effect of exercise training on small artery function in people with diabetes. No significant difference in microvascular occurred as a result of exercise training, however a measure of CMR trended towards significance. These results suggest exercise therapy is a potential intervention for vascular dysfunction in the lower limb in diabetes cohorts that is worthy of further investigation.



## List of abbreviations

ABI	ankle brachial index
ACE	angiotensin converting enzyme
ACh	acetylcholine
AGE	advanced glycosylation end products
AV	arterio-venous
CAD	coronary artery disease
CI	confidence interval
CVD	cardiovascular disease
CWD	continuous-wave Doppler
CMR	cutaneous microvascular reactivity
ET	exercise training
FFA	free fatty acid
HbA1c	glycated haemoglobin
HIIT	high-intensity interval training
IDF	International Diabetes Federation
LDF	laser-Doppler fluxmetry
MAC	medial arterial calcification
MI	myocardial infarction
NAFLD	non-alcoholic fatty liver disease
NGSP	national glycohaemoglobin standardisation program
NO	nitric oxide

OR	odds ratio
PAD	peripheral arterial disease
PN	peripheral neuropathy
PORH	post-occlusive reactive hyperaemia
P%BL	peak as a percentage of baseline
PPG	photoplethysmography
PRISMA	preferred reporting items for systematic reviews and meta-analyses
RPE	rating of perceived exertion
ROS	reactive oxygen species
SD	standard deviation
TBI	toe brachial index
TcPO <sub>2</sub>	transcutaneous oxygen tension
TtPeak	time to peak
VO <sub>2</sub> max	maximal oxygen consumption
VPT	vibration perception threshold