RESPONSES IN VASCULAR FUNCTION TO EXERCISE IN WOMEN AGED 65-74 YEARS WITH TYPE 2 DIABETES

Submitted in total fulfilment of the requirements of the degree Doctor of Philosophy

by

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CORRESPONDENCE

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NAVIGATION OF THESIS

This thesis is made up of five chapters. Chapter One provides an overview of the literature with specific focus on the role of the microvasculature in the development of cardiovascular disease, particularly in women. Background information on the theory and methodology behind automated measurement of both retinal vessel calibre and fractal dimension is also described in detail. In Chapter One, the purpose and aims of this thesis are outlined.

Following Chapter One are three experimental studies, presented as three individual chapters (Chapters Two, Three, and Four). Each of the three experimental studies (Study One, Two, and Three) are distinct bodies of work that address the experimental aims of this thesis.

Chapter Five presents a discussion and conclusion section summarising the findings of the experimental studies in this thesis and provides information regarding the possible practical and/or clinical application of these findings.
ABSTRACT

The primary aim of this thesis is to examine changes in retinal microvascular structure and asymmetric dimethylarginine (ADMA) concentration in women aged 65-74 yr with type 2 diabetes, following twelve weeks of controlled and supervised exercise training at individual gas-exchange threshold ($T_{ge}$). In particular, this thesis examined the relationship between retinal vessel calibre/fractal analysis and measures of physiological functional capacity and endothelial function. Data from this thesis provide new knowledge on the effects of moderate intensity exercise on retinal microvascular morphology [retinal vessel calibre (RVC) and fractal dimension ($D_f$)] and ADMA concentration in women with type 2 diabetes. The same subjects were recruited for all studies.

**Study One**

The purpose of Study One was to investigate the relationship among retinal vessel calibre, fractal dimensions and physiological functional capacity in females aged 65-74 years with and without type 2 diabetes. Forty females (19 with type 2 diabetes and 21 without type 2 diabetes) underwent graded treadmill exercise testing to voluntary fatigue. Retinal photographs were obtained at a clinical eye examination from which retinal vascular calibre and fractal dimensions were quantified using a computer-based program (IRIS and IVAN) and summarized as the central retinal artery equivalent (CRAE) or central retinal vein equivalent (CRVE) and $D_f$. Subjects with type 2 diabetes had significantly lower peak oxygen uptake, peak heart rate, peak respiratory exchange ratio and time to exhaustion compared to age and gender-match subjects without type 2 diabetes. There were no significant differences between subjects with or without type 2 diabetes in CRAE (with diabetes 153.3±3.8 µm vs. without diabetes 154.7±2.7 µm, $p = 0.760$), CRVE (with diabetes 220.2±4.4 µm vs. without diabetes 230.8±4.9 µm, $p = 0.121$), or fractal dimension (with diabetes 1.45±0.004 vs. without diabetes 1.45±0.004, $p = 0.595$). In this sample of women aged 65-74 years, retinal vascular complexity (branching pattern) assessed as $D_f$ was found to be significantly correlated ($r = 0.48$, $p = 0.04$) with time to exhaustion in individuals with type 2 diabetes. These findings provide the first evidence of a significant association between measures of physiological
functional capacity and retinal branching patterns in individuals with type 2 diabetes, which is considered a key parameter for the efficiency of microcirculation.

**Study Two**

While exercise training has been prescribed as a preventive and therapeutic intervention for cardiovascular disease in individuals with type 2 diabetes, the effects of exercise training on the retinal microvascular responses are not well described. Study Two investigated the effect of twelve weeks of supervised walking exercise on retinal vessel calibre and fractal dimension - markers of early microvascular complications - in women aged 65-74 years with type 2 diabetes. Fifteen women completed twelve weeks of supervised walking (120 minutes per week) at an intensity equivalent to their individual \( T_{ge} \). Retinal photographs were taken and microvascular responses to exercise (via maximal exercise tests) were assessed before and after a 6-week intervention-free control period, and again after 6 and 12-weeks of exercise training. Twelve weeks of exercise training at \( T_{ge} \) resulted in significant increases in time to exhaustion (\( p < 0.001 \)), peak oxygen uptake (\( VO_{2\text{peak}} \) (\( p = 0.016 \)), \( VO_{2\text{peak}} \) relative to body mass (\( p = 0.026 \)), respiratory exchange ratio (\( p = 0.040 \)), \( VO_{2} \) at \( T_{ge} \) (\( p = 0.030 \)), heart rate at \( T_{ge} \) (\( p = 0.033 \)) as well as significant reductions in systolic (\( p = 0.014 \)) and diastolic (\( p = 0.032 \)) blood pressure. However, no significant changes in mean retinal vessel calibre or retinal fractal dimension were found after six or twelve weeks of exercise training. We could not document any significant changes in either RVC or \( D_{f} \) after twelve weeks of moderate-intensity, walking exercise in this sample of older women with type 2 diabetes. This contrasts with other studies showing that mild physical activity is associated with less adverse retinal microvascular signs.

**Study Three**

Basal plasma concentration of ADMA, an endogenous, competitive inhibitor of nitric oxide synthase, is elevated in patients with type 2 diabetes. ADMA may contribute to the endothelial dysfunction and associated vascular complications observed in individuals with type 2 diabetes. The purpose of Study Three was to investigate the effect of twelve weeks (120 minutes per week) of supervised walking exercise on plasma ADMA concentration in women aged 65-74 years with type 2 diabetes. Fourteen women (aged 69 ± 3 yrs) with uncomplicated type 2 diabetes, completed twelve weeks of supervised
walking at an intensity equivalent to their individual $T_{ge}$. Blood was sampled for ADMA concentration before and after a 6-week intervention-free control period, and again after six and twelve weeks of exercise training. Plasma ADMA concentration was found to be significantly lower after twelve weeks of exercise training when compared with baseline (wk 0) measurements. These results were accompanied by significant increases in time to exhaustion, relative and absolute VO$_2$peak, and VO$_2$ at $T_{ge}$. Regular, moderate-intensity exercise decreases circulating ADMA concentrations in older women with type 2 diabetes. These results suggest that ADMA may play a role in the training-induced reduction in cardiovascular disease risk seen with exercise training in individuals with type 2 diabetes.

**Conclusion**

The findings presented in this thesis support the use of regular, moderate-intensity exercise as an effective intervention for the management of type 2 diabetes in older women aged 65-74 years.
DECLARATION

This thesis is submitted to Bond University in total fulfilment of the requirements of the degree of Doctor of Philosophy. This thesis represents my own original work towards this research degree and contains no material which has been previously submitted for a degree or diploma at this University of any other institution, except where due acknowledgement is made.

Kevin Serre
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<td>ACEI</td>
<td>angiotensin-converting enzyme inhibitor</td>
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<td>ADMA</td>
<td>asymmetric dimethylarginine</td>
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<tr>
<td>ARB</td>
<td>angiotensin-receptor blocker</td>
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<td>ARIC</td>
<td>atherosclerosis risk in communities</td>
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<tr>
<td>AVR</td>
<td>arteriole-to-venule ratio</td>
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<tr>
<td>BDES</td>
<td>beaver dam eye study</td>
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<tr>
<td>BMES</td>
<td>blue mountain eye study</td>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<td>blood pressure</td>
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<td>CKD</td>
<td>chronic kidney disease</td>
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<tr>
<td>CRAE</td>
<td>central retinal artery equivalent</td>
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<td>central retinal vein equivalent</td>
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<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
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<tr>
<td>$D_f$</td>
<td>fractal dimension</td>
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<tr>
<td>DDAH-1</td>
<td>dimethylarginine dimethylaminohydrolase 1</td>
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<td>EDTA</td>
<td>ethylenediaminetetraacetic acid</td>
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<td>FEV$_1$</td>
<td>forced expiratory volume in 1 second</td>
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<td>FPG</td>
<td>fasting plasma glucose concentration</td>
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<td>FVC</td>
<td>forced vital capacity</td>
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<td>GLUT-4</td>
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<td>guanosine monophosphate</td>
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<td>GP</td>
<td>general practitioner</td>
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<td>HbA1c</td>
<td>glycosylated haemoglobin</td>
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<td>HDL</td>
<td>high-density lipoprotein</td>
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<td>HRR</td>
<td>heart rate reserve</td>
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<td>IFG</td>
<td>impaired fasting glucose</td>
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<tr>
<td>IGT</td>
<td>impaired glucose tolerance</td>
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<tr>
<td>IRIS</td>
<td>international retinal imaging software</td>
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<td>computer-based retinal grading program</td>
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<td>LDL</td>
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<td>multi-ethnic study of atherosclerosis</td>
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<td>SBP</td>
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<td>singapore cohort study of the risk factors for myopia</td>
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<tr>
<td>TE</td>
<td>time to exhaustion</td>
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<td>T_{ge}</td>
<td>gas-exchange threshold</td>
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<td>TV</td>
<td>television</td>
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<td>V_{E,BTPS}</td>
<td>expired minute ventilation</td>
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