Acute, Short- and Medium-term Cardiometabolic Outcomes of High-intensity Interval Training Compared to Moderate-intensity Continuous Training in Men Living with Type 2 Diabetes

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Abstract

Type 2 diabetes (T2D) is a progressive disease, requiring the adoption of behaviours to help delay the progression of life-threatening diabetic complications. Literature indicates high-intensity interval training (HIIT) as a suitable option, in the short-term, for pursuing improved cardiometabolic health in individuals with T2D. However, no randomised controlled trial (RCT) has been conducted using HIIT combined with resistance training (HIIT+RT) to determine the glycaemic control and markers of macro- and microvascular complication effects in people with T2D - nor compared the durability of such effects. The study aimed to compare the acute, short- and medium-term effects of HIIT+RT to moderate-intensity continuous training (MICT+RT), on glucose control and diabetic complication markers. My study recruited T2D men about to exercise in a real-world setting and, firstly, compared the acute physiological responses (APR) to a HIIT+RT or MICT+RT session; secondly, compared the short-term effects of a 12-week structured intervention of either HIIT+RT or MICT+RT on glucose control and complication markers; and finally, compared the medium-term durability of benefits from such training interventions after a 6-month follow-up.

Twenty-three men having moderate-duration T2D presented as sedentary, class II obese (≥35.0 kg/m^2), and while taking prescribed medications had elevated glycated haemoglobin (HbA1c) and were pre-hypertensive. Participants performed supervised MICT+RT (progressing to 26-min at 55% maximum estimated workload [eWLmax]) or HIIT+RT (progressing to two variations in which twelve 1-min bouts at 95% eWLmax interspersed with 1-min recovery bouts, alternated with eight 30-sec bouts at 120% eWLmax interspersed with 2:15 min recovery bouts).

In assessing the APR, peak heart rate, workload and perceived exertion were higher for HIIT+RT (P=0.04, P<0.001 and P<0.001, respectively), although energy expenditure and peak systolic and diastolic blood pressure responses

were similar between groups (*P*=0.47, *P*=0.71, *P*=0.56, respectively). The acute blood glucose responses were similar across all time points (*P*>0.05). However, there were acute exaggerated responses (using exercise termination indicators) reported to a similar extent (*P*=0.39) for both MICT+RT (64%) and HIIT+RT (36%) participants.

To account for fixed and random effects within the study sample, mixed-effect models were used to determine significance of change and to evaluate group*time interactions. Beyond improvements in aerobic capacity (P<0.001) for both groups, both training modalities elicited similar group*time interactions (P>0.05) while experiencing benefits for HbA1c (P=0.01), subcutaneous adiposity (P<0.001) and heart rate variability (P=0.02) during the 12-week intervention. Adiposity (P<0.001) and aerobic capacity (P<0.001) were significantly maintained in both groups at the 6-month follow-up. In addition, during the interventions, SPs in both MICT+RT and HIIT+RT experienced favourable reductions in medication usage. The study reported inter-individual variability of change, exaggerated physiological responses and the precautionary respite afforded to the participants. The findings appear to indicate that, over the short- or medium-term, HIIT+RT is not superior to MICT+RT for the improvements experienced in both groups for HbA1c, subcutaneous adiposity and heart rate variability. This indicates that current guidelines are efficacious and exercise professionals can be confident including MICT+RT (cognisant of appropriate supervision) into their training prescriptions to help men with T2D reduce the progression of macro- and microvascular complication markers.

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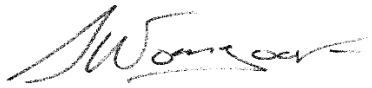
Attestation of Authorship

I hereby declare that this submission is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person (except where explicitly defined in the acknowledgements), nor material which to a substantial extent has been submitted for the award of any other degree or diploma of a university or other institution of higher learning.



04 June 2018

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Shohn G Wormgoor Date

Publications arising from this PhD thesis

Chapter Three of this thesis represents a paper that is published in a peer-reviewed journal.

Chapter Four of this thesis represents a paper that has been accepted and has been published ahead of print in a peer-reviewed journal.

Chapter Five represents a paper currently in preparation for submission in a peer-reviewed journal.

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Wormgoor, S. G., Dalleck, L.C., Zinn, C., & Harris, N.K. (2017). Effects of high-intensity interval training on people living with T2D: A narrative review. *Canadian Journal of Diabetes, 41,* 5, 536-547. doi: 10.1016/j.jcjd.2016.12.004

Contribution: Shohn Wormgoor 85%; Nigel Harris, Lance Dalleck and Caryn Zinn 15%

SW – Search and review of literature, data extraction, analysis and manuscript writing.

NH – Guidance on data analysis, interpretation and review of manuscript.

LD – Guidance of data interpretation and review of manuscript.

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SW – Data collection, extraction and analysis and manuscript writing.

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Contribution: Shohn Wormgoor 85%; Nigel Harris, Lance Dalleck, Robert Borotkanics and Caryn Zinn 15%

SW – Data collection, extraction and analysis and manuscript writing.

RB – Mixed-effects modelling.

NH, RB & LD – Guidance on data analysis, interpretation and review of manuscript.

CZ – Guidance of data interpretation and review of manuscript.

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Ethical Approval

All experimental studies contained within this thesis received ethics approval on 15 December 2014 from the Auckland University of Technology Ethics Committee (AUTEC approval number 14/396).

This study was registered with the Australian/New Zealand Clinical Trials Registry: (ACTRN12617000582358) http://www.anzctr.org.au/default.aspx.

List of Abbreviations

Abbreviation	Full description
1RM	One repetition maximum
ACCORD	Action to Control Cardiovascular Risk in Diabetes
ACSM	American College of Sports Medicine
ADA	American Diabetic Association
AIT	Aerobic interval training
APR	Acute physiological response
ANOVA	Analysis of variance
AUTEC	Auckland University of Technology Ethics Committee
BG	Blood glucose
BMI	Body mass index
BP	Blood pressure
C90	90% confidence ellipse area
CAD	Coronary artery disease
CAN	Cardiac autonomic neuropathy
CEP	Clinical Exercise Physiologist
CHO	Carbohydrates
Consort	Consolidated standards of reporting trials
CV	Cardiovascular
CVD	Cardiovascular disease
DAN	Diabetic autonomic neuropathy
DBP	Diastolic blood pressure
DF	Dorsi-flexion
DPN	Diabetic peripheral neuropathy
ECG	Electrocardiogram
ES	Effect size
eWLmax	Estimated maximum workload
FBG	Fasting blood glucose
FMD	Flow-mediated dilation

Abbreviation	Full description
GLUT1	Glucose transport protein-1
GLUT4	Glucose transport protein-4
GXT	Graded exercise test
HbA1c	Glycated haemoglobin
HDL	High-density lipoprotein cholesterol
HGP	Hepatic glucose production
HIIT	High-intensity interval training
HOMA-IR	Homeostatic model for insulin resistance
HR	Heart rate
HR_{rest}	Resting heart rate
HRR	Heart rate reserve
HRV	Heart rate variability
hs-CRP	High sensitivity C-reactive protein
IDF	International Diabetes Federation
IPAQ	International Physical Activity Questionnaire
LDL	Low-density lipoprotein cholesterol
LFT	Liver function test
Look AHEAD	Action of Health in Diabetes
METs	Metabolic equivalent of resting metabolic rate
MI	Myocardial infarction
MICT	Moderate-intensity continuous training
MoH	Ministry of Health
NZ	New Zealand
NZANS	New Zealand Adult Nutrition Survey
OGTT	Oral glucose tolerance test
PA	Physical activity
PACES	Physical Activity Enjoyment Scale
PF	Plantar flexion
RCT	Randomised controlled trial
RPE	Rate of perceived exertion

Abbreviation	Full description
rpm	Revolutions per minute
RT	Resistance training
SBP	Systolic blood pressure
SD	Standard deviation
SIT	Sprint interval training
SP	Study participant
SPSS	Statistical Package for the Social Sciences
T2D	Type 2 diabetes mellitus
TC	Total cholesterol
TG	Triglycerides
TL	Trace length
TNF-α	Tumour necrosis factor - alpha
uACR	Urine albumin-to-creatinine ratio
VO_2	Volume of oxygen consumption (aerobic capacity)
W	Watts

CHAPTER ONE

Thesis rationale

The burden of diabetes is reflected not only in the increasing numbers of people with diabetes, but also in the growing number of premature deaths due to diabetes. Type 2 diabetes mellitus (T2D), the most common type of diabetes, is one of the largest global health emergencies of the 21st century (International Diabetes Federation [IDF], 2015). The deleterious effects of long-term hyperglycaemia are generally separated into macrovascular (affecting the larger arteries within the body) and microvascular complications (affecting the microvasculature of the eye, kidney and nerves), and these diabetic complications need to be controlled to reduce the insidious impact of T2D (Fowler, 2008; IDF, 2013; Russell & Cooper, 2015). According to the IDF (2015) the burden of T2D is enormous, provoking approximately 5.0 million adult deaths internationally (one death every six seconds). For any given age, level of cholesterol or blood pressure (BP), the risk of mortality from atherosclerotic coronary artery disease (CAD) and stroke is 3-5 and 2-4 folds higher, respectively, among people with diabetes compared to people without diabetes (Fowler, 2008; IDF, 2013).

Typically, many people are initially able to manage their T2D through the intervention cornerstones of a healthy diet, oral medication and/or increased physical activity (IDF, 2013) with the goal of management striving to achieve and maintain optimal blood glucose, lipid and BP levels in order to prevent or delay the chronic complications (Colberg et al., 2010; Fowler, 2008; IDF, 2013). Although the cornerstone strategies have had varied success (individually and collectively) in improving glycaemic control, diabetes is a progressive disease and further strategies or progressions are required for the desired remission of the disease, and the potential reversing of complications. Wing et al. (2013), reporting on the Action for Health in Diabetes (Look AHEAD) project, concluded that intensive lifestyle interventions that focused on weight loss, counselling and increased, unsupervised, moderate-intensity physical activity (PA) did not reduce cardiovascular events in adults with T2D. Hence, the optimum strategy for the treatment of T2D remains unclear and further investigations into alternate strategies that focus

on the comprehensive reduction of cardiometabolic risks, for example, structured exercise interventions and/or alternative dietary approaches, are warranted.

An emerging profession in New Zealand is that of a Clinical Exercise Physiologist (CEP). The implementation of structured exercise interventions by CEPs are used to manage the health outcomes of patients with chronic diseases, and such exercise professionals need to confidently design and progress exercise training interventions that lead to the best possible health outcome. These structured training programmes are supervised sessions that typically include a cardiovascular (CV) and resistance training (RT) component (Colberg et al., 2010; Umpierre et al., 2011). To this extent, the focus of this thesis will be on the comparison of structured programmes that progress the CV component to either longer duration moderate-intensity continuous training (MICT) or high-intensity interval training (HIIT) in people with T2D. Enhanced knowledge of exercise prescription modalities that optimise available resources with regards to addressing T2D complications, will enable CEPs to deliver a more effective exercise intervention programme. The resultant beneficial effects of structured training on the cardiometabolic health of people living with T2D potentially include the reduction of hyperglycaemia and the staving off of macrovascular complications. Furthermore, the progression rate of the microvascular complications that lead to cardiovascular disease, lower-limb amputations and dialysis (Hameed, Manzar, Raza, Shareef, & Hussain, 2012; Hovanec, Sawant, Overend, Petrella & Vandervoort, 2012) can potentially be reduced.

Originality of the thesis

- Currently no study has compared combined training (sessions that include both a CV and RT component) using HIIT to combined MICT in people living with T2D.
- While previous studies have reported the acute glucose responses to a MICT and HIIT session, no study has compared acute BP responses.
- Additional to being the first study to determine the above responses, my study included a nuanced reporting of adverse effects occurring during training sessions.
- Currently only one pilot study has reported on the durability of cardiometabolic benefits gained subsequent to a HIIT and MICT intervention. My study will be the first randomly controlled trial to determine the durability of cardiometabolic benefits.

- No study has compared the short- and medium-term efficacy in microvascular complication markers in people with T2D

Research objectives

Overarching research question

This thesis was designed to address the following overarching research question:

Do structured interventions in middle-aged men with T2D that progress to HIIT, combined with RT, produce more pronounced acute physiological responses as well as greater short- and medium-term effects on cardiometabolic and microvascular complication markers, than combined MICT training?

The chapters of this PhD consist of a review of the literature and a study constructed to address specific research aims and objectives central to the overarching research question.

Aims

The overarching aim of this research was to conduct a cohesive investigation to compare the effects of two structured, combined training modalities in a group of men living with T2D.

Study structure and design

The original overarching design approach of the study was a systematic quantitative investigation of the effects of HIIT and MICT (both combined with RT) in people living with T2D (Figure 1.1).

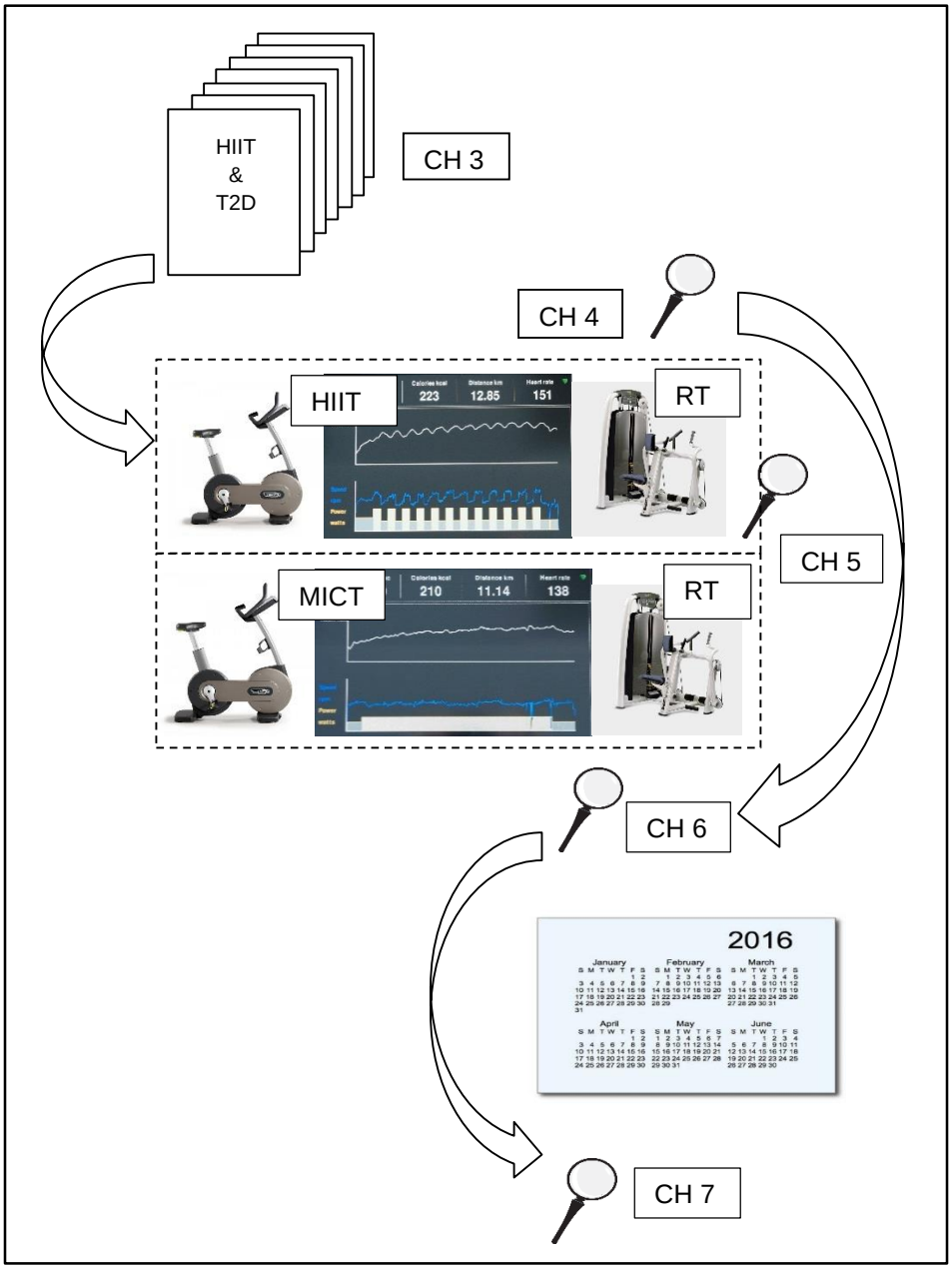

Figure 1.1: Simple flow diagram depicting the original planning of the study chapters. CH3, literature review; CH4, baseline characteristics of study participants; CH5 acute physiological response comparisons; CH6, short-term effect comparisons; CH7 medium-term durability of effects. HIIT, high-intensity interval training; MICT, moderate-intensity continuous training; RT, resistance training; T2D, type 2 diabetes mellitus; , data analysis.

Specific objectives developed

During the planning of the study the following specific objectives were envisaged:

1. To firstly present a brief summary of the pathophysiology of T2D and to provide an overview of the exercise intervention concepts central to this thesis **(Chapter Two)**.

2. To review and summarise the central characteristics of HIIT protocols used in the treatment of people with T2D, and then to objectively compare the reported effects of HIIT on cardiometabolic markers **(Chapter Three)**. The findings of this literature review would help inform my study design in terms of study participant characteristics (e.g., inclusion criteria) and intervention training variables (i.e., frequency, duration, intensity and duration) for the HIIT component.

3. My next envisaged study objective was a cross-sectional analysis of the physiological profile of the recruited men with T2D prior to the commencement of a structured intervention programme. Originally, if recruitment resulted in the appropriate number of study participants (SPs), I wanted to determine associations between the pre-exercise screening characteristics and markers of diabetic complications **(Chapter Four)**. As associations do not determine causation, it was important to focus on the intervention phase to determine the short-term effects of HIIT and MICT on diabetic control.

4. My initial objective relating to the training interventions in men living with T2D was a quantitative comparison of the acute responses of heart rate (HR), BP and blood glucose concentrations during each participant's first full combined (with RT) exercise session that incorporated a CV modality that had become more challenging (i.e., progressed) to either longer MICT or isocaloric HIIT sessions **(Chapter Five)**.

5. The novel and primary objective of my study planning was to quantitatively compare the short- and medium-term effects for both training modalities after a 12-week intervention and 6-month follow-up phase, respectively. **Chapter Six** was the main chapter of my thesis plan to report both the short- and medium-term effects for the cardiometabolic outcomes (i.e., aerobic capacity, glucose control and macro- and microvascular complication markers) following the RCT in men living with T2D.

Thesis overview

Thesis organisation

The final thesis consists of a further five chapters and is presented as a sequential progression of my study. Chapter Two describes the basic pathophysiology of T2D and presents central concepts related to exercise interventions. Chapter Three reports the central characteristics of HIIT protocols currently reported in literature to treat patients with T2D and objectively describes the short-term effects of all the reported HIIT studies. Chapter Four is concerned with the acute responses to my participants' first trial of their progressed programme for both the HIIT and MICT groups. Additionally, Chapter Four serves as a methodology section for the dependent variables of the study, provides the general methodology for group randomisation, the independent variables (including the RT), SP supervision and the exaggerated acute response indicators. Chapter Five is the major intervention chapter of my study and is concerned with determining and comparing the efficacy of my study's alternate progressive interventions on the cardiometabolic and macro- and microvascular complication markers in men living with T2D. Furthermore, Chapter Five reports on the durability of the effects following a medium-term, 6-month follow-up period. Of note, due to low SP recruitment numbers, determining baseline associations between pre-exercise screening data and markers of diabetic complications could not be pursued. However, learnings from this study related to SP recruitment numbers, baseline testing protocols and statistical analyses will be employed in future projects.

Chapters Three, Four and Five have been prepared as separate chapters for publication in peer-reviewed journals; therefore some repetition of information occurs. Although the chapters are close in content to their published (or submitted for review) journal articles, to enhance thesis continuity (and to reduce redundancy particularly around study methodology), limited deviations from the published form do occur. However, all data, outcomes and interpretations are identical to the published versions. Chapter Six serves to assemble the study findings and outcomes, and answers the overarching research question; emphasises the study's contribution to the advance in knowledge in the field of clinical exercise physiology and T2D health; and considers the implications of this research on delaying diabetic complications in men with T2D and the prescription of exercise by health professionals.

References are included and an overall reference list from the entire thesis has been collated at the end of the final chapter. For consistency, all referencing is in the APA (version 6) format, which may differ from the referencing styles evident in the respective journals where articles have been, or will be, published.

Thesis methodology

Being in the employ of the Universal College of Learning's clinical exercise physiology clinic (U-Kinetics) afforded me the opportunity to design a cohesive study that determined the acute, short- and medium-term exercise-induced effects in a group of people living with T2D. Although it would impact on the number of participants that could be enrolled in the study, I aimed to investigate these effects in a relatively similar study sample so as to limit the influence of gender and aging. As such, I screened all middle-aged men with T2D that were referred to the clinic over the study period. All potential participants were individually consulted using a staggered structure of one or two participants per fortnight (as per their referral to the clinic). Initially, my study was divided into three phases in which consenting SPs were to undergo a 12-week monitoring-only phase (during which all SPs would serve as a waitlist control group). The control phase was to be followed by a 12-week progressive training intervention phase incorporating either combined MICT or combined HIIT, after which all SPs would complete a 6-month follow-up phase. Power calculations indicated that for 80% power an n = 12 in each exercise training group would be sufficient to detect significant changes in glycaemic control, but after an initial 12-month enrolment period only 15 SPs were randomised into the two intervention groups. (A flow diagram of the final participant recruitment can be seen in Figure 5.1 in Chapter Five). To meet the planned sample size, the enrolment period was extended by six months, enrolling an additional eight SPs. However, due to resource limitations, these eight SPs (after randomisation) entered the study at the intervention phase. Consequently, the control group data was not used in any statistical analyses.

My involvement with both UCOL (for providing the electrocardiogram, stability force plate, the isokinetic dynamometer as well as provision for qualified CEPs to assist in SP monitoring), and AUT (for support and guidance from speciality supervisors) has allowed for a thesis of superior quality than could have been achieved under normal doctoral resources.

Candidate contribution

This thesis fulfils the terms of an Auckland University of Technology Doctoral Degree through a significant, original contribution to knowledge regarding alternate structured exercise interventions in men with T2D, via an objective narrative review and the completion of systematic quantitative investigations.

The development of the research questions were solely undertaken by myself in response to personal challenges. While implementing exercise training programmes with people who are living with type 2 diabetes, I always want to ensure that my decisions, as a CEP, on how to progress training will address their clinical needs optimally. As each person with T2D overcomes many barriers, and invests resources, to physically attend their training sessions, it is my role to ensure that, beyond improvements in general fitness, the insidious complications of diabetes are limited. To this end, I designed the study, was responsible for all the data collection, supervised all the training interventions and statistically analysed the data. During this study process, I developed my research measurement techniques and enhanced my understanding of T2D. Through the process of independent work, the resultant chapters of this thesis demonstrate well developed skills of research, critical analysis and application. In addition, dissemination of research findings to the international academic community, and exercise professionals, is being conducted in the form of peer-reviewed journal articles.

The appendices present relevant peripheral material including ethical approval (Appendix A), the participant information sheet (Appendix B), informed consent (Appendix C) and assistants' confidentiality agreement (Appendix D).

CHAPTER TWO

The burden of diabetes is reflected not only in the increasing numbers of people with diabetes, but also in the growing number of premature deaths due to diabetes. Type 2 Diabetes Mellitus (T2D), the most common type of diabetes, is one of the most common non-communicable diseases and is one of the most challenging health problems of the 21st century (IDF, 2015).

T2D has been conventionally defined as a chronic metabolic disease characterised by insulin resistance, relative pancreatic beta (β)-cell dysfunction and resultant hyperglycaemia that contribute to the development of progressive, life-threatening health complications (IDF, 2013; Li et al., 2012; Russell & Cooper, 2015; Strasser & Pesta, 2013). T2D has long been regarded as inevitably progressive, requiring increasing numbers of oral antihyperglycaemic agents and eventually exogenous insulin. However, T2D is reversible in certain well-motivated individuals adhering to appropriate guidelines and, as such, forms an underlying theme of this thesis. T2D should rather be understood as a potentially reversible metabolic state (at least early in its course) with a critical mass of β-cells not permanently damaged, but merely metabolically inhibited (Taylor, 2013). In T2D of duration greater than 10 years, the cellular changes do appear to pass a point of no return, but before then T2D can be regarded as a reversible β-cell response to a chronic positive calorie balance (White, Shaw & Taylor, 2016).

The purpose of this chapter is to provide a concise description of the fundamental concepts related to T2D and its 'management'. Initially, relevant terminology will be expanded upon, followed by a discussion on the pathophysiology (and possible reversibility) of T2D, proceeding with brief explanations of diabetic complications and the factors that perpetuate these complications. Hereafter, the chapter presents the current intervention strategies typically available to people living with T2D, before concluding with a focus on exercise as a therapeutic intervention.

Diabetes Related Terminology

Glycaemic control. According to the American Diabetes Association (ADA; 2016) glycaemic control is when people living with T2D are managing their blood glucose concentrations and

maintaining blood glucose to as close to normal (non-diabetic) as possible with the aim to prevent or slow the process of developing diabetic complications. Traditionally, ideal glycaemic control means maintaining blood glucose concentrations between 3.9 and 7.2 mmol/l before meals, and less than 10.0 mmol/l two hours after starting a meal, and in addition, having a glycated hemoglobin (HbA1c) concentration of around 53.0 mmol/mol when achieved by advanced antihyperglycaemic (i.e., exogenous insulin) therapy (Skyler et al., 2009). However, in adult patients with T2D only using an insulin sensitiser (e.g., Metformin), a target HbA1c concentration of 42 - 53 mmol/mol is recommended (Bertoluci et al., 2014; Saudek, 2009).

The importance of protecting the body from hypo- and hyperglycemia cannot be overstated as poor glycaemic control affects the macro and microvascular systems and is a major source morbidity and mortality in diabetes (Fowler, 2008; Inzucchi et al., 2012). T2D is clinically diagnosed by identifying chronic hyperglycaemia with the current diagnostic measure having two of the following three criteria: A fasting blood glucose exceeding 6.9 mmol/L, a 2-hour oral glucose tolerance test greater than 11.1 mmol/L and/or an HbA1c greater than 48 mmol/mol (Durstine et al., 2016). HbA1c, a well-accepted index of chronic hyperglycaemia, is used primarily to assess long-term glycaemic control in people with diabetes and is frequently considered as a clinical indicator of treatment efficacy (O'Hagan, De Vito & Boreham, 2013; Strasser & Pesta, 2013). The average life span of the red blood cell is 60-90 days and the concentration of glycation (the non-enzymatic attachment of sugars) to adult haemoglobin is therefore a reflection of glycaemic control over the 8-12 weeks preceding the test. HbA1c concentration also explains most of the excess mortality risk of diabetes, with an increase of 11 mmol/mol being associated with a 28% increase in risk of death, independent of other well-established cardiovascular risk factors (Khaw et al., 2001).

Glucose transport proteins. The regulation of glucose uptake into cells relies on numerous physiological factors, including the delivery of glucose, glucose transport (GLUT) proteins and glucose metabolism. GLUT1 and GLUT4 are two of thirteen facilitative GLUT proteins and can be viewed as potential access ports for glucose entry into cells. While GLUT1s are common in most cells, the expression of GLUT1s are relatively low in skeletal muscle. GLUT4s are most abundantly expressed in adipose tissue and cardiac and skeletal muscle, yet, in a resting muscle, GLUT4s are mainly retained within the intracellular vesicle structures. As such, it is

generally believed that glucose transport across the cell membrane is the rate-limiting step for muscle glucose uptake (Richter & Hargreaves, 2013). However, it must be emphasised that insulin is not required for the exclusive uptake of glucose by insulin-sensitive tissue. Even in the fasting state, or in a state of absolute insulin deficiency, there are sufficient glucose transporters in place within the cell membranes of all cells to allow glucose uptake to exceed that of a normal individual when the gradient of glucose concentration across the cell membrane is sufficiently high (Sonksen & Sonksen, 2000). Yet, this 'non-requirement' for insulin to enable glucose transport has both positive and adverse effects that will be discussed throughout this chapter.

Insulin actions. Insulin has two classes of action being both excitory (e.g., accelerating glucose uptake and stimulating lipid synthesis) and, more importantly, inhibitory (e.g., inhibiting lipolysis, glycogenoylsis, gluconeogenesis, proteolysis and ketogenesis). Both these actions occur simultaneously in people who are not insulin resistant (Sonksen & Sonksen, 2000).

Insulin resistance. Insulin resistance can succinctly be explained as the presence of insulin *not* causing the appropriate response in the body's organs/tissues. This resistance occurs in central (liver, pancreas and other visceral organs) and peripheral tissues, in particular, skeletal muscle, causing glucose intolerance in people living with T2D. While the mechanisms underlying insulin resistance are unclear, they likely involve defects in insulin signalling (Cusi et al., 2000; Samuel & Shulman, 2016), the binding of insulin to its receptor, and in post-receptor events such as glucose transport (Durstine, Moore, Painter, Macko, Gordon & Grous, 2016; Herman & Kahn, 2006; Samuel & Shulman, 2016), and/or lipotoxicity (Cusi, 2016; Roden et al., 1996) due to the body's exposure to a chronic energy supply (Samuel & Shulman, 2016).

Similarly, skeletal muscle insulin resistance refers to the state in which, despite the presence of insulin in the bloodstream, cells are resistant causing a decreased muscular response to the insulin (Deshmukh, 2016). As such, people living with T2D have a relative insulin deficiency and while having either elevated, normal or reduced insulin levels (depending on their β-cell dysfunction severity), still present with hyperglycaemia. Such deficiency is also termed insulin insufficiency and is discussed in further detail in the next section.

The Development of Type 2 Diabetes.

Although there is overlap between the aetiology, pathophysiology and complications of T2D, for the purpose of explanations in this chapter, these interrelated factors have been separated and will be discussed in a progressive sequence.

Aetiology

Of the many risk factors for T2D not all of them can be reduced/modified by the individual and include advancing age (Colberg, 2013), genetic predisposition or family history (Colberg, 2013; Groop & Lyssenko, 2008; Hornsby & Albright, 2009; Pendergrass et al., 2007), and the environment - including the impact of urbanisation and economic development (Hornsby & Albright, 2009; IDF, 2013). However, many risk factors are modifiable and include poor diet, physical inactivity and a rise in an individual's adiposity (Strasser & Pesta, 2013). As the majority of people living with T2D are overweight, 'obesity', as defined by the population-based measure of body mass index (BMI), has traditionally been directly associated with T2D (Hornsby & Albright, 2009). However, many individuals with a BMI < 25 kg/m^2 have been diagnosed with T2D and, conversely, many individuals with a BMI > 30 kg/m^2 do not have T2D. Taylor and Holm (2014) hypothesise rather that each individual has a personal fat threshold which, if exceeded makes likely the development of T2D. Subsequent weight loss, sufficient to take the individual below their level of susceptibility, should allow return to normal to normal glucose control. This personal fat threshold is independent of BMI and clarifies the understanding of the development of T2D in the 'non-obese', and remission of diabetes after substantial weight loss in people who remain 'obese' by definition. Taken together, these risk factors all contribute to the twin-cycle hypothesis for the aetiology of T2D.

The twin-cycle hypothesis. Insights into the behaviour of the liver and pancreas during hypocaloric dieting contributed to the twin-cycle hypothesis of the aetiology and pathogenesis of T2D (Taylor, 2008). During long-term intake of more calories than are expended each day, all excess carbohydrate must undergo *de novo* lipogenesis, which promotes a fatty liver. In turn, the increased liver fat will cause relative resistance to insulin suppression of hepatic glucose production (HGP). Chronically, a modest increase in fasting glucose concentrations will stimulate increased basal insulin secretion rates to maintain euglycaemia. Consequently, the hyperinsulinaemia further increases the conversion of unused calories to liver fat. Herein, a

cycle of hyperinsulinaemia and blunted suppression of HGP is established. Furthermore, a fatty liver (and elevated plasma glucose) leads to an increased export of very low density lipoprotein triacylglycerol, which increases fat delivery to all tissues, including the pancreatic islets (Adiels et al., 2006). The excess fatty acid availability in the islets impairs postprandial insulin secretion resulting in enhanced hepatic lipogenesis, thereby spinning the liver cycle faster and driving the pancreas cycle (the self-reinforcing twin-cycle) steadily increasing β-cell, fatty acid-mediated, dysfunction. Thus, T2D is precipitated by the single cause of chronic excess intraorgan fat (Samuel & Shulman, 2016) but, although not a distinct abnormality, the earliest predictor of the development of T2D is low insulin sensitivity in the more peripheral skeletal muscle (Taylor, 2013) which then diverts ingested glucose to the liver, resulting in increased hepatic *de novo* lipogenesis and hyperlipidaemia (Samuel & Shulman, 2016). In prediabetic individuals, raised plasma insulin levels compensate and allow normal plasma glucose control. But, because the process of *de novo* lipogenesis is stimulated by hyperinsulinaemia, the mechanism for hepatic fat accumulation becomes (centrally) activated and, in both prediabetes and established T2D, liver fat is supranormal (Petersen et al., 2005) akin to non-alcoholic fatty liver disease. Moreover, the resultant diminished transport of glucose across the myocellular membranes, due to skeletal muscle insulin resistance, further contributes to higher concentrations of circulating glucose in the bloodstream. Eventually, the fatty acid and glucose inhibitory effects on the islets reaches a trigger level that leads to a relatively sudden onset of clinical diabetes (Taylor, 2008).

The IDF's estimates in 2012/13 indicate that 8.3% of adults, representing 382 million people worldwide, have diabetes (with 3 new cases [~90% T2D] being diagnosed every 10 seconds) and they predict that this will increase to 10.1 % by 2035 (592 million people - an increase of 55%); with New Zealand currently reporting 10.9% diabetic adults. The majority of the current 382 million people living with diabetes are aged between 40 and 59, and 80% of them live in low- and middle-income countries (IDF, 2013). Additionally, T2D disproportionally affects ethnic minorities with its prevalence rates about twofold greater in Pacific Islander, Asian, Native Americans, African Americans, Hispanic and Latino populations (Colberg, 2013).

Pathophysiology

The pathophysiology of T2D is complex, however, insulin resistance in the muscle and liver as well as pancreatic β-cell failure represent the triumvirate core pathophysiologic defects in T2D (DeFronzo, 2009).

The deranged adipocyte metabolism and the altered fat topography that are implicated in the pathogenesis of glucose intolerance induce the following disturbances; referred to as lipotoxicity (or ectopic lipid accumulation). Chronically increased plasma free fatty acid concentrations stimulate gluconeogenesis (Ferrannini, Barrett, Bevilacqua & DeFronzo, 1983), induce HGP, promote skeletal muscle insulin resistance (Roden et al., 1996), and impair insulin secretion (Bays et al., 2008; Kashyap et al., 2003). Additionally, enlarged fat cells are insulin resistant themselves and have a limited capacity to store more fat resulting in an overflow of lipids into muscle, liver and pancreatic β-cells (Bray et al., 1977) – further promoting muscle and hepatic insulin resistance, and insulin insufficiency (Cnop, 2008; Hull, Westermark, Westermark & Kahn, 2004), respectively. Specifically within the central organs, the pathophysiology of insulin resistance in the liver is manifested by an overproduction of glucose during the basal state by as much as 0.5 mg/kg/min - despite the presence of fasting hyperinsulinaemia. For a 100 kg person fasting overnight, the increased basal HGP amounts to the addition of 36 g of glucose into the bloodstream (~9 teaspoons extra glucose each night) (DeFronzo, Ferrannini & Simonson, 1989). Additionally, in an insulin-stimulated state, as occurs after a meal, there is an impaired suppression of HGP (Ferrannini et al., 1988) and decreased hepatic glycogen synthesis (Samuel & Shulman, 2016).

Further to the fatty acid deposition in the islets (DeFronzo, 2009), oxidative stress (Roma, Pascal, Duprez & Jonas, 2012) and a diminished incretin effect (Ahrén, Gomis, Standl, Mills & Schweizer, 2004) are considered to contribute to β-cell dysfunction. Chronic increases in circulating blood glucose (glucotoxicity) result in the pancreatic β-cells trying to secrete more insulin (Rossetti, Giaccari & DeFronzo, 1990), but this additional insulin is usually ineffective and may contribute to further insulin resistance. Over time the β-cells become exhausted and insulin secretion subsequently progresses from β-cell compensation to β-cell dysfunction to β-cell failure (Prentki & Nolan, 2006), and this progressive β-cell failure determines the rate of T2D progression (DeFronzo, 2009).

Of note, excess lipids can also overflow into arterial vascular smooth cells, leading to the acceleration of atherosclerosis (DeFronzo, 2009). In addition, dysfunctional fat cells fail to secrete normal amounts of insulin-sensitising adipocytokines, such as adiponectin, and produce excessive amounts of insulin resistance-inducing, inflammatory and atherosclerotic provoking adipocytokines (Bays et al., 2008). Taken together, the pathophysiology of T2D includes another central organ. Heart disease is the leading cause of morbidity and mortality in people living with T2D (IDF, 2013), with more than a quarter of people living with T2D (older than 60 years) presenting with heart failure (Boonman-de Winter et al., 2012). Early changes in left ventricular structure and function have been identified in people living with T2D despite explicit cardiac disease. These changes include left ventricular remodelling (Dawson, Morris & Struthers, 2005; De Jong et al., 2017), reduced end-diastolic blood volume (Rijzewijk et al., 2009), alterations to strain patterns and diastolic and systolic dysfunction (Cassidy et al., 2015a), and energy metabolism (Mizuno et al., 2017; Rijzewijk, et al., 2009).

Akin to central organ dysfunction, insulin resistance in resting peripheral skeletal muscle is manifested by an impaired glucose uptake following the ingestion of a carbohydrate meal and results in postprandial hyperglycaemia (Ferrannini et al., 1988). Such muscle insulin resistance results in a 50% slower rate of insulin-stimulated glucose disposal, accounting for over 85% of the impairment in total body glucose disposal in people living with T2D (Pendergrass et al., 2007). Furthermore, muscle insulin resistance impedes insulin signalling/translocation of insulin receptor substrate (IRS)-1, thereby not only restricting glucose transport across the myocellular membrane, but also impeding the release of nitric oxide causing endothelial dysfunction, and leading to multiple defects in intramyocellular glucose metabolism (Krook et al., 2000; Morino et al., 2005). In contrast to the decrease in IRS-1 activation, there is an increase in the mitogen-activated protein kinase pathway which leads to the activation of a number of intracellular pathways involved in inflammation, cellular proliferation and atherosclerosis (Draznin, 2006; Wang, Goalstone & Draznin, 2004)

In addition to the triumvirate core and adipose tissue (accelerated lipolysis), the gastrointestinal tract (incretin deficiency) also plays an important role in the development of glucose intolerance. The secretion of glucagon-like peptide-1 (GLP-1) in people living with T2D is decreased, and

even though the secretion of glucose-dependent insulinotropic peptide (GIP) is near normal in people living with T2D, its insulinotropic effect on the pancreatic β-cells is greatly reduced (Holst & Gromada, 2004) due to the reversible effects of glucotoxicity (DeFronzo, 2009; Hojberg et al., 2009). This not only contributes to altered gastrointestinal signalling decreasing insulin production but also affect satiety. Worth mentioning, pancreatic α-cells (releasing excess glucagon), the kidneys (increased glucose reabsorption) and the brain (compromised appetite suppression) (DeFronzo, 2009), and, more recently reported, sleep disturbances (Reutrakul & Van Cauter, 2018) also drive the pathophysiology of T2D. Consequently, all these organ/tissue dysfunctions lead to hyperglycaemia and if not appropriate managed, particularly in early T2D, lead to the complications associated with diabetes.

Diabetic complications

The deleterious effects of long-term hyperglycemia are generally separated into macrovascular (affecting the larger arteries within the body) and microvascular (affecting the microvascular of the eye, kidney and nerves) complications (Fowler, 2008; IDF, 2013; Russell & Cooper, 2015). Unfortunately, T2D is often only clinically diagnosed once complications have developed (IDF, 2013). According to the IDF (2013) the burden of T2D is enormous, provoking more than 5.1 million deaths internationally (one death every six seconds). Aspects of T2D that form central themes for my thesis will now be discussed and will be referred to again in subsequent sections.

As the prevalence of T2D grows, so too does the impact of the costly – in both human and economic terms – diabetic complications. The costs associated with disability from diabetes include increased use of healthcare services, productivity loss and disability, which can be a considerable and debilitating burden to not only those affected and their families, but also on their communities and economies (IDF, 2013). In financial terms, the worldwide burden of diabetes is vast, resulting in USD 548 billion in healthcare spending (11% of the total healthcare budget) in 2013. In the United States of America in 2017, people diagnosed with diabetes incurred an average of USD 16 750 in direct medical expenditures alone (American Diabetes Association, 2018). In New Zealand during 2013 USD 1.38 billion (an average of USD 4040 per person with diabetes) was spent on diabetic healthcare and in 2035 this amount will increase by USD 157 million to USD 1.54 billion (IDF, 2013); equating currently to a USD 7 million increase

in annual healthcare costs for New Zealand alone. In order to decrease these costs, cardiometabolic health and diabetic microvascular complications will need to be effectively managed. Cardiometabolic health is an umbrella term used to describe the aerobic capacity, glucose control and the general macrovascular complication markers of hypertension, adiposity and dyslipidaemia. Cardiometabolic health and microvascular complication markers are major dependent variables in my thesis.

Macrovascular Complications

In patients with diabetes, atherosclerotic disease occurs at a younger age and progresses more rapidly, and plaque rupture leading to major vessel occlusion is more common (Bilous & Donnelly, 2010). For any given age, level of cholesterol or BP, the risk of mortality from atherosclerotic coronary artery disease and stroke is 3-5 and 2-4 folds higher respectively among people with diabetes compared to people without diabetes (Bilous & Donnelly, 2010; Fowler, 2008; IDF, 2013). Histologically, atherosclerotic disease in people with diabetes is similar to that in people without diabetes, but plaques tend to be more diffuse in nature and involve more distal smaller arteries, making revascularization less feasible (Bilous & Donnelly, 2010). The following macrovascular complications that occur, to varying degrees, in most people living with T2D, need to be controlled to reduce the insidious impact of T2D.

***Hypertension*.** Diabetes alone increases the cardiovascular disease (CVD) risk 2-4 fold, but in the presence of hypertension there is an additive effect and the risk for coronary artery disease is further increased (Bilous & Donnelly, 2010; Fowler, 2008). For every 20 mmHg or 10 mmHg increase, above 115/75 mmHg, in systolic (SBP) and diastolic blood pressure (DBP) respectively, the risk for CVD doubles, there is an 18% increase in risk for myocardial infarction, and a 29% increase for the risk of a stroke (Bilous & Donnelly, 2010).

Hypertension is more common in people with diabetes with insulin resistance, hyperinsulinaemia, and oxidative stress providing causative mechanisms. These possible mechanisms have been linked to an increased sympathetic nervous system stimulation, a decrease in vascular endothelial nitric oxide generation and to increased intracellular calcium (leading to increased contractility of vascular smooth muscle cells), raised sodium retention,

direct endothelial damage (leading to increased permeability), and to an increased stimulation of inflammation and growth factors (Bilous & Donnelly, 2010).

Hypertension is defined as SBP ≥140 mmHg or DBP ≥90 mmHg (Bertoluci et al., 2014) with a clinical recommendation for blood pressure management being <120/75 mmHg (Ministry of Health, 2018). Multiple drug therapy, however, is generally required to control hypertension in people living with T2D.

Dyslipidaemia. Abnormalities of blood lipids are a common characteristic in patients with T2D, even when there is reasonable glycaemic control (Bilous & Donnelly, 2010; Chudyk & Petrella, 2011; Yavari, Najafipoor, Aliasgarzadeh, Niafar & Mobasseri, 2012). The characteristic dyslipidaemia of T2D consists of elevated very low-density lipoprotein (VLDL) and triglyceride (TG) levels, reduced high-density lipoprotein (HDL) and minimal change in total and low density lipoproteins (LDL) cholesterol concentrations. Bilous & Donnelly (2010) reported that these abnormalities collectively interacted to substantially increase the risk of CVD by overproduction of hepatic TG-rich VLDL and impaired TG clearance by peripheral endothelial lipoprotein lipase. The profile of LDL subfractions in T2D is more atherogenic due to greater proportions of small dense LDL particles which are more susceptible to oxidation. Lipid goals for adults living with T2D should be an LDL < 1.8 mmol/L (Ministry of Health, 2018), HDL > 1.3 mmol/L, and fasting triglycerides < 1.7 mmol/L (Fowler, 2008).

Adiposity**.** Excess adipose tissue and T2D is a complicated situation, partly because the two conditions are interrelated and partly because the presence of diabetes increases cardiovascular risk and the microvascular complications of diabetes (Durstine, Moore, Painter, Macko, Gordon & Grous, 2016). In 2006 it was reported that an estimated 86% of individuals with T2D were, as defined by BMI, overweight or obese (Daousi et al., 2006). In T2D fatty acid metabolism in skeletal muscle is dysregulated, resulting in the accumulation of lipids within the muscle cell (Bonen et al., 2004). These intramuscular lipid products interfere with insulin signalling and contribute to insulin resistance (Shulman, 2000). Additionally, the lifetime risk of CAD (women 67% and men 78%) for people living with T2D is exacerbated by excess adiposity (Colberg et al., 2010). Traditionally, weight loss of as little as 4 kg has been reported to ameliorate hyperglycaemia (Bilous & Donnelly, 2010), but to increase remission rates weight

loss needs to be significantly higher at 20% of the individual's weight (as is common after bariatric surgery) or significant calorie-reduced diets (Lim et al., 2011).

Inflammation. Increased platelet adhesion, hypercoagulability and atheroma formation are evident in people living with T2D and the central pathological mechanism in macrovascular disease is the process of atherosclerosis. Atherosclerosis is suggested to result from chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system (Fowler, 2008; Patil & Ganu, 2014). Ultimately, inflammatory mediators activate a series of receptors and transcription factors which lead to β-cell dysfunction and apoptosis, impaired insulin signalling in insulin-sensitive tissues, and altered vascular flow (Goldberg, 2009); as well as systemic endothelial dysfunction resulting in an accumulation of monocytes and macrophages at the site of plaque rupture (Patil & Ganu, 2014). A significant relation between inflammation and glycaemic control in people living with T2D has been reported (Goldberg, 2009; King, Mainous, Buchanon & Pearson, 2003; Patil & Ganu, 2014).

C - reactive protein (CRP) is considered as a systemic inflammatory marker with increases in serum CRP levels reflecting the development and progression of atherosclerosis. Consequently, high-sensitivity CRP (hs-CRP) results can be considered as a marker for chronic low-grade inflammation; with people living with T2D presenting with higher levels (7.02 ± 3.94 mg/l) in comparison to a matched non-diabetic sample (1.78 ± 1.68 mg/l) for adults older than 40 years (Patil & Ganu, 2014).

Endothelial dysfunction. The vascular endothelium plays an important role in the regulation of arterial tone and local platelet aggregation, in part, through the release of endothelium-derived relaxing factors such as nitric oxide. These endothelium-dependent functions are impaired in people living with T2D (Fletcher et al., 2001; Fowler 2008).

Microvascular Complications

The smaller arteries and arterioles are damaged further by microvascular disease affecting the vasa vasorum, which makes the medial layer of the arteries prone to calcification (Bilous &

Donnelly, 2010). These microvascular complications affect small vessels of the kidney, nerves and retina, with the complications resulting from impaired autoregulation of blood flow, altered permeability, inflammation, extracellular matrix accumulation, hypoxia, cell loss, neovascularisation and fibrosis (Russell & Cooper, 2015). As a result of these complications, diabetes is the most common single cause of end-stage renal failure worldwide, the consequences of neuropathy make it the most common cause of non-traumatic lower limb amputations and diabetes is the most common cause of blindness in those of working age (Bilous & Donnelly, 2010). As diabetes accelerates the progress of many age related and degenerative conditions, the recognised scope of diabetic complications has continued to expand. Diabetes is reported to promote joint immobility, obstructive sleep apnoea, certain skin conditions, cardiomyopathy and, more recently, cognitive decline (Russell & Cooper, 2015). Of interest, Russell & Cooper (2015) also reported that these diabetic complications, in disparate tissues, could be the result of a combination of common pathological processes. The scope of this thesis will include the microvascular complications nephropathy, and peripheral and autonomic neuropathy.

***Nephropathy*.** Diabetes-related kidney disease is the most common cause worldwide of kidney failure requiring treatment by dialysis or kidney transplantation. Additionally while cardiovascular disease represents the major cause of diabetes-related death, it is the presence or absence of nephropathy and albuminuria that most powerfully predicts mortality in people living with T2D (Russell & Cooper, 2015). The disease is caused by damage to renal capillaries and reduced filtration, causing the kidneys to be less and less efficient (Bilious & Donnelly, 2010; IDF, 2013). Therefore the early detection and management of microalbumin is crucial.

Screening for diabetic nephropathy or microalbuminuria can be accomplished by either a 24-hour urine collection or, more conveniently for the person, a spot urine measurement of microalbumin (Fowler, 2008; IDF, 2013). Of note, while measurement of the microalbumin-to-creatinine ratio assists in accounting for the concentration, or dilution, of urine, falsely elevated urine protein levels could be produced by conditions such as urinary tract infections, exercise, and hematuria (Fowler, 2008). Normoalbuminuria for males would be a urine albumin:creatinine ratio of <2.5 mg/mmol, while microalbuminuria and clinical nephropathy are defined by having a ratio of 2.5-30.0 mg/mmol and >30.0 mg/mmol respectively (Bilous & Donnelly, 2010). In people

living with T2D the prevalence of microalbuminuria ranges from 19.4 – 42.1% and clinical nephropathy 9.2 – 32.9% (Bilous & Donnelly, 2010).

Increased proteinuria is preceded and accompanied by accumulations of matrix material (collagen and laminin) in the mesangium due to both overproduction and reduced breakdown and clearance. This accumulation ultimately destroys the capillary and reduces filtration leading to renal failure (Bilous & Donnelly, 2010). Without intervention, diabetic patients with microalbuminuria typically progress to proteinuria and overt diabetic nephropathy (Fowler, 2008). Bilious & Donnelly (2010) highlight that many people have hypertension when diagnosed with T2D and warn that these individuals are at higher risk of nephropathy. These authors also state that with increasing albuminuria, glomerular filtration rate (GFR) declines (from being greater than 90 mL/min/1.73m^2) by up to 4mL/min/year in those individuals with well controlled blood pressure, and the rate of loss is greater (up to 10-12mL/min/year) in those with clinical nephropathy and higher systemic blood pressure.

The risk of kidney failure, and the rate at which it develops, can be reduced by maintaining near-normal levels of blood glucose and blood pressure (Fowler, 2008; IDF, 2013). While good glycaemic control can prevent the development of microalbuminuria, Bilous & Donnelly (2010) emphasized that there was little evidence to suggest that it could prevent/delay the progress of nephropathy once it was established. They report that this is probably because after nephropathy has been initiated (by largely glucose-dependent mechanisms) it is continued by pathways that are no longer sensitive to changes in glycaemia. The factors that perpetuate these complications will be discussed in more detail later in this chapter.

Once people living with T2D develop clinical nephropathy their renal function declines towards end-stage renal disease and while tight glycaemic control can prevent nephropathy developing, once it is established, the cornerstone of medicinal treatment is blood pressure lowering, primarily with agents that block the renin-angiotensin-aldosterone system (RAAS) (Bilous & Donnelly, 2010).

***Peripheral neuropathy*.** As with other microvascular complications, risk of developing diabetic neuropathy is proportional to both the magnitude and duration of hyperglycaemia (Fowler, 2008)

and up to 33% of patients with diabetes have evidence of diabetic neuropathy (Bilous & Donnelly, 2010; Colberg, 2013; Kluding et al., 2012). Colberg (2013) states that some people living with T2D possibly develop their neuropathy only after a few years of known poor glycaemic control, and suggest that they may even had it at the time of diagnosis. The pathophysiology of diabetic neuropathy is complex, but microvascular disease affecting the vasa vasorum that supply oxygen and nutrients to peripheral nerves results in ischemia and metabolic neuronal injury via activation of several biochemical pathways. These pathways include the polyol pathway, non-enzymatic glycation and the formation of advanced glycation end-products (AGEs) and the accumulation of reactive oxygen species (ROS) (Bilous & Donnelly, 2010; Fowler, 2008; Koska et al., 2018).

Diabetic neuropathy is a term that encompasses a heterogeneous group of disorders (Bilous & Donnelly, 2010). Diabetic neuropathy is classified into multiple types with chronic sensorimotor distal symmetric polyneuropathy being the most common (Bilous & Donnelly, 2010; Colberg, 2013; Fowler, 2008; Kluding et al., 2013) and will be referred to in this thesis as diabetic peripheral neuropathy (DPN). DPN results from the distal dying back of axons (involving both small and large nerve fibres) that begin in the longest nerves; thus, the feet are affected first in a sock- then stocking-like distribution, and later there may be progressive involvement of the upper limbs (Bilous & Donnelly, 2010). While small fibre neuropathy frequently leads to foot ulcerations, subsequent gangrene and possible lower extremity amputations, large fibre neuropathy generally results in numbness of the feet, lack of co-ordination, impaired activities of daily living (ADL's) and causing falls and fractures.

Characteristics of DPN include mild weakness of the foot and impaired proprioception with symptoms of numbness and loss of balance, especially with eyes closed (Colberg, 2013). Neurological examination shows a symmetrical sensory loss, reduced/absent ankle or knee reflexes and small muscle wasting of the feet and hands, with symptoms being painful or non-painful (Bilous & Donnelly, 2010). With increased duration of diabetes, DPN may lead to decreased nerve conduction velocity, decreased vibratory sensation, decreased reflexes, decreased pressure sensation, lower limb deformity (including neuropathic oedema and Charcot arthropathy) and foot ulceration (Bilous & Donnelly, 2010). This loss of feeling is particularly dangerous because it can allow injuries to go unnoticed, leading to serious

infections and ulceration, diabetic foot disease, and major amputations (IDF, 2013). People living with diabetes face a risk of amputation that may be more than 25 times greater than that in people without diabetes (IDF, 2013). In identifying feet at risk of ulceration, the 10 g monofilament test has a sensitivity of 86-100% (Bilous & Donnelly, 2010) and this test determines the ability of a person living with T2D to feel the monofilament when it is applied (with sufficient pressure to buckle the filament) to selected areas of the foot.

According to McCarty (2002) there are several factors which could all contribute to impaired perfusion and hypoxia of peripheral nerves. These factors include a decreased endothelial production of the vasodilator nitric oxide, an unfavourable alteration in the endothelial prostacyclin/thromboxane balance, structural modifications of the microvascular that narrow capillary diameter and impede oxygen perfusion, the development of arteriovenous shunts that compromise capillary perfusion, and unfavourable rheologic changes (including an increase in blood viscosity and a decrease in blood filterability).

***Autonomic neuropathy*.** The autonomic nervous system (ANS) is responsible for regulation of internal organs and glands. The parasympathetic system of the ANS is responsible for stimulation of activities that occur when the body is at rest (salivation, lacrimation, urination, digestion and sexual arousal) with its action complementary to the sympathetic nervous system; which is responsible for stimulating activities associated with the fight-or-flight response (Vinik Erbas & Casellini, 2013). HR at rest reflects the dynamic balance between the sympathetic and parasympathetic divisions as the intrinsic rate of depolarization of the sinoatrial node in adults is 100 beats per minute (bpm) but the influence of the parasympathetic nervous reduces resting HR to a much lower 60-80 bpm (Brubaker & Kitzman, 2011). While the balance between sympathetic and parasympathetic activity modulates cardiovascular activities, enhanced sympathetic nervous system activity seems to be associated with an increased risk of cardiac events (Fletcher et al., 2001). In people living with diabetes, numerous abnormalities can be demonstrated in organs that receive an autonomic innervation (Bilous & Donnelly, 2010).

Common manifestations of such autonomic neuropathy include excess and gustatory sweating, diarrhoea and impotence as well as, more importantly for this study, hypertension, orthostatic hypotension (SBP fall >30 mmHg on standing), silent angina, and hypoglycaemia

“unawareness” (Bilious & Donnelly, 2010). Individuals with diabetic cardiac autonomic neuropathy (CAN) exhibit an increased heart rate and reduced HR variation to deep breathing at rest; and do not have a normal haemodynamic response to physical activity. The haemodynamic abnormalities include depressed maximal HR, lower maximal BP and a decreased maximal aerobic capacity and cardiac output (Colberg, Swain & Vinik, 2003; Vinik et al., 2013). Furthermore CAN contributes significant to morbidity (including heart failure) and mortality (Fowler, 2008).

Factors that Perpetuate Diabetic Complications

Although the scope of diabetic complications seems vast, not all cell populations are prone to complications. Those affected include vascular endothelia, renal mesangial and proximal tubular cells, glomerular epithelial cells, neurons and glial cells. In these tissues, facilitated diffusion of glucose occurs in an insulin-independent manner via GLUT1s (Heilig et al., as cited in Russell & Cooper, 2015). The resultant intracellular hyperglycaemia is possibly a key initiating factor in the development of diabetic complications (Russell & Cooper, 2015). Pathways leading to diabetic complications are complex, interlinked and, after the initial metabolic insult, thought to be self-perpetuating. Furthermore, pathways activated by these metabolic insults are amplified by aetiological co-factors including ageing, dyslipidaemia, smoking, hyperinsulinaemia and hypertension (Russell & Cooper, 2015).

The various principle mechanisms by which intracellular hyperglycaemia cause the macro- and microvascular complications associated with diabetes are:

- Intracellular hyperglycaemia results in the intracellular production of AGEs which are formed by the reaction of glucose and other glycating compounds (such as methylglyoxal) with proteins (Bilous & Donnelly, 2010) and possibly by excess ROS (Russell & Cooper, 2015). Early glycation products are reversible, but eventually they undergo irreversible changes through cross-linking. AGEs can cause damage and ultimately the complications of diabetes in three ways: firstly as a result of cross-linkage of matrix proteins (such as collagen and laminin), leading to thickening and stiffening of blood vessels which can affect permeability and elasticity. Secondly, AGE-modified circulating proteins bind to specific receptors (RAGEs) on several types of cells,

including monocyte/macrophages, glomerular mesangial cells and endothelial cells (Bilous & Donnelly, 2010). AGE-modifications of these proteins are pathogenic because they can disrupt intracellular enzymes and transcription factors. Thirdly, AGEs diffuse extracellularly and disrupt the function of extracellular matrix proteins (Russell & Cooper, 2015).

- The binding of AGEs to RAGE leads to the further generation of ROS, activation of secondary messengers such as protein kinase C (PKC), release of a transcription factor (NFkB) and stimulation of cytokine and growth factor production, which can result in inflammatory cell adhesion, procoagulant protein expression and increased vascular permeability (Bilous & Donnelly, 2010).

- Intracellular hyperglycaemia can increase the synthesis of diacylglycerol from intermediate steps in glycolysis, which in turn lead to the further activation of PKC, the promotion of AGE formation and resultant increases in oxidative stress (Bilous & Donnelly, 2010; Russell & Cooper, 2015)

- An increased flux of intracellular hyperglycaemia can result in the activation of the aldose reductase (also referred to as the polyol, hexosamine and polyol, or the sorbitol-aldose reductose) metabolic pathway (Bilous & Donnelly, 2010; Russell & Cooper 2015). Aldose reductase is a ubiquitous enzyme found in many tissues but specifically nerve cells, retinal cells, the glomerulus and kidney tubule and blood vessel walls (Bilous & Donnelly, 2010). This pathway is normally inactive but in the presence of hyperglycaemia there is a resultant increase accumulation of glucose-derived substances such as methylglyoxal and acetol, which can rapidly glycate proteins. Likewise, this disruption in glycolysis can also lead to the activation of many genes which possibly increase insulin resistance and promote thrombosis formation. Additionally, sorbitol does not diffuse easily across membranes and damage may occur to the cell because of osmotic stress (Bilous & Donnelly, 2010).

- Activation of the RAAS is of particular importance in the development of diabetic complications. Although it is not clear whether the RAAS is over activated systemically

in people living with T2D prior to the development of complications, angiotensin II and aldosterone combine with hyperglycaemia to amplify downstream inflammatory and fibrotic pathways (Russell & Cooper 2015).

The mechanisms listed above have a common effect of increasing ROS and thus increasing oxidative stress and the formation of highly atherogenic endproducts such as oxidized-LDL in the endothelial wall (Bilous & Donnelly, 2010; Fowler, 2008). Moreover, the increase in ROS can overwhelm antioxidant defences, damage structures including cellular and mitochondrial DNA, possibly leading to increased selective mitochondrial autophagy (resulting in decreased mitochondrial density), failure of energy-dependent cellular functions and activation of cell death pathways (Russell & Cooper, 2015).

These factors that perpetuate the diabetic complications are also promoted by the co-factors of underlying genetic susceptibility, hyperinsulinaemia, insulin resistance and the traditional risk factors of smoking, stress, family history, aging and unhealthy diets (Russell & Cooper, 2015). As such, echoing DeFronzo (2009), effective treatment of T2D requires multiple therapies focused further than simply the reduction of HbA1c.

Intervention Strategies

The goal of traditional management in T2D is to achieve and maintain optimal blood glucose, lipid and BP levels in order to prevent or delay the chronic complications (Bilous & Donnelly, 2010; Colberg et al., 2010; Fowler, 2008; IDF, 2013). Typically, many people are initially able to manage their T2D through a healthy diet, oral medication or increased physical activity (IDF, 2013). While these strategies have had varied success (individually and collectively) in improving glycaemic control, diabetes, if not correctly managed, is a progressive disease and further strategies or progressions are required for the desired remission of the disease, and the reversal of macro- and micro vascular complications.

The nature of unmanaged T2D is that there is a progressive decline in β-cell function and insulin sensitivity, which results in deteriorating glycaemic control and a constant need to revise and

intensify treatment (Bilous & Donnelly, 2010) and many people living with T2D will ultimately require insulin therapy alone or in combination with other agents to maintain control (Inzucchi et al., 2012). While diet and medication are not the focus of this thesis, a brief discussion of these intervention strategies soon follows along with an introduction of physical activity. However, the established effects of exercise will be discussed later in this chapter and to a greater degree for structured exercise interventions, particularly HIIT, in Chapter Three.

Remission

Complete remission of diabetes, as defined by Gregg et al. (2012) is the transition from meeting diabetes criteria to a prediabetes or nondiabetic level of glycaemia (fasting blood glucose concentrations of <7 mmol/L and HbA1c of <48 mmol/mol) with no antihyperglycaemic medication or surgical therapy. While these authors emphasise that complete remission is rare they also suggest that remission, according to glycaemic and pharmacologic criteria, does not encompass the underlying health of β-cell function and insulin action throughout the body and, as such, cannot be used to define a cure for diabetes. Weight regain and failure to maintain positive changes in diet and physical activity may lead to a deterioration of glycaemic control and recurrence of diabetes. However, partial remission, defined as a transition to prediabetic or normal glucose levels without drug treatment for a specific period, is an obtainable goal for some people living with T2D (Gregg et al., 2012). Further the authors reported that rates of any remission were notably higher (15%-21%) amongst people with significant weight loss or fitness change, shorter duration of extant diabetes, a lower HbA1c level and in those not using insulin. As such, as reported more recently, the reversal of lipotoxicity holds potential to modify the natural history of T2D (Cusi, 2016).

Antihyperglycaemic medication

A healthy diet and physical activity are sufficient to achieve adequate glycaemic control in <10% of people living with T2D; when control worsens, oral hypoglycaemic agents and/or exogenous insulin are introduced with the individual drug treatment being decided on the basis of the balance of β-cell impairment and insulin resistance (Bilous & Donnelly, 2010). Because the trajectory of T2D is primarily insulin resistance leading to hyperinsulinaemia and the eventual islet failure with subsequent requirement for exogenous insulin, the general paradigm for diabetes medical management is to start with medication that increase insulin sensitivity,

advancing to drugs that increase insulin levels and then to provide exogenous insulin (Durstine et al., 2016). Typically people living with T2D are likely to be insulin resistant and the insulin sensitiser, Metformin, is an initial choice (Bilous & Donnelly, 2010; Phung, Scholle, Talwar & Coleman, 2010). With substantial β-cell failure, sulphonylureas (which stimulate insulin secretion) are likely to be effective (Bilous & Donnelly, 2010) before the decision of introducing insulin becomes warranted. The different classes of non-insulin anti-diabetic drugs (when added to maximum metformin therapy for a mean trial duration of 32 weeks) were associated with HbA1c reductions of 7.0-10.7 mmol/mol when compared with placebo (Phung et al., 2010).

In 1998 data from the U.K. Prospective Diabetes Study demonstrated the effectiveness of diabetic medication and reported that for every 11 mmol/mol reduction in HbA1c, there was a possible 35% reduction in microvascular complications, but the authors also stated that results were dependent on the severity of disease progression, namely T2D duration and degree of glycaemic control (UKPDS, 1998).

Results from three large randomized controlled trials (ACCORD, ADVANCE and VADT) were summarized by Bilous & Donnelly (2010). These studies involved over 23 000 people living with T2D who were either allocated a strategy of intensive or less intensive glycaemic control drug therapy; and for whom the main outcome variable was macrovascular disease. In contrast to the UKPDS study, these trials showed no benefit of improved glycaemic control on the cardiovascular (macrovascular) endpoints of fatal and non-fatal endpoints namely, myocardial infarction and stroke. These authors postulated that the reason for this discrepancy in the macrovascular and microvascular disease benefits, probably related to their pathogenesis. Retinopathy, nephropathy and neuropathy are virtually diabetes specific and therefore hyperglycaemia was the main driving force, while atherosclerosis was more multifactorial and although blood glucose was important, it was only one of many factors which contributed (Bilous & Donnelly, 2010). Gæde, Lund-Anderson, Parving and Pedersen (2008) reported that intensive intervention in people living with T2D had sustained beneficial effects with respect to microvascular complications (and on rates of death from any cause and from cardiovascular causes), however their intensive interventions included multiple drug combinations (with tight glucose regulation and the use of RAAS inhibitors, aspirin, and lipid-lowering agents) as well as behaviour modification.

Despite substantial progress in the improvements in the pharmaceutical management of hyperglycaemia, currently available drug therapies remain insufficient to prevent diabetic complications (Russell & Cooper, 2015; Zoungas et al., 2014). Multiple drugs targeting downstream pathways that lead to diabetic complications have been tested and while a variety of these complication drivers have been under active investigation for multiple decades (including the polyol pathway and agents that inhibit this pathway, the PKC-β inhibitor ruboxistaurin, receptor inhibitors for AGEs and blockade of the RAAS) clinical results have been unimpressive due to limited efficacy and/or resultant side effects (Russell & Cooper, 2015). As many of the targetable pathways of inflammation and fibrosis are intrinsic to host energy production and immune defence, this makes side effects of effective agents highly likely. Furthermore, the extensive interlinking of diabetic complication mechanisms introduces redundancy, meaning that targeting one pathway is unlikely to be effective (Russell & Cooper, 2015). More recently, sulfonylureas and exogenous insulin itself have been associated with non-alcoholic fatty liver disease progression and adverse outcomes (Mazzotti, Caletti, Marchignoli, Forlani & Marchesini, 2017).

Weight-loss surgery

Interestingly, the precipitous decrease in caloric intake linked with weight-loss surgery results in a sudden reversal of calories into fat stores and causes a profound change in the intracellular concentration of fat metabolites (Colles, Dixon, Marks, Strauss & O'Brien, 2006). While bariatric surgery is an increasingly recognized treatment option for very obese (BMI >35) people living with T2D's (Bilous & Donnelly, 2010), this expensive surgical option is also outside the scope of this thesis, but the effects of dramatically reducing dietary intake will be highlighted next.

Reduced caloric intake

Storage of liver fat occurs when daily caloric expenditure is less than intake (Taylor, 2013). In a study of people with T2D before and during an 8-week strict 600 kcal/day diet, liver fat decreased by 30% in the first seven days and hepatic insulin sensitivity normalised. In addition, there was a gradual decrease in pancreatic fat content and normalisation of β-cell function was achieved by the end of the study. The authors reported that with dietary energy restrictions alone, the reductions of pancreatic and liver triglyceride stores observed at Week 8 were

associated with a normalisation in function to these central organs related to T2D (Lim et al., 2011). Interestingly, under hypocaloric conditions, fat is mobilized first from the liver (with normalisation of hepatic insulin sensitivity) and other ectopic sites rather than from visceral, subcutaneous or intramyocellular stores; with no change in the insulin resistance of skeletal muscle (Petersen et al., 2005). However, such dietary interventions do not address medium-term durability nor the peripheral skeletal muscle insulin resistance; and raised plasma insulin levels expedite the accumulation of liver fat by stimulation of *de novo* lipogenesis (Petersen et al., 2007).

With regards to dietary management of T2D, current "best practice" in New Zealand constitutes the Ministry of Health's Food and Nutrition recommendations; which are to consume a diet high in carbohydrate and low in dietary fat. However, it needs to be recognised that this set of "best practice" guidelines are currently being challenged in the nutrition-related academic and practice arena (Feinman et al., 2014). The contemporary argument is in favour of carbohydrate restriction, with a greater emphasis on dietary fat as evidence appears to indicate superior outcomes compared to "best practice" for the management of insulin resistant individuals. (Of note: No dietary advice was provided to participants of this study and nutrition was only monitored).

Even with the array of tools modern medical care uses to confront the disease (i.e., pharmaceutical interventions, advanced technology, ever-improving nutritional and lifestyle education aimed at controlling hyperglycaemia), the fight to protect people from diabetes and its disabling, life-threatening complications is currently being lost (Fowler, 2008; IDF, 2015). Moreover, while dietary interventions are potentially more potent (particularly in early T2D) in improving insulin resistance in the central organs (i.e., the liver and pancreas), they do not address peripheral (skeletal muscle) insulin resistance. As such, a need for more comprehensive interventions, that address physical activity and structured exercise modalities are required.

Physical activity

Published guidelines for the management of T2D all include the common triad of medication, nutrition therapy and engagement in physical activity. Though these guidelines generally

provide extensive discussion of the evidence bases, mechanisms of action and recommended dosage regimes for pharmacological therapies as well as comprehensive recommendations for medical nutritional therapy, O'Hagan et al. (2013) point out that physical activity recommendations are seldom afforded the same degree of promotion.

Glucose and physical activity

During resting conditions, only trace amounts of glucose enter skeletal muscle and adipose cells resulting in fatty acids being metabolised as the primary energy substrate (McArdle, Katch & Katch, 2015). Any glucose not immediately catabolised for energy either stores as glycogen or is synthesised to triglycerides. However, glucose is an important fuel for contracting skeletal muscle during physical activity. Glucose uptake by contracting muscle occurs by facilitated diffusion - dependent on the presence and expression of GLUT4s in the surface membrane and an inward diffusion gradient for glucose. During physical activity, coordinated increases in skeletal muscle blood flow, capillary recruitment, insulin-independent GLUT4 translocation (from their intracellular sites to the sarcolemma and T-tubules), and metabolism are all important for glucose uptake and oxidation (Richter & Hargreaves, 2013).

To commence the discussion of physical activity interventions the following terms need clarification:

- 'Physical activity' refers to the expenditure of energy, above that of resting, by the contraction of skeletal muscle to produce any form of bodily movement and includes a vast range of occupational, leisure and daily activities (Hovanec et al., 2012; Sigal, Kenny, Wasserman & Castaneda-Sceppa, 2004).
- 'Exercise', a subset of physical activity, refers to planned and/or structured physical activity and involves repetitive bodily movements performed to improve or maintain one or more of the components of physical fitness: aerobic capacity (or cardiovascular/endurance capacity), muscular strength, muscular endurance, flexibility and body composition. (Hovanec et al., 2012; Sigal et al., 2004).
- 'Physical activity advice' is an intervention in which participants receive formal instructions to engage in regular physical activity but receive no individualized exercise prescription or supervision (Umpierre et al., 2011).

- ‘Structured exercise training’ is an intervention in which participants engage in planned, individualized, and supervised/monitored exercise programmes (Umpierre et al., 2011) in which the exercise is undertaken regularly and could include varying types of exercise (Colberg et al., 2010).
- ‘Clinical Exercise Physiologists’ are qualified exercise practitioners who specialise in the prescription and delivery of structured exercise training, as well as lifestyle and behavioural modification programmes for the prevention and management of chronic conditions (CEPNZ, n.d.).

The common issues in physical activity with T2D include biomechanical difficulties and increased thermal stress (due to increased adiposity), decreased exercise capacity, key health sequelae (e.g., skeletal joint pain, hypertension and dyslipidaemia), silent ischemia and adverse hypo- and hyperglycaemic responses. Of note, the effect of T2D during exercise depends on several factors including the type, dose and timing of antihyperglycaemic medication, amount, type and timing of previous food intake, blood glucose level prior to exercise, presence and severity of diabetic complications (including silent ischemia and hypoglycaemic awareness), use of other medication secondary to diabetic complications and the planned type, duration and intensity of exercise (Hornsby & Albright, 2009). However, in people with stable and well-controlled T2D who have stable blood glucose responses, the exercise response is more affected by the sequelae of diabetes and any unrelated comorbidities than to diabetes per se. Nevertheless, exercise training is perhaps the most important medical prescription for any person living with T2D (Durstine et al., 2016). Although the general benefits of exercise include improvements in blood glucose control, improved insulin sensitivity (reduced insulin resistance) lowering medication requirements, reduction in body fat and decreased risk of cardiovascular disease (Durstine et al., 2016), more specifically, these benefits are achieved by the following mechanisms:

- Exercise-stimulated signal transduction can restore glucose metabolism in insulin-resistant muscle through acute activation of GLUT4 across the myocellular membrane. This process is distinct from those activated by insulin and emphasises exercise as a therapeutic cornerstone for people living with diabetes (Sylow, Kleinert, Richter & Jensen, 2017).

- Glucose is a major fuel source during exercise and glucose uptake by skeletal muscle can increase by up to 50-fold during bouts of exercise with intensity and duration of the exercise being key determinants of glucose uptake volume by skeletal muscle (Sylow et al., 2017).
- Regulation of exercise-induced glucose uptake by skeletal muscle requires three simultaneously-stimulated steps of glucose delivery, glucose transport across the cell membrane and intramyocellular metabolism. Any of these steps could be rate-limiting during various exercise conditions, but all three steps are improved in an exercise-trained state due to increases in capillarisation, GLUT4 expression and translocation, and hexokinase and mitochondrial expression, respectively (Sylow et al., 2017).
- Insulin sensitivity and responsiveness become elevated in the exercise-trained state (Sylow et al., 2017).
- Physical activity reduces pancreatic insulin secretion and is associated with a lower liver fat content (Cassidy et al., 2015b; Perseghin et al., 2007)
- Contracting skeletal muscle is an endocrine-secretory organ and myokines and other peptides are produced, expressed and released by muscles that exert either autocrine, paracrine or endocrine effects in other tissues and organs (Pedersen & Febbraio, 2012). Amongst other myokines, myostatin, interleukin-6 and interleukin-7 are involved in muscle hypertrophy and myogenesis, whereas interleukin-6 is involved in AMP-activated protein kinase (AMPK)-mediated fat oxidation. Interleukin-6 also appears to have systemic effects on the liver, adipose tissue and the immune system, and mediates crosstalk between intestinal L-cells and pancreatic islets. Additionally, other myokines affect endothelial function of the vascular system. However, the authors suggest that many proteins produced by skeletal muscle are dependent upon contraction and that an altered myokine response, as a result of sedentary behaviour, may be the potential mechanism associated with many chronic diseases such as T2D (Pedersen & Febbraio, 2012).

For these reasons, prescribing structured exercise to people living with T2D must form part of a comprehensive intervention strategy.

Types of Structured Exercise Training

Cardiovascular alone training

CV alone training is land- or water-based activities that use equipment that provides continuous rhythmic movement for the same large muscle groups of the lower and/or upper extremities enabling 'aerobic endurance' focused training (Hovanec et al., 2012; Yavari et al., 2012). Such exercise (e.g. walking, bicycling and swimming) can be performed 3-6 days each week at 40 – 80% of maximal effort, with the lower intense sessions performed more frequently. The duration of these aerobic alone sessions is at least 10-50 minutes (depending of the intensity of training) and when performed at lower-moderate intensities are often referred to as long slow distance training, continuous exercise, or steady-state training. Physiological benefits of CV training include increased maximal oxygen utilization (via increased mitochondrial density/capacity) and cardiopulmonary fitness, and increased fatty acid oxidation (Sigal et al., 2004; Holloszy & Coyle, 1984). While there are these beneficial aspects to CV training, it does have some limitations. Some find aerobic exercise monotonous and forms of aerobic exercise are challenging in people with severe obesity and are not always advisable for those people with advanced peripheral neuropathy (Sigal et al., 2004).

Typically the intensity of CV training can be structured according to a percentage of a multitude of parameters (e.g. VO_2max, predicted VO_2max, VO_2peak, VO_2reserve, HRmax, HRpeak, HRreserve, peak workload or estimated maximum workload) and can be described as "moderate" when it is at 40–60% of VO_2max (~50–70% of HRmax; ~55% of predicted VO_2max) and "vigorous" when it is at >60% VO_2max (>70% of HRmax; ~70% of predicted VO_2max). (Balducci et al., 2012; Colberg et al., 2010; Sigal et al., 2004). To assist exercise practitioners, the self-reported rating of perceived exertion (RPE) 6-20 Borg scale can supplement in judging the degree of intensity; in general, a Borg RPE scale >18 indicates the participant has performed maximal exercise, and values of 15 to 16 suggest that the anaerobic threshold, or vigorous training, has been exceeded (Fletcher et al., 2001; Sigal et al., 2004; Vinik et al., 2013).

Resistance alone training

Resistance training (RT) activates the muscular system to generate force against a resistive load typically using gym-based activities such as isotonic machines and/or free-weights and performed on 2-3 non-consecutive days each week. According to the American College of Sports Medicine (ACSM) and the American Diabetes Association (ADA) recommendations, such exercise modalities normally progress to have a 'muscular strength' focus (1-4 sets of 8-10 repetitions at 75-80% of 1-repetition maximum [1-RM] with adequate recovery between sets). The RT alone session duration is 30 -50 minutes and includes 5-10 compound and/or isolated exercises that target the major muscle groups across the upper body, lower body and core (Colberg et al, 2010). When prescribed for an individual, the sequencing of these exercises are commonly from the larger muscle groups (compound exercises) to the smaller muscle groups (isolated exercise) while alternating between upper- and lower-body exercises so as to allow for adequate rest of that muscle group. When prescribed for groups circuit-type training designs can be employed in which gym equipment layout, and participant numbers, influences/alters the prescription sequence.

Essentially each repetition (comprising a concentric contraction and an eccentric return-to-start action) spans 3-4 seconds and a typical set of ~10 repetitions therefore only lasts 30-40 seconds. RT alone, aimed at increasing muscle mass, often causes more rapid changes in functional status than CV alone training and might therefore be more immediately rewarding to participants (Pesta, Goncalves, Madiraju, Strasser & Sparks, 2017) and because each session involves many different resistance exercises, some people find it less monotonous than CV training. (Sigal et al., 2004). From a clinical perspective, skeletal muscles are the largest postprandial glucose uptake and glycogen storage sites in the human body and are integral in maintaining glucose homeostasis. (Hovanec et al., 2012).

The intensity of RT can be described as "high" if the resistance is ≥75% of 1-RM and "moderate" if resistance is 50–74% of 1-RM and RT, for people living with T2D, is considered as a safe training modality; even at the higher intensities (Sigal et al., 2004).

Combined training

When either CV or RT is performed exclusively for the duration of an intervention period it is referred to as CV alone or RT alone training, respectively. Alternatively, both modalities can be performed together during an intervention period, but in two separate variations, both being referred to as combined training. Firstly, MICT and RT sessions can be performed on alternating days such that 2-3 sessions of each are performed each week (i.e. a total of 4-6 exercise sessions per week). In contrast, both MICT and RT can be performed during the same exercise session (i.e. 2-3 sessions per week on non-consecutive days) but necessitates either a longer training session (i.e. > 60 minutes) or other adjustments (e.g. shorter MICT and/or modifications to the RT variables) if the training session time is limited. It has been recommended that people living with chronic conditions adopt this modality as a means to provide the benefits of both CV and RT (Bilous & Donnelly, 2010; Colberg et al., 2010). Combined training sessions typically last for 60 minutes with 20-30 minutes allocated to each component. Flexibility training may be included but should not be undertaken in place of these recommended types of physical activity (Colberg et al., 2010).

Moderate-intensity continuous training

MICT is a structured progression of CV training. In order to elicit continued CV improvements the progression principle states that the exercise stimulus (achieved via the manipulation of the intensity, duration and/or frequency training variables) must increase over time (Swain & Leutholtz, 2007); with the rate of progression dependent on the individual's health status, exercise tolerance and training goals (ACSM, 2010). As such, MICT programmes can progress from light (< 40% VO_2max) to moderate (40-59% VO_2max) or from moderate to vigorous (60-84% VO_2max) intensity. As with initial CV training, Swain and Leutholtz (2007) note that MICT can be performed 3-6 days each week depending on the intensity and training goal, while the duration of each MICT session can increase to 20-60 minutes. More recently Colberg (2013) recommends that the CV component for T2D training to have an intensity range of 40% HRreserve (possibly lighter than an RPE of fairly light [11/20]) to 89% HRreserve eliciting an RPE of somewhat hard (13/20) to hard (15/20) but suggests that progressions initially increase in duration and frequency before increasing the MICT intensity. However she also states that adding in faster intervals during an exercise session is another possible progression.

High-intensity interval training

HIIT is an alternate CV training progression performed at a high intensity (>85% VO_2max) for a brief period of time (a few seconds to several minutes) interspersed with recovery intervals (several seconds to several minutes) at low-to-moderate intensity (Gibala, Little, Mac Donald and Hawley, 2012; Kessler, Sisson & Short, 2012; Shiraev & Barclay 2012). The modes of HIIT usually include running/walking on a treadmill or cycling on a cycle ergometer. The manipulation of the training variables (peak intensity, peak workload duration, number of intervals and intensity and duration of recovery periods) all determine training dose and can directly affects acute physiological responses and long-term adaptations (Gibala et al., 2012; Hansen, Dendale, van Loon & Meeusen, 2010; Tschakert & Hofmann, 2013). The premise of using HIIT in clinical populations is that the vigorous activity segments promote greater adaptations via increased cellular stress, yet their bouts of brief duration, and the ensuing recovery intervals, allow even untrained individuals to work harder than would otherwise be possible at steady-state intensity (Kessler et al., 2012). Furthermore, while HIIT is proposed as a time efficient form of CV training (Little et al., 2011; Shaban, Kenno & Milne, 2014) it is extremely demanding and may not be appealing for some individuals (Gibala et al., 2012; Shaban et al., 2014).

Researchers using HIIT on numerous population (healthy and clinical) groups have employed multiple variations of peak intensity, ranging from longer less-intense intervals, referred to as aerobic interval training (AIT), to very-short intense peak intervals with longer recovery periods, referred to as sprint interval training (SIT). The spectrum of these variations reported in research is evident in the following examples:

- 4-6 bouts of 4 minutes of high-intensity work at 85-95% maximal effort followed by a slightly shorter active recovery period of 3-4 minutes of less intense work (Kessler et al., 2012; Tjønna et al., 2008; Wisløff et al., 2007).
- 4 bouts of 1 minute at ~83% VO_2peak interspersed with 4 minute recovery intervals at ~55% VO_2peak (Mitranun, Deerochanawong, Tanaka & Suksom, 2014).
- 10 bouts of 1 minute at 90% maximum heart rate (HRmax) interspersed with 1 minute rest intervals (Little et al., 2011).
- 4 bouts of 30 seconds at 100% maximum estimated workload (eWLmax) interspersed with 4 minutes of recovery at 25% eWLmax (Shaban et al., 2014).

- 4-6 bouts of 30 seconds against a supra-maximal load (simulating the Wingate test) interspersed by up to 4 minutes of recovery with each session lasting 20-30 minutes (Gibala et al., 2012).
- 4-5 bouts of 30 seconds at supra-maximal load (200% VO_2max) interspersed with 2 minutes of rest (Tabata, Irisawa, Kouzaki, Nishimura, Ogita & Miyachi, 1997).
- 7-8 bouts of 20 seconds at supra-maximal load (170% VO_2max) interspersed with 10 seconds of rest (Tabata et al., 1996).
- 60 bouts of 8 seconds sprints interspersed with 12 seconds of recovery (Boutcher, 2011) with the training session reported to last 20 minutes (excluding warm-up and cool-down).

Additionally, these variations exclude the training variables of intervention duration and training frequency.

Clinical Exercise Physiologists

A new and emerging profession in New Zealand is that of a Clinical Exercise Physiologist (CEP). CEPs play an important role in a multi-disciplinary team by providing people living with T2D specialised screening and exercise testing (e.g. graded exercise testing with full ECG monitoring), prescribing individualized structured exercise training, as well as providing related education (within their professional scope of practice).

As the incidence of T2D is growing globally, and in all New Zealand communities, CEP's need to confidently design and progress exercise training interventions that lead to the best possible health outcome. Enhanced knowledge on exercise prescription parameters that optimise available resources with regards to addressing T2D, will enable CEPs to deliver a more effective exercise intervention programme that is beneficial to both the client's health by potentially staving off macrovascular and microvascular complications that lead to CVD, amputations and dialysis (Hammed et al., 2012; Hovanec et al., 2012) and the government's health-care costs.

CHAPTER THREE

Effects of high-intensity interval training on people living with type 2 diabetes: A narrative review

This chapter comprises the following paper published on 21 September 2017 in the Canadian Journal of Diabetes:

Wormgoor, S. G., Dalleck, L.C., Zinn, C., & Harris, N.K. (2017). Effects of high-intensity interval training on people living with T2D: A narrative review. *Canadian Journal of Diabetes*, *41,* 5, 536-547. doi: 10.1016/j.jcjd.2016.12.004

Abstract

People with type 2 diabetes mellitus (T2D) typically present with comorbidities, such as elevated blood pressure, high cholesterol, high blood glucose, obesity and decreased fitness, all contributive to increased risk of cardiovascular complications. Determination of effective exercise modalities for the management of such complications is important. One such modality is high-intensity interval training (HIIT). To conduct the review PubMED and EBSCOHost databases were searched through 01 June 2016, for all HIIT intervention studies conducted on people living with T2D. Thereafter, the central characteristics of HIIT were analysed to obtain a broader understanding of the cardiometabolic benefits achievable by HIIT. Fourteen studies were included for review, but the heterogeneity of the participants with T2D, the training equipment and HIIT parameters, accompanied by variations in supervision, dietary advice and medications prevented direct comparisons. However HIIT, regardless of the specific parameters employed, was a suitable option in pursuing improved glycaemic control, body composition, aerobic fitness, blood pressure and lipidaemia measures in individuals with T2D. HIIT is a therapy with at least equivalent benefit to moderate-intensity continuous training (MICT); hence, HIIT should be considered when prescribing exercise interventions for people living with T2D.

Introduction

T2D is one of the largest global health epidemics of the 21st century (IDF, 2015). Those afflicted typically present with comorbidities such as hypertension, dyslipidaemia and other risk factors (e.g., abdominal obesity and decreased aerobic fitness) all contributive to increased risk of cardiovascular complications (Fowler, 2008; Inzucchi et al., 2012). Established T2D management strives, via medication optimisation and/or lifestyle changes (Chamberlain et al., 2016), to reduce these risk factors, but has to date demonstrated varied success in improving glycaemic control and preventing diabetic complications. Two large scale, long-term follow-up studies on people living with T2D (The Action to Control Cardiovascular Risk in Diabetes [ACCORD] Study Group, 2016; Zoungas et al., 2014), in which all participants received education and lifestyle advice along with antihyperglycaemic medication to either maintain their glycaemic control target of achieving glycated haemoglobin (HbA1c) of around 53.0 mmol/mol or to intensify glycaemic control, achieving HbA1c below 48.0 mmol/mol, found that while there were positive effects on microvascular complications, long-term intensive glycaemic control did not lead to further long-term benefits with respect to mortality or macrovascular events. Wing et al. (2013), reporting on the Look AHEAD project, in which participants accumulated 175 minutes of moderate-intensity PA each week, coupled with a calorie-restricted diet, for one year, concluded that intensive lifestyle interventions focused on weight loss, counselling and increased, unsupervised, moderate-intensity PA did not reduce the cardiovascular events in adults with T2D. As evident from these investigations, the optimum glycaemic control strategy for the treatment of T2D and its macrovascular complications is unclear and, therefore, further investigations into alternate strategies that focus on the comprehensive reduction of cardiometabolic risks, for example, structured exercise interventions and/or low-carbohydrate dietary approaches, are warranted.

The lifestyle factors of diet and PA are central to the management of T2D as they both help treat the associated lipid, BP, body weight and blood glucose control abnormalities (Colberg et al., 2010), and it is recommended that when medications are used to control T2D, they should augment lifestyle improvements, not replace them (Colberg et al., 2010). Notwithstanding the influence of diet on T2D, this review will focus on exercise interventions. Structured exercise modalities have been promoted by several authors as a vital component to manage T2D (Chudyk & Petrella, 2011; Gibala et al., 2012; Hameed et al., 2012; Hovanec et al., 2012,

Jelleyman et al., 2015; Strasser & Pesta, 2013; Sukala et al., 2012; Umpierre et al., 2011; Umpierre, Ribeiro, Schaan & Ribeira, 2013). One such exercise modality is HIIT, and although it has recently attracted much attention (Biddle & Batterham, 2015; Bird & Hawley, 2012; Francois & Little, 2015; Gray, Ferguson, Birch, Forrest & Gill, 2016; Holloway & Spriet, 2015; Kessler et al., 2012; Lee & Oh, 2014; Olver & Laughlin, 2016; Wisløff, Coombes & Rognmo, 2015), the potential for prescribing HIIT for T2D has not been fully investigated. Limited reviews of the effects of HIIT interventions have been conducted on T2D (Adams, 2016; Curry et al., 2015) as well as in clinical conditions related to T2D, such as lifestyle-induced cardiometabolic disease (Weston, Wisløff & Coombes, 2014), vascular function (Ramos, Dalleck, Tjønna, Beetham & Coombes, 2015), glucose regulation and insulin resistance (Boutagy & Luff, 2013; Jelleyman et al., 2015) and, most recently, common metabolic diseases (Cassidy, Thoma, Houghton & Trenell, 2017). Moreover, the paucity of RCTs involving HIIT interventions on T2D is evident; only six such studies to date have been included for analysis across all six of these reviews. Hence, the rationale of this review was to look beyond RCTs and to conduct a review including all HIIT interventions reported on adults with T2D with the purpose being 3-fold: 1) the effects of HIIT on glycaemic control measures; 2) effects of HIIT on cardiometabolic risk factors; and 3) the summarisation of the central characteristics of HIIT.

Methods

Literature search

PubMED and EBSCOHost databases were searched with no date restrictions (until 01 June 2016) for HIIT intervention studies conducted in people with T2D. There is no universal definition of HIIT (Weston et al., 2014), so the following principle was applied to the search: intermittent bouts of vigorous (or higher intensity) exercise of up to 4-min per bout, interspersed with recovery periods of lower intensity exercise (or complete rest). Terminology frequently used to describe HIIT were searched in titles and abstracts using the following search terms: ‘high-intensity’, ‘HIIT’, ‘interval training’, ‘sprint interval’, ‘Wingate’ in combination with (using the Boolean AND command) ‘diabetes’, ‘type 2’, ‘glucose’, ‘glycaemic control’ and ‘glycemic control’. Titles and abstracts of returned articles were evaluated (and when further clarity was needed, the full-text was perused) so as to include only intervention studies of human participants with T2D. Additionally, the reference lists from the retrieved articles and reviews

were manually checked to search for further relevant articles. Full-text publications of controlled and uncontrolled HIIT intervention studies were included for review. Acute-response studies and studies not published in English were excluded. The entire literature search was conducted independently, with no blinding to study authors, institutions, or manuscript journals.

The number of studies investigating HIIT in T2D was limited and was compounded with considerable differences in HIIT application and use of comparison groups (if at all), so I chose to avoid systematically rating the quality of the research but, rather, to use a narrative review for a nuanced approach to my critique. The differences in the participants with T2D, study design and HIIT parameters utilised across the various studies are discussed throughout this review. Table 3.1 presents the study duration, participants' characteristics, T2D status, adherence rates and specific intervention protocol parameters used. For the purpose of this review, short- and medium-term interventions have been defined as 1-4 weeks and >4-26 weeks, respectively. Additionally, HIIT interventions that utilised high-intensity bouts of ≥60-sec and those ≤30-sec are referred to as aerobic interval training (AIT) or sprint interval training (SIT), respectively.

Study participant and intervention variables

After the full-text analysis of the retrieved articles, 14 studies involving adults with T2D were included for review. The studies, published between 2008 and 2016, involved 279 participants. As with all research in human participants, the SPs were volunteers who provided informed consent, thereby possibly constituting a positive attitude towards exercise and/or research as well as possibly being internally motivated to make changes to their lifestyles (Shaban, Kenno & Milne, 2014). The mean number of SPs with T2D across the intervention and comparison groups was 11.3 ± 3.4 and 11.0 ± 3.2, respectively.

Although the low numbers of SPs confound the ability to determine statistical significance within and between groups, they are possibly indicative of the low numbers of participants with T2D who volunteer for exercise interventions (Shaban et al., 2014), the logistics (including funding and other resources) of supervised HIIT interventions (Terada et al., 2013a) and/or the comorbidities associated with T2D that exclude many volunteers (Alvarez et al., 2016; Backx et al., 2011; Madsen, Thorup, Overgaard & Jeppesen, 2015). The studies reported drop-outs (in limited cases, 1-2 per group, and they were comparable among intervention groups) for various

reasons, including minor medical reasons (discussed under ‘Adverse Effects’) and non-medical reasons (transport, work-commitments) reasons (Alvarez et al., 2016; Backx et al., 2011; Cassidy et al., 2015b; Fex, Leduc-Gaudet, Filion, Karelis & Aubertin-Leheudre, 2015; Karstoft et al., 2013; Mitranun et al., 2014; Parpa, Michaelides & Brown, 2009).

The general SP exclusion criteria were similar for all studies (unless stated) and included severe retinopathy, severe cardiovascular disease, impaired liver function, macroalbuminuria, severe asthma, cancer, musculoskeletal injuries or any other contraindications to exercise. Seven studies excluded participants using exogenous insulin (Backx et al., 2011; Cassidy et al., 2015b; Karstoft et al., 2013; Little et al., 2011; Madsen et al., 2015; Revdal, Hollekim-Strand, & Ingul, 2016; Terada et al., 2013a). Additionally, participants underwent a screening process and those with electrocardiogram (ECG) abnormalities (Alvarez et al., 2016; Backx et al., 2011; Madsen et al., 2015; Mitranun et al., 2014) or severe hypertension (Shaban et al., 2014; Terada et al., 2013a) were excluded. The use of antihypertensive medication was explicitly reported in seven studies (Alvarez et al., 2016; Cassidy et al., 2015b; Little et al., 2011; Madsen et al., 2015; Parpa et al., 2009; Praet et al., 2008; Revdal et al., 2016) and statin use in two studies (Backx et al., 2011; Madsen et al., 2015). No study reported having smokers as participants; women were reported as being post-menopausal in some cases (Fex et al., 2015; Madsen et al., 2015; Terada et al., 2013a) and all SPs were instructed to maintain their medication regime and lifestyle (activities of daily living and current diet) in 12 of the studies; all except two (Backx et al., 2011; Cassidy et al., 2015b). Most participants were reported as not currently partaking in regular PA but because they were included initially, the SPs tended to represent the healthier side of the condition, except when specifically included for having diastolic dysfunction (Hollekim-Strand et al., 2014), diabetic polyneuropathy (Praet et al., 2008) or reduced heart rate variability (HRV) (Parpa et al., 2009).

Table 3.1: Summary of studies that used HIIT as a clinical intervention in people living with T2D

Study and study design	Modality, intervention duration, and run-in duration (if any)	Participant characteristics including prescribed antihyperglycaemic medication and resting blood pressure limitations (if any)	Training frequency, session duration, (additional aspects) and adherence	HIIT parameters: bouts, work - rest duration and intensities, progression and mode Comparison group parameters (if any): Steady state duration, intensity and mode
Alvarez et al. (2016) RCT	HIIT (AIT) 16-wk	*n* = 13 women Age = 45.6 ± 11.2 yrs T2D duration = 3.4 ± 4.0 yrs HbA1c = 51.9 (median) (Metformin and Glibenclamide)	3 x/wk 22 min *progressed to* ~38 min with 89.0 ± 5.0 % adherence	8 bouts 30 sec ~95 % HRR - 2 min ≤70 % HRR *progressed to* 14 bouts 58 sec ~95 % HRR - 1:36 min ≤70 % HRR using indoor sports court (jogging/walking)
	Control 16-wk	*n* = 10 women Age = 43.1 ± 4.7 yrs T2D duration = 3.6 ± 3.5 yrs HbA1c = 57.4 (median) (Metformin and Glibenclamide)	Instructed to remain sedentary	
Backx et al. (2011) Pilot study	HIIT (AIT) 12-wk including run-in of 2-wk MICT	*n* = 10 Age = 59.6 yrs (median) T2D duration = >0.25 yrs (newly diagnosed) HbA1c = 46.5 mmol/mol (median) (treatment naïve)	3 x/wk 35 min *progressed to* 60 min (plus 2 x/w MICT) with 63 % for HIIT and 78 % for MICT adherence	4 bouts 2 min ~85 % HRR - 2 min ~45 % HRR *progressed to* 8 bouts 3 min ~85 % HRR - 2 min 45 % HRR using cycle ergometer
	MICT advice 12-wk	*n* = 9 Age = 59.6 yrs (median) T2D duration = >0.25 yrs (newly diagnosed) HbA1c = 48.6 mmol/mol (median) (treatment naïve)	5x/wk 30 min with 69 % adherence	Advised to exercise at moderate-high intensity using self-selected modalities
Cassidy et al. (2015b) RCT	HIIT (AIT) 12-wk	*n* = 12 Age = 61.0 ± 9.0 yrs T2D duration = 5.0 ± 3.0 yrs HbA1c = 54.0 ± 11.0 mmol/mol (Metformin only)	3 x/wk 30 min *progressed to* 40 min (included 4 resistive band exercises) with > 89 % adherence	5 bouts 2 min ~16.5 RPE - 3 min ~11 RPE *progressed to* 5 bouts 3:50 min ~16.5 RPE - 3 min ~11 RPE using cycle ergometer
	Control 12-wk	*n* = 11 Age = 59.0 ± 9.0 yrs T2D duration = 4.0 ± 2.0 yrs HbA1c = 55.0 ± 6.0 mmol/mol (Metformin only)	Instructed to continue habitual lifestyle and not to change medication and body mass	.
Fex et al. (2015) Pilot study	HIIT (SIT) 12-wk	*n* = 16 of which 8 T2D Age 60.4 ± 6.1 yrs HbA1c = 45.0 ± 6.6 mmol/mol	3 x/wk 30 min with 88 % adherence	10 bouts 30 sec ~83 % HRR - 1:30 min ~63 % HRR using elliptical trainer

Study and study design	Modality, intervention duration, and run-in duration (if any)	Participant characteristics including prescribed antihyperglycaemic medication and resting blood pressure limitations (if any)	Training frequency, session duration, (additional aspects) and adherence	HIIT parameters: bouts, work - rest duration and intensities, progression and mode Comparison group parameters (if any): Steady state duration, intensity and mode
Hollekim-Strand et al. (2014) RCT	HIIT (AIT) 12-wk	*n* = 20 with diastolic dysfunction Age = 58.6 ± 5.0 yrs T2D duration = 4.2 ± 2.3 yrs HbA1c = 53.0 ± 9.1 mmol/mol	3 x/wk 40 min	4 bouts 4 min ~93 % HRmax - 4 min Low-intensity recovery Modality not reported
	MICT advice 12-wk	*n* = 17 with diastolic dysfunction Age = 54.7± 5.3 yrs T2D duration = 3.0 ± 2.6 yrs HbA1c = 50.0 ± 5.2 mmol/mol	Advised 210min/week	N/A
Karstoft et al. (2013) RCT	HIIT (AIT) 16-wk	*n* = 12 Age = 57.5 ± 8.3 yrs T2D duration = 3.5 ± 2.4 yrs HbA1c = 51.9 ± 7.6 mmol/mol (oral medication only)	5 x/wk 60 min with 85 ± 14 % adherence	10 bouts 3 min >70 % - 3 min <70 % of peak energy expenditure rate using free-living walking
	MICT Isocaloric 16-wk	*n* = 12 Age = 60.8 ± 7.6 yrs T2D duration = 6.2 ± 5.2 yrs HbA1c = 48.6 ± 7.6 mmol/mol (oral medication only)	5x/wk 60 min with 94 ± 21 % adherence	60 min at 60 % of peak energy expenditure rate using free-living walking
	Control 16-wk	*n* = 8 Age = 57.1 ± 8.5 yrs T2D duration = 4.5 ± 4.2 yrs HbA1c = 46.5 ± 6.2 mmol/mol (oral medication only)	Instructed to continue habitual lifestyle Pedometer data uploaded monthly	N/A
Little et al. (2011) Pilot study	HIIT (AIT) 2-wk	*n* = 8 Age = 62.5 ± 7.6 yrs HbA1c = 51.9 ± 7.7 mmol/mol (oral medication only)	3 x/wk 25 min with 100 % adherence	10 bouts 1 min ~90 % HRpeak - 1 min rest RPE peaked at 8/10 using cycle ergometer
Madsen et al. (2015) Pilot study	HIIT (AIT) 8-wk	*n* = 10 Age = 56.0 ± 6.3 yrs HbA1c = 65.0 ± 10.0 mmol/mol (oral medication only)	3 x/wk 30 min	10 bouts 1 min 90 % of PO at HRpeak - 1 min rest *progressed to* 10 bouts
	HIIT (AIT) 8-wk	*n* = 13 Non-T2D Age = 52.0 ± 7.2 yrs	3 x/wk 30 min	1 min 95 % of PO at HRpeak - 1 min rest using cycle ergometer
Mitranun et al. (2014)	HIIT (AIT)	*n* = 14 Age = 61.2 ± 2.8 yrs	3 x/wk 30 min *progressed to* 40 min	4 bouts 1 min 80 % VO_2peak - 4 min 50 % VO_2peak

Study and study design	Modality, intervention duration, and run-in duration (if any)	Participant characteristics including prescribed antihyperglycaemic medication and resting blood pressure limitations (if any)	Training frequency, session duration, (additional aspects) and adherence	HIIT parameters: bouts, work - rest duration and intensities, progression and mode Comparison group parameters (if any): Steady state duration, intensity and mode
RCT	12-wk including run-in of 2-wk MICT	T2D duration = 19.5 ± 0.4 yrs (long standing) HbA1c = 60.0 ± 7.5 mmol/mol		*progressed to* 6 bouts 1 min 85 % VO_2peak - 4 min 60 % VO_2peak using treadmill walking
	MICT Isocaloric 12-wk	*n* = 14 Age = 61.7 ± 2.7 yrs T2D duration = 20.5 ± 0.4 yrs (long standing) HbA1c = 61.0 ± 7.5 mmol/mol	3 x/wk 30 min *progressed to* 40 min	20 min at 60 % VO_2peak *progressed to* 30 min at 65 % VO_2peak using treadmill walking
	Inactive control 12-wk	*n* = 15 Age = 60.9 ± 2.4 yrs T2D duration = 21.1 ± 0.6 yrs (long standing) HbA1c = 62.0 ± 7.7 mmol/mol	Instructed to remain sedentary	
Parpa et al. (2009) Pilot study	HIIT (AIT) 12-wk	*n* = 14 with reduced HRV Age = 57.0 ± 6.7 yrs Moderate glycaemic control	4 x/wk 28 min with 94 ± 3 % adherence	6 bouts 2 min ~85 % - 2 min ~55 % of predicted HRmax using treadmill
Praet et al. (2008) Pilot study	HIIT (SIT) 10-wk	*n* = 11 men with signs of DPN Age = 59.1 ± 7.5 yrs T2D duration = 12.1 ± 7.0 yrs (long standing) HbA1c = 60.0 ± 11.0 mmol/mol (insulin treated)	3 x/wk 40 min *progressed to* 45 min (included 5 RT exercises) with 83 ± 13 % adherence	4 bouts 30 sec ~55 % Max W - 1 min Low-intensity recovery *progressed to* 8 bouts 30 sec ~55 % Max W - 1 min Low-intensity recovery using cycle ergometer
Revdal et al. (2016) Pilot study	HIIT (AIT) 12-wk	*n* = 9 Age = 56.5 ± 6.5 yrs T2D duration = 4.2 ± 2.1 yrs HbA1c = 48.0 ± 10.6 mmol/mol (oral medication only) and BP < 140/90 mmHg	3 x/wk 27 min with 96.0 % adherence	10 bouts 1 min ~90 % HRmax - 1:15min Low-intensity recovery using treadmill
	HIIT (SIT)	*n* = 9 Age = 49.6 ± 10.6 yrs T2D duration = 5.3 ± 2.5 yrs HbA1c = 62.4 ± 13.4 mmol/mol (oral medication only) and BP < 140/90 mmHg	3 x/wk 10 min with 95.4 % adherence	2 bouts 20 sec sprint - 3 min Low-intensity recovery using treadmill
Shaban	HIIT (SIT)	*n* = 9 Age = 40.2 ± 9.7 yrs	3 x/wk 23 min	4 bouts 30 sec 100 % eWLmax - 4 min 25 % eWLmax

Study and study design	Modality, intervention duration, and run-in duration (if any)	Participant characteristics including prescribed antihyperglycaemic medication and resting blood pressure limitations (if any)	Training frequency, session duration, (additional aspects) and adherence	HIIT parameters: bouts, work - rest duration and intensities, progression and mode Comparison group parameters (if any): Steady state duration, intensity and mode
et al. (2014)	2-wk	HbA1c = 61.8 ± nr mmol/mol and BP < 165/95 mmHg	with 100 % adherence	using cycle ergometer
Pilot study	Waitlist control	*n* = 9 Age = 40.2 ± 9.7 yrs HbA1c = 56.3 ± 13.2 mmol/mol and BP < 165/95 mmHg	Instructed to continue habitual lifestyle	N/A
Terada et al. (2013a) RCT	HIIT (AIT) Isocaloric 12-wk excluding run-in of 2-wk MICT	*n* = 8 Age = 62.0 ± 3.0 yrs T2D duration = 8.0 ± 4.0 yrs HbA1c = 48.6 ± 6.6 mmol/mol (oral medication only) and BP < 140/90 mmHg	4 x/wk 30 min *progressed to* 60 min (plus 1 x/w MICT) with 97.2 ± 2.7 % adherence	7 bouts 1 min 100 % VO_2 R - 3 min 20 % VO_2 R *progressed to* 14 bouts 1 min 100 % VO_2 R - 3 min 20 % VO_2 R using cycle ergometer alternating with treadmill walking
	MICT Isocaloric 12-wk excluding run-in of 2-wk MICT	*n* = 7 Age = 63.0 ± 5.0 yrs T2D duration = 8.0 ± 4.0 yrs HbA1c = 48.6 ± 9.9 mmol/mol (oral medication only) and BP < 140/90 mmHg	5 x/wk 30 min *progressed to* 60 min with 97.3 ± 3.7 % adherence	40 % VO_2R using cycle ergometer alternating with treadmill walking

Where reported data are means ± SD. Run-in represents an introductory training phase to habituate participants to exercise interventions, session duration is inclusive of warm-up, recovery intervals and cool down, and adherence is the percentage of eligible exercise sessions completed.

AIT, aerobic interval training; BP, blood pressure; DPN, diabetic peripheral neuropathy; eWLmax, estimated workload maximum; HbA1c, glycated haemoglobin a measure of glycaemic control; HIIT, high-intensity interval training; HR, heart rate; HRR, heart rate reserve; HRV, heart rate variability; MICT, moderate-intensity continuous training; N/A, not applicable; nr, not reported; PO, power output; RCT, randomised controlled trial; RPE, rate of perceived exertion (6-20 scale); RT, resistance training; SIT, sprint interval training; T2D, type 2 diabetes mellitus; VO_2, aerobic capacity; VO_2R, aerobic capacity reserve; W, watts; wk, week; x/wk, times per week.

Effects of HIIT on Cardiometabolic Risk Factors in T2D

Short-duration, short-term interventions

The two short-term intervention studies (Little et al., 2011; Shaban et al., 2014) recruited SPs without diabetic complications and performed 23-25 min (short-duration) of HIIT for a total of six sessions, to determine the effects of low-volume HIIT on blood glucose regulation, insulin resistance and skeletal muscle metabolic capacity. The middle-aged SPs (Shaban et al., 2014) experienced no improvement in body mass, fitness or the homeostatic model for insulin resistance (HOMA-IR) over the 2-wk intervention period, but the individuals who commenced the study with the highest HOMA-IR values showed the greatest benefit. The SPs with good glycaemic control (Little et al., 2011) experienced short-term blood glucose control benefits in average 24-hr blood glucose concentrations, area under the 24-hr blood glucose curve and the sum of 3-hr postprandial area under the glucose curves for breakfast, lunch and dinner. Little et al. (2011) stated that the mechanisms mediating the improvements in glycaemic control are not yet known, but they speculated that increases in skeletal muscle mitochondrial content, training-induced increases in glucose transport protein (GLUT4) content and/or training-induced alterations in hepatic glucose output could possibly be involved. The authors did highlight that their HIIT training time of 75-min/wk was 50% less than guidelines that called for 150-min/wk of moderate-vigorous exercise, but there was no comparison group, so it cannot be reported that these short-term findings would be more beneficial than MICT.

Short-duration, medium-term interventions

Similar short-duration HIIT sessions utilised in medium-term studies (Fex et al., 2015; Madsen et al., 2015; Parpa et al., 2009; Praet et al., 2008; Revdal et al., 2016) have also resulted in varied cardiometabolic improvements. Tables 3.2 - 3.6 present the effects of medium-term HIIT interventions on selected metabolic regulation, anthropometrics, aerobic fitness, BP and blood analysis results, respectively. The effects reported in the tables include change from baseline (as percentage), statistical significance ($P \leq 0.05$), and effect size (Cohen's *d* [quotient of the difference in means and pooled standard deviation]), with improvements positively depicted. Fex et al. (2015), for example, noted an improvement in fasting blood glucose (FBG) (effect size [ES] = 0.42) accompanied by a small improvement in HbA1c (ES = 0.18) following HIIT involving an elliptical trainer. Their study sample, including participants with both T2D and pre-T2D and being the most fit at baseline for all groups in this review (VO_2max 40.3 ± 8.0

ml/kg/min) (Table 3.4), experienced further moderate improvements in aerobic fitness (ES = 0.57) and SBP (ES = 0.58), but no improvement in body composition (ES = 0.03). Those with T2D who had the poorest fitness (VO_2max 21.9 ± 4.2 ml/kg/min) (Table 3.4) of the review (Madsen et al., 2015) compared HIIT in middle-aged people with T2D to HIIT in same-aged obese people without T2D. On conclusion of the 8-wk study, there were moderate-to-large improvements in HbA1c (ES = 0.33); FBG (ES =1.10); the post 2-hr oral glucose tolerance test (OGTT) (ES = 1.14); and HOMA-IR (ES = 1.40) in the people with T2D, which was ascribed to ameliorated pancreatic β-cell dysfunction, as well as moderate improvements in aerobic fitness (ES = 0.77) and body mass (ES = 0.27). However, there were also improvements in all of the results for the SPs without T2D, so no significant between-group differences were observed. Of note were the large improvements in SBP and DBP (Table 3.5) in the HIIT group (ES = 1.22 and 0.96, respectively), and they were accompanied by the largest relative reduction of TG (Table 3.6) found in this review. Although none of the results were significantly different from those found in people without T2D, it is encouraging to people with T2D and practitioners alike that individuals with T2D can still achieve meaningful benefits from an 8-wk HIIT intervention in parity with obese people without T2D.

Revdal et al. (2016) employed a novel extremely low-volume SIT protocol in which participants with T2D (without complications) were supervised performing two 20-sec maximal sprints (total session time 10-min) (Table 3.1). The protocol was applied thrice weekly for 12 weeks and was compared to a group with T2D (with significantly lower baseline HbA1c) using more established 27-min AIT sessions. SIT resulted in greater HbA1c and FBG reductions (ES = 0.28 and 0.48, respectively), and AIT resulted in greater HOMA-IR (ES =0.53) improvements, but neither was noted as being statistically significant. The AIT group's already well-controlled hyperglycaemia (48.0 ± 10.6 mmol/mol) at baseline is conceivably attributable to the lack of reported effect. For the SIT group, it was conjectured that the substantially reduced exercise volume was an influential factor. Additionally, the SIT group, while being approximately 16 kg heavier than the AIT group at baseline (Table 3.3), did not experience any improvements in body composition (ES =0.00).

Table 3.2: Metabolic control changes following medium-term HIIT intervention programmes in people living with T2D

Study	Metabolic control measure	HIIT group baseline	HIIT group change (%)	HIIT group effect size[a]	Comparison group modality	Comparison group baseline	Comparison group change (%)	Comparison group effect size[a]	Between-group difference (%)
Alvarez et al. (2016)	HbA1c	51.9 (median) [b]	16.84***	-	ADL control	57.4 (median) [b]	-1.90	-	18.75†
Backx et al. (2011)	HbA1c	46.5 (median)	9.41**	-	MICT: Advised	48.6 (median)	-2.25	-	11.66
Cassidy et al. (2015b)	HbA1c	54.1 ± 11.0	6.06	0.31	ADL control	55.2 ± 5.5	-3.96	-0.33	10.02†
Fex et al. (2015)	HbA1c	44.3 ± 6.6	2.47	0.18	-	-	-	-	-
Hollekim-Strand et al. (2014)	HbA1c	53.0 ± 13.2	8.25**	0.37	MICT: Advised	49.7 ± 7.7	4.40	0.30	3.85
Karstoft et al. (2013)	HbA1c HbA1c	51.9 ± 7.6	2.11	0.11	MICT: Isocaloric ADL control	48.6 ± 7.6 46.5 ± 6.2	0.00 -9.41	0.00 -0.55	2.11 11.52
Madsen et al. (2015)	HbA1c	65.6 ± 10.0[b]	5.00*	0.33	HIIT: Non-T2D	40.4 ± 1.3 [b]	-2.16	-0.67	7.16
Mitranun et al. (2014)	HbA1c HbA1c	60.0 ± 7.5	10.00*	0.80	MICT: Isocaloric ADL control	61.0 ± 7.5 62.0 ± 7.7	3.28 -5.00	0.21 -0.40	6.72 15.00†
Praet et al. (2008)	HbA1c	59.9 ± 10.9	3.28	0.18	-	-	-	-	-
Revdal et al. (2016)	HbA1c	48.0 ± 10.6	1.63	0.08	SIT	62.4 ± 13.4†	5.06	0.28	-3.43
Terada et al. (2013a)	HbA1c	48.6 ± 6.6	2.25	0.18	MICT: Isocaloric	49.7 ± 9.9	-6.59	-0.30	8.84
Alvarez et al. (2016)	FBG	7.7 ± 0.7 [b]	13.99***	1.46	ADL control	7.6 ± 0.3 [b]	-1.05	-0.18	15.04†
Backx et al. (2011)	FBG	7.2 (median)	8.33	-	MICT: Advised	8.0 (median)	-6.25	-	14.58
Cassidy et al. (2015b)	FBG	6.8 ± 1.6	0.00	0.00	ADL control	7.0 ± 1.0	-8.57*	-0.49	8.57
Fex et al. (2015)	FBG	7.1 ± 1.1	8.45*	0.42	-	-	-		
Karstoft et al. (2013)	FBG FBG	8.5 ± 2.8	1.18	0.03	MICT: Isocaloric ADL control	7.4 ± 1.4 7.3 ± 2.3	-4.05 -12.33	-0.15 -0.37	5.23 13.51
Madsen et al. (2015)	FBG	8.1 ± 0.8 [b]	10.19**	1.10	HIIT: Non-T2D	5.5 ± 0.1 [b]	3.64	-2.00	6.86
Mitranun et al. (2014)	FBG FBG	7.7 ± 0.8	13.73*	1.25	MICT: Isocaloric ADL control	7.7 ± 1.0 7.4 ± 0.9	12.94* 1.49	-1.09 -0.11	0.78 12.23
Praet et al. (2008)	FBG	10.2 ± 3.1	6.96	0.23	-	-	-	-	-
Revdal et al. (2016)	FBG	7.8 ± 1.7	6.13	0.30	SIT	9.4 ± 2.7	10.44	-0.48	-4.31
Terada et al. (2013a)	FBG	6.8 ± 0.8	1.47	0.13	MICT: Isocaloric	7.3 ± 1.7	-4.11	0.12	5.58
Backx et al. (2011)	Fasting insulin	100.6 (median)	19.28	-	MICT: Advised	139.5 (median)	11.43	-	7.86

Study	Metabolic control measure	HIIT group baseline	HIIT group change (%)	HIIT group effect size[a]	Comparison group modality	Comparison group baseline	Comparison group change (%)	Comparison group effect size[a]	Between-group difference (%)
Cassidy et al. (2015b)	Fasting insulin	65.5 ± 39.5	0.00	0.00	ADL control	81.5 ± 46.4	-7.98	-0.15	7.98
Karstoft et al. (2013)	Fasting insulin	91.8 ± 49.2	19.50	0.42	MICT: Isocaloric ADL control	88.3 ± 38.8 82.1 ± 30.3	-3.06 -43.73*	-0.06 -0.94	22.56 63.23††
Praet et al. (2008)	C-peptide	0.77 ± 0.56	9.09	0.13	-	-	-	-	-
Cassidy et al. (2015b)	OGTT	12.5 ± 3.1	6.40	0.26	ADL control	11.7 ± 3.1	-10.26**	-0.41	16.66†
Karstoft et al. (2013)	OGTT	16.5 ± 3.1	6.67	0.28	MICT: Isocaloric ADL control	14.8 ± 3.5 14.7 ± 4.0	-1.35 -6.80	-0.05 -0.25	8.02 13.47
Madsen et al. (2015)	OGTT	15.5 ± 2.1 [b]	15.48*	1.14	HIIT: Non-T2D	6.4 ± 0.5 [b]	3.13	0.40	12.36
Cassidy et al. (2015b)	HOMA-IR	1.30 ± 0.80	-7.69	-0.14	ADL control	1.60 ± 0.90	-12.50	-0.23	4.81
Hollekim-Strand et al. (2014)	HOMA-IR	2.70 ± 0.70	0.00	0.00	MICT: Advised	2.60 ± 1.00	3.85	0.11	-3.85
Madsen et al. (2015)	HOMA-IR	2.97 ± 0.40 [b]	18.18*	1.44	HIIT: Non-T2D	1.95 ± 0.20 [b]	-4.10	-0.34	22.28
Mitranun et al. (2014)	HOMA-IR	3.10 ± 5.24	19.35*	0.13	MICT: Isocaloric ADL control	2.80 ± 4.86 3.90 ± 4.65	17.86* -7.69	0.10 -0.06	1.50 27.05†
Revdal et al. (2016)	HOMA-IR	2.0 ± 0.5	11.27	0.53	SIT	2.4 ± 0.8	3.31	0.11	7.97

Unless stated as median data are means ± SD.

[a] Cohen's *d* (quotient of the difference in means and pooled SD), [b] data estimated from figures.

Statistical significance is reported as follows: * $P<0.05$, ** $P<0.01$, *** $P<0.001$ different from baseline; † $P<0.05$, †† $P<0.01$, ††† $P<0.001$ difference between HIIT and comparison groups.

ADL, activities of daily living; C-peptide (nmol/L); Fasting insulin (pmol/l); FBG, fasting blood glucose (mmol/L); HbA1c, glycated haemoglobin (mmol/mol); HIIT, high-intensity interval training; HOMA-IR, homeostasis model assessment for insulin resistance; MICT, moderate-intensity continuous training; OGTT, oral glucose tolerance test (post 2 hours) (mmol/L); SIT, sprint interval training; T2D, type 2 diabetes mellitus; -, indicates not stated.

Table 3.3: Body composition changes following medium-term HIIT intervention programmes in people living with T2D

Study	Body composition measure	HIIT group baseline	HIIT group change (%)	HIIT group effect size[a]	Comparison group modality	Comparison group baseline	Comparison group change (%)	Comparison group effect size[a]	Between-group difference (%)
Alvarez et al. (2016)	Body mass	73.8 ± 7.2	2.17*	0.23	ADL control	75.3 ± 5.1	0.00	0.00	2.17
Backx et al. (2011)	Body mass	91.7 (median)	4.14**	-	MICT: Advised	102.5 (median)	1.37	-	2.78
Cassidy et al. (2015b)	Body mass	90.0 ± 15.0	1.11	0.07	ADL control	90.0 ± 9.0	-1.11	-0.11	2.22†
Fex et al. (2015)	Body mass	89.4 ± 14.4	0.56	0.03	-	-	-	-	-
Karstoft et al. (2013)	Body mass	84.9 ± 17.0	4.95***	0.27	MICT: Isocaloric	88.2 ± 16.3	0.79	0.04	4.15†
					ADL control	88.5 ± 13.3	-0.79	-0.05	5.74††
Madsen et al. (2015)	Body mass	91.2 ± 11.2	3.29**	0.27	HIIT: Non-T2D	88.8 ± 14.3	1.93***	0.12	1.36
Mitranun et al. (2014)	Body mass	66.5 ± 13.8	3.16*	0.17	MICT: Isocaloric	65.8 ± 11.6	0.76	0.04	2.40
					ADL control	67.7 ± 1.4	0.89	0.04	2.27
Parpa et al. (2009)	Body mass	94.3 ± 23.8	4.07*	0.16	-	-	-	-	-
Praet et al. (2008)	Body mass	97.6 ± 16.1	0.10	0.01	-	-	-	-	-
Revdal et al. (2016)	Body mass	75.5 ± 15.9	0.79	0.04	SIT	91.4 ± 20.3	-0.11	0.00	0.90
Terada et al. (2013a)	Body mass	80.5 ± 9.9	0.99	0.08	MICT: Isocaloric	93.9 ± 18.3	1.38	0.07	-0.39
Alvarez et al. (2016)	BMI	30.6 ± 4.0	2.29*	0.18	ADL control	30.4 ± 1.3	0.00	0.00	2.29
Backx et al. (2011)	BMI	30.0 (median)	4.33**	-	MICT: Advised	32.3 (median)	0.93	-	3.40
Fex et al. (2015)	BMI	34.6 ± 5.4	0.58	0.04	-	-	-	-	-
Hollekim-Strand et al. (2014)	BMI	30.2 ± 2.8	1.66**	0.19	MICT: Advised	29.7 ± 3.7	1.01	0.08	0.65
Karstoft et al. (2013)	BMI	29.0 ± 4.5	4.83***	0.34	MICT: Isocaloric	29.9 ± 5.5	1.00	0.05	3.82†
					ADL control	29.7 ± 5.4	-0.34	-0.02	5.16†
Madsen et al. (2015)	BMI	31.1 ± 3.9	3.37**	0.27	HIIT: Non-T2D	30.5 ± 3.0	1.93***	0.19	1.44
Mitranun et al. (2014)	BMI	29.3 ± 1.9	2.73*	0.52	MICT: Isocaloric	29.4 ± 2.6	0.68	0.08	2.05
					ADL control	29.7 ± 1.5	1.01	0.15	1.72
Praet et al. (2008)	BMI	32.2 ± 4.0	0.00	0.00	-	-	-	-	-
Revdal et al. (2016)	BMI	26.3 ± 3.0	0.76	0.07	SIT	29.5 ± 3.9	0.00	0.00	0.76
Terada et al. (2013a)	BMI	28.4 ± 4.1	1.06	0.07	MICT: Isocaloric	33.1 ± 4.5	1.51	0.11	-0.45

Study	Body composition measure	HIIT group baseline	HIIT group change (%)	HIIT group effect size[a]	Comparison group modality	Comparison group baseline	Comparison group change (%)	Comparison group effect size[a]	Between-group difference (%)
Fex et al. (2015)	BF %	42.3 ± 10.4	1.18	0.05	-	-	-	-	-
Hollekim-Strand et al. (2014)	BF %	27.9 ± 7.7	1.08	0.04	MICT: Advised	27.5 ± 7.3	1.09	0.04	-0.02
Madsen et al. (2015)	BF %	33.1 ± 8.1	1.81	0.07	HIIT: Non-T2D	31.7 ± 7.0	1.45	0.04	0.36
Mitranun et al. (2014)	BF %	32.6 ± 7.9	6.75*	0.27	MICT: Isocaloric ADL control	33.7 ± 7.5 33.9 ± 4.3	7.72* -1.77	0.36 -0.13	-0.97 8.52
Praet et al. (2008)	BF %	27.0 ± 2.8	0.00	0.00	-	-	-	-	-
Revdal et al. (2016)	BF %	28.8 ± 6.7	4.51*	0.19	SIT	31.4 ± 6.2	-0.32	-0.02	4.83
Terada et al. (2013a)	BF %	36.1 ± 10.9	5.26**	0.18	MICT: Isocaloric	41.6 ± 6.3	3.61*	0.25	1.66
Cassidy et al. (2015b)	Visceral fat: cm^2	201.0 ± 80.0	9.95*	0.26	ADL control	159.0 ± 58.0	1.58	0.05	8.37
Karstoft et al. (2013)	Visceral fat: %	4.7 ± 2.8	10.64***	0.19	MICT: Isocaloric ADL control	4.5 ± 1.0 4.7 ± 1.1	6.67 2.13	0.24 0.09	3.97 8.51
Alvarez et al. (2016)	Waist girth	101.1 ± 8.7	4.06**	0.50	ADL control	98.7 ± 4.7	-0.61	-0.13	4.66†
Backx et al. (2011)	Waist girth	101.4 (median)	4.14*	-	MICT: Advised	111.1 (median)	3.15*	-	0.99
Fex et al. (2015)	Waist girth	109.0 ± 10.3	3.67*	0.38	-	-	-	-	-
Hollekim-Strand et al. (2014)	Waist girth	108.6 ± 7.7	2.39***	0.36	MICT: Advised	106.5 ± 8.7	1.88**	0.25	0.52
Praet et al. (2008)	Waist girth	112.6 ± 12.1	0.98	0.09	-	-	-	-	-
Revdal et al. (2016)	Waist girth	93.8 ± 8..2	1.39	0.16	SIT	103.3 ± 106	-0.87	-0.08	2.26
Terada et al. (2013a)	Waist girth	102.6 ± 7.2	0.39	0.06	MICT: Isocaloric	116.3 ± 11.0†	1.03	0.11	-0.64
Alvarez et al. (2016)	∑4 skinfolds	147.0 ± 21.6	19.05***	1.52	ADL control	144.0 ± 15.8	-2.08	-0.19	21.13†††

Unless stated as median data are means ± SD. [a] Cohen's *d* (quotient of the difference in means and pooled SD).
Statistical significance is reported as follows: * $P<0.05$, ** $P<0.01$, *** $P<0.001$ different from baseline; † $P<0.05$, †† $P<0.01$, ††† $P<0.001$ difference between HIIT and comparison groups.
ADL, activities of daily living; Body mass (kg); BF %, body fat percentage; BMI, body mass index (kg/m^2); HIIT, high-intensity interval training; MICT, moderate-intensity continuous training; SIT, sprint interval training; T2D, type 2 diabetes mellitus; waist girth (cm); ∑4, sum of four skinfolds (mm); -, indicates not stated.

Table 3.4: Aerobic fitness changes following medium-term HIIT intervention programmes in people living with T2D

Study	Aerobic fitness measure	HIIT group baseline	HIIT group change (%)	HIIT group effect size[a]	Comparison group modality	Comparison group baseline	Comparison group change (%)	Comparison group effect size[a]	Between-group difference (%)
Fex et al. (2015)	VO_2 max	40.3 ± 8.0	12.66*	0.57	-	-	-	-	-
Karstoft et al. (2013)	VO_2 max	27.1 ± 5.2	16.24***	0.67	MICT: Isocaloric ADL control	26.1 ± 4.8 24.8 ± 5.1	2.68 1.61	0.12 0.07	13.55† 14.62†
Madsen et al. (2015)	VO_2 max	21.9 ± 4.2	13.14**	0.77	HIIT: Non-T2D	26.0 ± 6.6	7.43**	0.31	5.70
Mitranun et al. (2014)	VO_2 max	24.2 ± 6.0	25.21*	1.15	MICT: Isocaloric ADL control	23.8 ± 3.7 24.4 ± 5.0	13.87* -2.05	0.80 -0.11	11.34† 27.26†
Hollekim-Strand et al. (2014)	VO_2 peak	31.5 ± 6.1	13.02***	0.66	MICT: Advised	33.2 ± 7.4	3.61*	0.16	9.40††
Praet et al. (2008)	VO_2 peak	24.3 ± 1.4	3.70	0.64	-	-	-	-	-
Revdal et al. (2016)	VO_2 peak	31.5 ± 5.8	10.48**	0.59	SIT	32.0 ± 9.5	4.38*	0.15	6.10
Terada et al. (2013a)	VO_2 peak	22.8 ± 5.4	6.58	0.23	MICT: Isocaloric	18.1 ± 2.7	4.42	0.23	2.16
Madsen et al. (2015)	Max wattage	203.5 ± 35.3	10.32**	0.57	HIIT: Non-T2D	229.2 ± 44.4	10.57***	0.53	-0.25
Praet et al. (2008)	Max wattage	152.0 ± 39.0	13.82**	0.54	-	-	-	-	-
Terada et al. (2013a)	Max wattage	145.0 ± 46.0	11.72*	0.33	MICT: Isocaloric	118.0 ± 34.0	8.47	0.29	3.25
Alvarez et al. (2016)	2-km walk test	23.2 ± 0.7	9.48***	2.39	ADL control	22.3 ± 0.9	-0.45	-0.12	9.93†

Data are means ± SD. [a] Cohen's *d* (quotient of the difference in means and pooled SD).
Statistical significance is reported as follows: * $P<0.05$, ** $P<0.01$, *** $P<0.001$ different from baseline; † $P<0.05$, †† $P<0.01$, ††† $P<0.001$ difference between HIIT and comparison groups.
ADL, activities of daily living; HIIT, high-intensity interval training; MICT, moderate-intensity continuous training; SIT, sprint interval training; VO_2, aerobic capacity (ml/kg/min); Walk test (min); -, indicates not stated.

Table 3.5: Resting blood pressure and flow mediated dilatation changes following medium-term HIIT intervention programmes in people living with T2D

Study	Measure	HIIT group baseline	HIIT group change (%)	HIIT group effect size[a]	Comparison group modality	Comparison group baseline	Comparison group change (%)	Comparison group effect size[a]	Between-group difference (%)
Alvarez et al. (2016)	SBP	131.0 ± 3.6	2.27*	0.83	ADL control	130.0 ± 3.2	-0.77	-0.43	3.04
Fex et al. (2015)	SBP	134.0 ± 12.2	5.22***	0.58	-	-	-	-	-
Hollekim-Strand et al. (2014)	SBP	142.1 ± 18.3	-0.28	-0.02	MICT: Advised	135.4 ± 11.9	0.37	0.04	-0.65
Karstoft et al. (2013)	SBP	138.0 ± 11.4	0.14	0.02	MICT: Isocaloric ADL control	155.0 ± 18.7 142.0 ± 12.2	-0.97 0.70	-0.07 0.09	1.11 -0.56
Madsen et al. (2015)	SBP	134.8 ± 9.2	8.31***	1.22	HIIT: Non-T2D	136.5 ± 13.0	5.64**	0.65	2.67
Mitranun et al. (2014)	SBP	133.0 ± 18.7	9.02*	0.64	MICT: Isocaloric ADL control	133.0 ± 18.7 131.0 ± 19.4	3.76 -0.76	0.30 -0.05	5.26 9.79
Parpa et al. (2009)	SBP	134.0 ± 11.0	5.22*	0.70	-	-	-	-	-
Praet et al. (2008)	SBP	147.4 ± 12.3	5.16	0.62	-	-	-	-	-
Revdal et al. (2016)	SBP	129.3 ± 16.3	2.32	0.19	SIT	135.3 ± 11.0	3.40	0.43	-1.08
Alvarez et al. (2016)	DBP	77.0 ± 3.6	0.00	0.00	ADL control	78.0 ± 3.2	-1.28	-0.32	1.28
Fex et al. (2015)	DBP	81.3 ± 8.4	1.97*	0.17	-	-	-	-	-
Hollekim-Strand et al. (2014)	DBP	81.7 ± 6.9	4.16	0.42	MICT: Advised	80.9 ± 7.1	0.12	0.01	4.04
Karstoft et al. (2013)	DBP	85.0 ± 9.7	0.12	0.01	MICT: Isocaloric ADL control	90.0 ± 6.2 86.6 ± 9.9	0.44 -2.31	0.05 -0.22	-0.33 2.43
Madsen et al. (2015)	DBP	87.5 ± 6.6	7.31***	0.96	HIIT: Non-T2D	87.9 ± 8.3	--7.17***	0.88	0.15
Mitranun et al. (2014)	DBP	79.0 ± 11.2	-2.53	-0.21	MICT: Isocaloric ADL control	81.0 ± 7.5 83.0 ± 11.6	0.00 1.20	0.00 0.09	-2.53 -3.74
Parpa et al. (2009)	DBP	84.0 ± 6.0	4.76*	0.72	-	-	-	-	-
Praet et al. (2008)	DBP	82.5 ± 7.1	2.67	0.31	-	-	-	-	-
Revdal et al. (2016)	DBP	76.8 ± 7.2	1.17	0.11	SIT	85.4 ± 12.0	6.67*	0.57	-5.50
Hollekim-Strand et al. (2014)	FMD	9.2 ± 9.6	101.09**	0.97	MICT: Advised	13.0 ± 9.8	0.00	0.00	101.09†
Mitranun et al. (2014)	FMD	5.4 ± 4.1	37.04*	0.53	MICT: Isocaloric ADL control	4.8 ± 6.0 5.1 ± 5.0	27.08* 9.80	0.20 0.08	9.95† 27.23†

Data are means ± SD. [a] Cohen's *d* (quotient of the difference in means and pooled SD).
Statistical significance is reported as follows: * $P<0.05$, ** $P<0.01$, *** $P<0.001$ different from baseline; † $P<0.05$, †† $P<0.01$, ††† $P<0.001$ difference between HIIT and comparison groups.
ADL, activities of daily living; DBP, diastolic blood pressure (mmHg); FMD, flow mediated dilatation (%); HIIT, high-intensity interval training; MICT, moderate-intensity continuous training; SBP, systolic blood pressure (mmHg); SIT, sprint interval training; -, indicates not stated.

Table 3.6: Lipid profile and selected blood variable changes following medium-term HIIT intervention programmes in people living with T2D

Study	Measure	HIIT group baseline	HIIT group change (%)	HIIT group effect size[a]	Comparison group modality	Comparison group baseline	Comparison group change (%)	Comparison group effect size[a]	Between-group difference (%)
Alvarez et al. (2016)	TC	4.84 ± 0.40	2.07	0.04	ADL control	5.10 ± 0.50	-0.98	-0.10	3.05
Backx et al. (2011)	TC	6.30 (median)	13.21*	-	MICT: Advised	4.80 (median)	2.08	-	11.12
Cassidy et al. (2015b)	TC	4.00 ± 1.00	-12.50	-0.71	ADL control	4.50 ± 0.90	-2.22	-0.11	-10.28
Karstoft et al. (2013)	TC	5.00 ± 1.04	2.00	0.11	MICT: Isocaloric ADL control	5.30 ± 1.04 5.40 ± 0.57	-3.77 -9.26*	-0.19 -0.56	5.77 11.26†
Madsen et al. (2015)	TC	4.21 ± 1.42	9.03	0.26	HIIT: Non-T2D	5.26 ± 0.65	3.99	0.35	5.03
Mitranun et al. (2014)	TC	4.89 ± 0.67	10.02	0.73	MICT: Isocaloric ADL control	4.71 ± 0.56 5.12 ± 0.58	2.12 -5.08*	0.18 -0.46	7.90 15.10
Terada et al. (2013a)	TC	3.90 ± 0.40	-2.56	-0.13	MICT: Isocaloric	3.90 ± 0.50	2.56	0.15	-5.13
Alvarez et al. (2016)	TG	1.45 ± 0.30	17.24*	0.99	ADL control	1.47 ± 0.30	-6.80	-0.33	24.04†
Backx et al. (2011)	TG	1.90 (median)	15.79	-	MICT: Advised	1.80 (median)	0.00	-	15.78
Cassidy et al. (2015b)	TG	1.10 ± 0.30	-9.09	-0.28	ADL control	1.10 ± 0.40	-9.09	-0.25	0.00
Karstoft et al. (2013)	TG	3.00 ± 4.85	16.67	0.13	MICT: Isocaloric ADL control	1.30 ± 0.69 1.60 ± 0.57	-15.38 -18.75	-0.23 -0.42	32.05 35.42
Madsen et al. (2015)	TG	1.78 ± 1.01	24.72	0.54	HIIT: Non-T2D	1.40 ± 0.72	7.14	0.18	17.58
Mitranun et al. (2014)	TG	1.66 ± 0.75	12.05	0.27	MICT: Isocaloric ADL control	1.63 ± 0.71 1.80 ± 0.81	3.68 2.78	0.08 0.06	8.37 9.27
Praet et al. (2008)	TG	2.30 ± 0.40	8.70	0.50	-	-	-	-	-
Terada et al. (2013a)	TG	1.50 ± 0.40	-6.67	-0.14	MICT: Isocaloric	2.10 ± 0.80	23.81	0.59	-30.48
Alvarez et al. (2016)	HDL	1.29 ± 0.20	20.16*	1.75	ADL control	1.14 ± 0.20	-2.63	-0.19	22.79†
Backx et al. (2011)	HDL	1.40 (median)	-7.14	-	MICT: Advised	0.90 (median)	0.00	-	-7.14
Karstoft et al. (2013)	HDL	1.10 ± 0.35	0.00	0.00	MICT: Isocaloric ADL control	1.40 ± 0.35 1.40 ± 0.28	0.00 0.00	0.00 0.00	0.00 0.00
Madsen et al. (2015)	HDL	1.40 ± 0.32	5.00	0.23	HIIT: Non-T2D	1.29 ± 0.40	6.20	0.23	-1.20
Mitranun et al. (2014)	HDL	1.06 ± 0.15	29.25*	1.83	MICT: Isocaloric ADL control	1.37 ± 0.15 1.11 ± 0.19	5.84 4.50	0.47 0.29	23.41 24.74†
Terada et al. (2013a)	HDL	1.20 ± 0.20	0.00	0.00	MICT: Isocaloric	1.30 ± 0.40	0.00	0.00	0.00

Study	Measure	HIIT group baseline	HIIT group change (%)	HIIT group effect size[a]	Comparison group modality	Comparison group baseline	Comparison group change (%)	Comparison group effect size[a]	Between-group difference (%)
Alvarez et al. (2016)	LDL	3.31 ± 0.40	1.51	0.12	ADL control	3.34 ± 0.40	-2.10	-0.17	3.61
Backx et al. (2011)	LDL	3.20 (median)	18.75*	-	MICT: Advised	2.90 (median)	0.00	-	18.75†
Karstoft et al. (2013)	LDL	3.20 ± 0.69	12.50*	0.58	MICT: Isocaloric ADL control	3.30 ± 0.69 3.40 ± 0.28	-3.03 -8.82	-0.18 -0.47	15.53 21.32†
Madsen et al. (2015)	LDL	1.99 ± 1.14	11.56	0.19	HIIT: Non-T2D	3.32 ± 0.76	6.02	0.28	5.53
Mitranun et al. (2014)	LDL	3.34 ± 0.56	21.86*	1.34	MICT: Isocaloric ADL control	3.41 ± 0.56 3.49 ± 0.58	16.72* 4.30	1.05 0.27	5.14 17.56
Praet et al. (2008)	LDL	3.40 ± 0.40	2.94	0.25	-	-	-	-	-
Terada et al. (2013a)	LDL	2.00 ± 0.20	-10.00	-0.45	MICT: Isocaloric	1.80 ± 0.70	0.00	0.00	10.00
Cassidy et al. (2015b)	LFT - ALT	36.0 ± 11.0	16.67*	0.57	ADL control	34.0 ± 16.0	2.94	0.07	13.73
Cassidy et al. (2015b)	LFT - AST	27.7 ± 7.0	13.36*	0.57	ADL control	27.6 ± 10.4	3.99	0.11	9.37
Cassidy et al. (2015b)	LFT - ALP	66.0 ± 17.0	4.55	0.18	ADL control	59.2 ± 16.8	-3.38	-0.12	7.92†
Cassidy et al. (2015b)	Liver fat	6.9 ± 6.9	39.13	0.49	ADL control	7.1 ± 6.8	-8.45	-0.09	47.58††
Hollekim-Strand et al. (2014)	hs-CRP	3.70 ± 2.80	43.24*	0.73	MICT: Advised	1.60 ± 1.20†	0.00	0.00	43.24†
Praet et al. (2008)	hs-CRP	2.07 ± 1.77	-10.14	-0.12	-	-	-	-	-
Praet et al. (2008)	TNF-α	7.20 ± 1.50	-1.39	-0.07	-	-	-	-	-

Unless stated as data values are means ± SD. [a] Cohen's *d* (quotient of the difference in means and pooled SD).
Statistical significance is reported as follows: * *P*<0.05, ** *P*<0.01, *** *P*<0.001 different from baseline; † *P*<0.05, †† *P*<0.01, ††† *P*<0.001 difference between HIIT and comparison groups.
ADL, activities of daily living; ALP, alkaline phosphatase (IU/L); ALT, alanine aminotransferase (IU/L); AST, aspartate transaminase (IU/L); HDL, high density lipoprotein cholesterol (mmol/L); HIIT, high-intensity interval training; hs-CRP, high sensitivity C-reactive protein (mg/L); LDL, low density lipoprotein cholesterol (mmol/L); LFT, liver function test; MICT, moderate-intensity continuous training; sICAM, soluble intercellular adhesion molecule-1 (ng/mL); TC, total cholesterol (mmol/L); TNF-α, tumour necrosis factor alpha (ng/L); TG, triglycerides (mmol/L); T2D, type 2 diabetes mellitus; -, indicates not stated.

The previous three studies' SPs had T2D without diabetic complications, but Praet et al. (2008) included SPs with diabetic polyneuropathy, and Parpa et al. (2009) included those with reduced HRV. Including only a HIIT group (Praet et al., 2008), the middle-aged participants, with long-standing T2D and using exogenous insulin, commenced each session with about 25-min of RT before concluding each training session with brief (~15-min) of HIIT. The RT included three upper- and two lower-body exercises (2 sets of 10 repetitions) and progressed to 60% of predicted 1-RM. After the 10-wk intervention, only a small change in HbA1c was reported (ES = 0.18); however it was noted that instead of the SPs having an increased 3.6 ± 2.6 international units per day (IU/d) of insulin requirement (extrapolated from their pre-study 2-yr trends), participants actually required 4.8 IU/d less insulin. Additionally, small improvements (ES = 0.13) in the C-peptide concentrations were evident. No improvements in body composition (ES = -0.01) were experienced, but although presenting with the highest baseline SBP of this review (147.4 ± 12.3 mmHg) (Table 3.5) and performing a large proportion of RT, moderate improvements in the SBP (ES = 0.62) and TG (ES = 0.50) were reported. However, small increases in high sensitivity-CRP (hs-CRP) (ES = -0.12) and tumour necrosis factor alpha (TNF-α) (ES =-0.07) and a small decrease in adiponectin (ES = -0.04) were also reported (Table 3.6).

Although Parpa et al. (2009) did not report on aerobic fitness or on any metabolic markers, these authors did report a small reduction in body mass (ES = 0.16), and moderate improvements in both SBP and DBP (ES = 0.70 and 0.72, respectively) were experienced alongside a significant improvement in HRV (ES = 1.01). This beneficial effect on autonomic regulation may have clinical importance in preventing adverse cardiovascular events in people with T2D, a concept supported by Vinik and colleagues (2013), who reported that autonomic dysfunction was associated with cardiovascular risk and sudden death in those with T2D and that restoration of autonomic balance was possible with increased PA.

Although these five medium-term, short-duration HIIT studies demonstrated positive effects on multiple cardiometabolic risk factors, no study included a comparative MICT or inactive control group. Therefore, although this review cannot conclude that short-duration HIIT sessions are of greater benefit than MICT sessions, these medium-term pilot studies demonstrate that cardiometabolic benefits can be achieved with regular, supervised, short-duration HIIT (<30 min per session) in individuals with T2D.

Long-duration, medium-term interventions

Using longer training session durations (40-60 min) and including control groups, five studies (Backx et al., 2011; Cassidy et al., 2015b; Hollekim-Strand et al., 2014; Mitranun et al., 2014; Terada et al., 2013a) applied 12-wk HIIT, in training facilities, for a minimum of three days a week to people with T2D. Elderly people living with T2D for about 5 yrs and without complications (Cassidy et al., 2015b) either trained 40-min thrice weekly, incorporating an upper-body resistive band exercise (for 1-min) into each of the four HIIT recovery bouts or formed part of the inactive control, continuing with habitual lifestyles. The control group demonstrated significant deterioration in FBG and OGTT and a small to moderate worsening of HOMA-IR, fasting insulin and HbA1c (ES = -0.49, -0.41, -0.23, -0.15 and -0.33, respectively). However, the participants in the HIIT group, who showed good training adherence (even though they were not directly supervised beyond the initial session), experienced moderate improvements in HbA1c (ES = 0.31) and, when compared to the controls, according to the authors, there was a significant between-group difference for both HbA1c and the OGTT (Table 3.2). A significant but small between-group difference for body mass was reported (Table 3.3) and, although a rise in total cholesterol (TC) was evident (ES = -0.71), liver markers significantly improved (Table 3.6). Furthermore, it was highlighted that the reduction in liver fat was not only the first reported on HIIT studies, but also that it was the greatest reduction to be reported following any exercise intervention in participants with T2D and that those who lost the greatest liver fat had the largest reductions in FBG.

Backx et al. (2011) recruited newly diagnosed (< 0.25 yrs) people with T2D who were treatment-naïve and who had trained five days a week in either a MICT (unsupervised) or a HIIT (supervised) group, with the HIIT group completing three HIIT and two MICT sessions each week. The HIIT group received a nutrition class midway through the intervention period (K. Backx, personal communication, May 12, 2016; the details have not been stated), which does somewhat confound my ability to compare the exercise effects with other research. The HIIT group's median HbA1c improvement (from a good baseline 46.5 mmol/mol) (Table 3.2) was significant, reportedly through enhanced pancreatic β-cell function. The MICT group's HbA1c and FBG worsened non-significantly, but the low number of participants limited analyses. Likewise, the reduction of 3.8 kg (4.14%) in body mass (Table 3.3) in the HIIT group was not different to the 1.4 kg (1.37%) in the MICT group, but the reduction in LDL, was significantly

greater in the HIIT group (Table 3.6). The HIIT sessions progressed to 60-min while the MICT group was advised to train for about 30-min per session, so these results should be considered in context to total training time.

Hollekim-Strand et al. (2014) supervised three 40-min HIIT sessions each week in a group with T2D presenting with diastolic dysfunction. The study's control group (statistically younger by ~4 yrs) was advised to perform MICT (unsupervised) for 210 min/wk. Although HIIT was more beneficial than MICT in improving diastolic dysfunction (ES = 1.83 vs. 0.54) and aerobic fitness (ES = 0.66 vs. 0.16) (Table 3.4), the improvements in HbA1c and waist circumference in the HIIT group (ES = 0.37 and 0.36, respectively) were no different from those of the MICT group's improvements (ES = 0.30 and 0.25, respectively). Additionally, Hollekim-Strand et al. (2014) demonstrated significant improvements with HIIT for hs-CRP in comparison to MICT, although the HIIT group did have higher baseline measures (Table 3.6).

Mitranun et al. (2014), randomised elderly sedentary SPs, with long-standing diabetes of about 20 yrs into performing HIIT or MICT (both with 40-min sessions) and an inactive control. After the intervention, the HIIT participants showed significant improvements in HbA1c, FBG and HOMA-IR (ES = 0.80, 1.25 and 0.13, respectively) when compared to the control group (ES = -0.40, 0.11 and -0.06, respectively) but not in comparison to the MICT group (ES = 0.21, 1.09 and -0.10, respectively). Similarly, the overweight SPs experienced improvements in body composition, but neither intervention was superior (Table 3.3). However, aerobic fitness improved to a greater extent in the HIIT group (ES = 1.15) and was the intervention that improved aerobic fitness the most (VO_2max increased >25%) across all the groups in this review. In addition, the increased HDL concentration in the HIIT group was large (ES = 1.83) in comparison to the MICT group (ES = 0.47) and was also the greatest of all the groups in this review (Table 3.6). Mitranun et al. (2014) and Hollekim-Strand et al. (2014) reported significant improvements in brachial artery flow-mediated dilation (FMD), both within-group and between-MICT groups (Table 3.5), but the changes in resting BP did not appear consistent with the improvements in FMD. Mitranun et al. (2014) reported significant SBP improvements (ES = 0.64) and a small increase in the normotensive DBP (ES = -0.21) in their HIIT group with long-standing T2D, while Hollekim-Strand et al. (2014) reported a small increase in the hypertensive SBP (ES = -0.02) and a moderate improvement in the normotensive DBP (ES = 0.42) in their

group presenting with diastolic dysfunction, indicating that differences in the extent of diabetes in SPs may influence findings.

Although Terada et al. (2013a) recruited participants with good glycaemic control and without diabetic complications, they were the oldest (62 ± 3 yrs and 63 ± 5 yrs for the HIIT and MICT, respectively) considered in this review. After a 2-wk introductory phase, the SPs trained five days a week (the HIIT group performed four HIIT and one MICT session each week) for 60-min sessions. On conclusion of this high volume training, the HIIT group experienced small improvements in HbA1c and FBG (ES = 0.18 and 0.13, respectively) and a significant but small reduction in body fat percentage (ES = 0.18), which is encouraging for practitioners prescribing programmes for elderly patients with T2D. A small improvement in body fat percentage was also evident in the MICT group (ES = 0.25), but they experienced small deteriorations in HbA1c and FBG (ES = -0.30 and -0.12).

In addition to the studies that trained using ergometry style equipment in training facilities, two studies (Alvarez et al., 2016; Karstoft et al., 2013) utilised more freely accessible training environments. These medium-term studies had longer intervention periods, and although both included non-exercising controls, only Karstoft et al. (2013) included an additional MICT comparison group. They studied middle-aged people with T2D for about 3.5 yrs, and the mode of the 16-wk intervention was free-living walking (unsupervised) five days a week. The authors reported good adherence (Table 3.1) for both exercise groups (60-min sessions) for the possible 80 sessions (the study with the greatest number of sessions in this review), but significant differences between the HIIT and MICT groups were not evident for HbA1c, FBG, fasting insulin and OGTT (Table 3.2). It is of note that the HIIT group experienced the greatest reduction in body mass (4.2 kg) (4.95% and ES = 0.27) of all the groups in this review. The HIIT group also experienced significantly improved aerobic fitness in comparison to the MICT group (ES = 0.67 vs. 0.12); however, even with elevated baseline resting SBP, DBP and TG, no meaningful improvements were evident (ES = 0.02, 0.01 and 0.14, respectively) with HIIT. Alvarez et al. (2016) who used HIIT thrice weekly (38-min sessions) to a group of overweight/obese women with T2D, interspersed jogging/running with walking on an indoor sports court. Using this mode for 16 weeks, HIIT SPs experienced significant improvements in HbA1c, FBG (ES = 1.46), waist girth (ES = 0.50), sum of four skinfolds (ES = 1.52), 2-km

endurance run (ES = 2.39), SBP (ES = 0.83), TG (ES = 0.99) and HDL (ES = 1.75) that were more beneficial than their inactive control group, who experienced small deteriorations across the same measures. A noteworthy observation was that seven (more than half) of the HIIT SPs reduced their antihyperglycaemic medication and the three SPs on BP medication were recommended by their physician during the 16-wk intervention to discontinue use of those medications.

Adverse effects

Although there was suboptimal explicit reporting of adverse effects, three studies did report that HIIT was well tolerated and that no complications arose during the interventions (Alvarez et al., 2016; Little et al., 2011; Mitranun et al., 2014). Although no study reported serious musculoskeletal injury or cardiovascular events, only a limited number of studies reported adverse events explicitly. The onset of asthmatic symptoms and exercise-related calf-pain required one (Karstoft et al., 2013) and two (Revdal et al., 2016) SPs, respectively, to discontinue their HIIT intervention and knee-pain required one SP (Karstoft et al., 2013) to discontinue their MICT intervention. Of the SPs, seven needed to reduce their oral antihyperglycaemic medication during the course of the HIIT intervention (Alvarez et al., 2016) due to episodes of post-exercise (1-hr post session) hypoglycaemia. Praet et al. (2008) reported, for their SPs who were all using exogenous insulin, that of the possible 330 training sessions conducted during the course of the study, there were four (1.21%) mild and uncomplicated hypoglycaemic readings (post-exercise capillary blood glucose 2.7 – 3.8 mmol/L). As such, this review demonstrates that HIIT is feasible and safe for the participants with T2D of this review (i.e., with controlled cardiometabolic risk factors). But it must be noted that these low levels of adverse effects can be attributed to the research process, namely pre-screening for exercise contraindicators and study exclusion criteria, as well as the progression, monitoring and supervision of participants during the majority of the HIIT intervention (12 of 14 studies provided full supervision).

Discussion

Several inconsistent variables within and across all the studies confounded direct comparisons. First, the heterogeneity of SPs. For example the age range of 40.2 ± 9.7 (Shaban et al., 2014)

to 63.0 ± 5.0 yrs (Terada et al., 2013a) and the range of T2D duration from newly diagnosed (Backx et al., 2011) to long-standing T2D (Mitranun et al., 2014; Praet et al., 2008). The Fex et al. (2015) SP group comprised an equal number of participants with both T2D and pre-diabetes, and Madsen et al. (2015) compared HIIT between participants with T2D and obese participants without diabetes. Three studies specifically recruited SPs with diabetic complications (Hollekim-Strand et al., 2014; Parpa et al., 2009; Praet et al., 2008). Additionally, Terada et al. (2013a) reported using fitter (by 4.7 ml/kg/min) HIIT participants in comparison to their MICT group, and Hollekim-Strand et al. (2014) reported that their MICT group was younger (54.7 ± 5.3 yrs) than their HIIT group (58.6 ± 2.3 yrs).

The second was the total duration of the individual HIIT sessions (including warm-up, recovery intervals and cool-down) that ranged from 10-min (Revdal et al., 2016) to 60-min (Backx et al., 2011; Karstoft et al., 2013; Terada et al., 2013a). It is interesting that of the five studies that included a MICT control group, four reported equal HIIT session durations (40-60 minutes) to their MICT group (Hollekim-Strand et al., 2014; Karstoft et al., 2013; Mitranun et al., 2014; Terada et al., 2013a) and one (Backx et al., 2011) reported HIIT sessions to be about 30-min longer than those of MICT; hence, the purported time-efficiency of HIIT should be taken in this context, particularly given the oft-touted potential appeal of HIIT's relative time expediency. Furthermore, the HIIT intervention periods included short-term, 2-wk studies (Little et al., 2011; Shaban et al., 2014) to the longest 16-wk study (Karstoft et al., 2013); the majority of the studies (8 of 14) being medium-term, of 12-wk duration, possibly because this duration aligns with the time needed to observe changes in HbA1c in patients with T2Ds whose therapy has changed (Chamberlain et al., 2016).

Other noteworthy factors within the study interventions potentially compounding the ability to directly compare relative efficacy were inclusion of isotonic (Praet et al., 2008) and resistive-band exercises (Cassidy et al., 2015b) during HIIT sessions and the addition of one (Terada et al., 2013a) and two (Backx et al., 2011) MICT sessions per week to HIIT interventions. While Backx et al. (2011) dedicated one of their HIIT sessions to a nutrition class (K. Backx, personal communication, May 12, 2016), but Cassidy et al. (2015b) instructed their participants to maintain their body mass via caloric intake. Moreover, most studies included qualified, direct supervision for all their groups' training sessions, but Karstoft et al. (2013) did not supervise any

of their groups, Cassidy et al. (2015b) did not supervise beyond the initial session, and Backx et al. (2011) and Hollekim-Strand et al. (2014) did not supervise their MICT comparison group. Finally, the adherence of completing SPs was reported as 100% for both of the 2-wk intervention studies (Little et al., 2011; Shaban et al., 2014) but ranged from 63% (Backx et al., 2011) to 97.2 ± 2.7% (Terada et al., 2013a) for the medium-term HIIT groups.

Taken together, the broad range of baseline age, T2D duration, level of glycaemic control, diabetic complication presence and insulin usage, along with variations in session and intervention duration, supervision, lack of information about dietary management, type of HIIT protocol used and required reductions to antihyperglycaemic medication (Alvarez et al., 2016; Praet et al., 2008) limit my ability to make direct comparisons among studies.

Nevertheless, all 14 studies included in this review demonstrate that HIIT is effective in people with T2D for improving multiple cardiometabolic risk factors. Therefore, HIIT is a suitable option, regardless of the precise parameters employed, for pursuing such improvements in middle-aged/elderly individuals with T2D who present with reasonably controlled hyperglycaemia, as in this review (mean baseline HbA1c for HIIT participants, 54.3 ± 6.6 mmol/mol). All 12 medium-term HIIT intervention groups showed improvement in HbA1c, with four studies (Backx et al., 2011; Hollekim-Strand et al., 2014; Madsen et al., 2015; Mitranun et al., 2014) reporting significant improvements, whereas no comparison group experienced significant improvements (Table 3.2).

Although no study reported class II obese (> 35.0 kg/m^2) mean baseline body mass index (BMI) values (Table 3.3), improvements in body composition were achievable, via HIIT, in overweight/obese people with T2D. The absolute body weight reductions for the four most effective studies were modest at 4.2 kg in 16 weeks (Karstoft et al., 2013), 3.8 kg in 12 weeks (Backx et al., 2011; Parpa et al., 2009) and 3.0 kg in eight weeks (Terada et al., 2013a), noting that Backx et al. (2011) included a nutrition class, and although Parpa et al. (Parpa et al., 2009) did report that nine of 14 SPs were on insulin therapy, the remaining three studies excluded SPs who used exogenous insulin, suggesting that insulin usage may influence the potential of HIIT to affect weight loss. Additionally, HIIT was beneficial for aerobic fitness (Table 3.4) in SPs with T2D, with a range in baseline maximal oxygen consumption of 21.9 ± 4.2 ml/kg/min

(Madsen et al., 2015) to 40.3 ± 8.0 ml/kg/min (Fex et al., 2015). Similarly, for people with T2D who presented with controlled baseline hypertension (Table 3.5) and hyperlipidaemia (Table 3.6), medium-term HIIT interventions did appear to impact most measures positively.

In the five studies that included a comparison to MICT, there was no evidence of HIIT being significantly superior for glycaemic control, BP, lipidaemia and body composition improvements, except for one study reporting a greater reduction in body mass (Karstoft et al., 2013). With regards to aerobic fitness, three studies (Hollekim-Strand et al., 2014; Karstoft et al., 2013; Mitranun et al., 2014) noted that HIIT was more beneficial than MICT, though none of these studies reported HIIT session durations shorter than 40 minutes.

Conclusion

The current review included many pilot studies, and only two of the 14 studies reporting on both MICT and usual-care comparison groups. The heterogeneity of the SPs with T2D, the training equipment and the HIIT parameters, accompanied by variations in supervision, dietary advice and medications confounded direct comparisons. Moreover, this review only included full-text English articles, and the number of participants included in the studies can be considered small, thus contributing to diminished statistical power. Nonetheless, this review summarised the central characteristics of HIIT interventions and demonstrated beneficial effects of HIIT on various cardiometabolic risk factors in adults with T2D.

In the future, authors should report on specific HIIT parameters (clearly stating total session duration, intensity and duration of the activity and recovery bouts), supervision, progression, adverse effects, baseline medication, background PA and dietary habits and how these changed during the course of the intervention. Specific questions that still need to be addressed in order to further the understanding obtained in this review include determining a minimum dose of HIIT that elicits beneficial responses in all cardiometabolic risk factors and ascertaining whether there is a maximum dose of HIIT beyond which no further improvement in metabolic regulation can be observed. Until further RCTs have been conducted, the impact of the various HIIT parameters on the various cardiometabolic risk factors, both individually and collectively, remains unclear, and whether HIIT is of more benefit when compared to MICT in persons with

T2D will remain speculative. Nonetheless, despite the stated limitations, the evidence for the effectiveness of HIIT on improvements in the range of symptoms associated with T2D supports its use as a component of lifestyle treatments. Although this review cannot recommend a single preferred HIIT protocol, practitioners are presented with alternatives from which to select; however, I recommend that practitioners prescreen individuals with T2D for contraindications to exercise and implement a HIIT intervention option, or a combination of HIIT options, via progressed and supervised programmes.

Brief update since publication

Since the publication of my narrative review through 03 August 2017, four medium-term HIIT intervention studies using T2D participants have been published and their central HIIT characteristic are presented in the following table (Table 3.7). Maillard et al. (2016), using 16 elderly post-menopausal women with long-standing T2D (two SPs using exogenous insulin), compared adiposity benefits gained from SIT to isocaloric MICT. Following a 16-week intervention in which the elderly women trained twice a week under supervision on a cycle ergometer, their HIIT intervention was more effective than MICT in reducing central obesity.

In a non-randomised trial Støa et al. (2017) compared the cardiometabolic benefits achieved from a 12-week HIIT or MICT intervention in 38 middle-aged people with T2D. The intervention groups were separated by five months and their HIIT group commenced the training presenting with a significantly higher HbA1c (P = 0.02) and almost significantly longer T2D duration (P = 0.07). However, the authors reported that thrice weekly AIT of 52 min duration was superior to their isocaloric 60-min MICT intervention in improving HbA1c and aerobic capacity.

Using a randomised crossover 8-week study, Ruffino et al. (2017) compared SIT cycling to a walking MICT intervention in 16 middle-aged men with T2D that were not using exogenous insulin. Their SIT group trained under supervision three days per week. The SIT sessions only included two 20 seconds sprints and took 10 min to complete while their MICT group trained five days a week (three sessions supervised) for 30-min sessions. Although the SIT achieved superior improvements in aerobic capacity and both groups were associated with decreases in BP, neither group improved their glucose control.

Unlike the three studies above that did not include any RT component, the most recent study to be published (Francois et al., 2017) investigated whether the addition of a post-exercise milk or protein beverage, following HIIT and RT sessions, would augment cardiometabolic health benefits in people living with T2D. Although no group performed MICT and that post-exercise nutrition did not augment changes, this RCT demonstrated that HIIT performed as combined aerobic and resistance exercise was beneficial to people with T2D.

Table 3.7: Summary of the HIIT studies, using people living with T2D, that were published after my narrative review

Study and study design	Modality, intervention duration, and run-in duration (if any)	Participant characteristics including prescribed antihyperglycaemic medication (if any)	Training frequency, session duration, (additional aspects) and adherence	HIIT parameters: bouts, work - rest duration and intensities, progression and mode Comparison group parameters (if any): Steady state duration, intensity and mode
Maillard et al. (2016) RCT	HIIT (SIT) 16-wk	*n* = 8 women Age = 68.2 ± 2.4 yrs T2D duration = 14.5 ± 2.1 yrs (long-standing) HbA1c = 57.4 ± 9.3	2 x/wk 30 min	60 bouts 8 sec ~81 % HRmax – 12 sec low-intensity recovery using cycle ergometer
	MICT Isocaloric 16-wk	*n* = 8 women Age = 70.1 ± 2.4 yrs T2D duration = 14.5 ± 2.1 yrs (long-standing) HbA1c = 59.6 ± 9.3	2x/wk 50 min	40 min ~58 % HRR using cycle ergometer
Støa et al. (2017) Non-randomised	HIIT (AIT) 12-wk	*n* = 19 Age = 59.0 ± 11.0 yrs T2D duration = 9.0 ± 7.0 yrs HbA1c = 61.5 ± 15.2 mmol/mol	3 x/wk 52 min	4 bouts 4 min ~90 % HRpeak - 3 min 70 % HRpeak using outdoor jogging/walking
	MICT Isocaloric 12-wk	*n* = 19 Age = 59.0 ± 10.0 yrs T2D duration = 6.0 ± 5.0 yrs HbA1c = 51.3 ± 9.6 mmol/mol	3x/wk 60 min	~57 min ~73 % HRpeak using outdoor walking
Ruffino et al. (2017) Randomised crossover study	HIIT (SIT) 8-wk	*n* = 16 men Age = 55.0 ± 5.0 yrs T2D duration = 4.0 ± 4.0 yrs HbA1c = nr (Metformin only)	3 x/wk 10 min with 99 % adherence	2 bouts 10 sec cycle sprint against wattage (65% of LBM) *progressed to* 2 bouts 20 sec cycle sprint against wattage (65% of LBM) using cycle ergometer
	MICT 8-wk		5x/wk 30 min with 97 % adherence	30 min 40 % HRR *progressed to* 30 min 55 % HRR using a walking mode

Study and study design	Modality, intervention duration, and run-in duration (if any)	Participant characteristics including prescribed antihyperglycaemic medication (if any)	Training frequency, session duration, (additional aspects) and adherence	HIIT parameters: bouts, work - rest duration and intensities, progression and mode Comparison group parameters (if any): Steady state duration, intensity and mode
Francois et al. (2017) RCT	HIIT (AIT) 12-wk	*n* = 18 (post exercise consumption: Milk) Age = 62.0 ± 8.0 yrs T2D duration = 6.0 ± 6.0 yrs HbA1c = 54.1 ± 8.8mmol/mol (oral medication only)	2 x/wk (HIIT) 13 min *progressed to* 25 min plus 1 x/wk (RT) 13 min *progressed to* 25 min	4 bouts 1 min 90 % HRmax – 1 min light recovery *progressed to* 10 bouts 1 min 90 % HRmax – 1 min light recovery using cycle ergometer, treadmill or elliptical Whole body resistance exercises 4 bouts 1 min "Hard" – 1 min recovery *progressed to* 10 bouts 1 min "Hard" – 1 min recovery using resistance bands or a multigym
	HIIT (AIT) 12-wk	*n* = 16 (post exercise consumption: Macronutrient control) Age = 56.0 ± 9.0 yrs T2D duration = 7.0 ± 7.0 yrs HbA1c = 51.9 ± 8.8 mmol/mol (oral medication only)	As above	As above
	HIIT (AIT) 12-wk	*n* = 19 (post exercise consumption: Placebo) Age = 55.0 ± 9.0 yrs T2D duration = 5.0 ± 6.0 yrs HbA1c = 51.9 ± 8.8 mmol/mol (oral medication only)	As above	As above

Where reported data are means ± SD. Session duration is inclusive of warm-up, recovery intervals and cool down, and adherence is the percentage of eligible sessions completed. AIT, aerobic interval training; HbA1c, glycated haemoglobin a measure of glycaemic control; HIIT, high-intensity interval training; HR, heart rate; HRR, heart rate reserve; LBM, lean body mass; MICT, moderate-intensity continuous training; nr, not reported; RCT, randomised controlled trial; RT, resistance training; SIT, sprint interval training; T2D, type 2 diabetes mellitus; W, watts; wk, week; x/wk, times per week.

CHAPTER FOUR

Acute blood glucose, cardiovascular and exaggerated responses to high-intensity interval training and moderate-intensity continuous training in men with type 2 diabetes

This chapter comprises the following paper accepted for publication by the Journal of Sports Medicine and Physical Fitness on 30 August 2017:

Wormgoor, S. G., Dalleck, L.C., Zinn, C., & Harris, N.K. (published ahead of print). Acute blood glucose, cardiovascular and exaggerated responses to high-intensity interval training and moderate-intensity continuous training in men with type 2 diabetes mellitus. *The Journal of Sports Medicine and Physical Fitness.* doi: 10.23736/S0022-4707.17.07639-3

Abstract

Optimising exercise-induced physiological responses without increasing the risk of negative exaggerated responses is an important aspect of exercise prescription for people with type 2 diabetes mellitus (T2D). However, knowledge of acute responses, including exaggerated responses, of different training modalities is limited. The study objective was to compare acute physiological responses of moderate-intensity continuous training (MICT) and high-intensity interval training (HIIT) in T2D. Baseline data were used to randomly assign male participants into supervised training groups for a 12-week intervention. During week 7, participants trialled either a fully progressed MICT (*n*=11) or HIIT (*n*=11) (combined with resistance training) session. The MICT included 26-min at 55% estimated maximum workload (eWLmax) while the HIIT included twelve 1-min bouts at 95% eWLmax interspersed with 1-min bouts at 40% eWLmax. Although energy expenditure and peak systolic and diastolic blood pressure responses were similar between groups ($P = 0.47$, $P = 0.71$, $P = 0.56$, respectively), peak heart rate, workload and perceived exertion were higher in the HIIT group ($P = 0.04$, $P < 0.001$ and $P < 0.001$, respectively). Acute exaggerated responses were similar ($P = 0.39$) for MICT (64%) and HIIT (36%) participants. While structured MICT and HIIT sessions resulted in comparable

acute physiological responses, the individual variations and exaggerated responses, even after preparatory training, necessitated precautionary respite in T2D men.

Introduction

Structured exercise modalities, including RT and various modes of cardiovascular exercise have been promoted by several authors as a vital therapy in the management of T2D (Colberg et al., 2010; Gibala et al., 2012; Hameed et al., 2012; Russell & Cooper, 2015; Strasser & Pesta, 2013; Umpierre et al., 2013; Zoungas et al., 2014) with HIIT recently proposed as an alternate modality to MICT in improving cardiometabolic function (Adams, 2013; Boutagy & Luff, 2013; Cassidy et al., 2017; Curry et al., 2015; Jelleyman et al., 2015; Levinger et al., 2015; Ramos et al., 2015; Weston et al., 2014) . However, while studies have compared acute responses between two cardiovascular modes (Hollekim-Strand, Malmo, Follestad, Wisløff & Ingul, 2015; Karstoft et al., 2013; Lima et al., 2008; Mackenzie et al., 2012; Terada et al., 2016) and a study compared a MICT session with RT (Gordon, Bird, MacIsaac & Benson, 2013), no study has reported the acute responses of combined training in which RT was performed subsequent to either a MICT or HIIT session. Additionally, an important aspect of exercise prescription for people with T2D is optimising exercise-induced physiological responses without concomitantly increasing the risk of acute negative exaggerated responses. Such exaggerated responses are typically not reported in sufficient detail in studies on acute responses to exercise sessions in people with T2D (Hollekim-Strand et al., 2015; Hordern et al., 2011; Gillen et al., 2012; Karstoft, Christensen, Pedersen & Solomon, 2014; Lima et al., 2008; Mackenzie et al., 2012; Mendes et al., 2013; Oguri, Adachi, Ohno, Oshima & Kurabayashi, 2009). Furthermore, the use of exogenous insulin by the T2D participants is frequently an exclusion criterion which, along with other stringent exclusion criteria (e.g., hypertension), arguably confound application to the broader T2D population. Consequently, the acute physiological responses, and acute exaggerated responses of HIIT compared to MICT, in people with more advanced T2D remains unclear.

Hence, the primary aim of this study was to compare the acute responses of HR, BP and BG to both MICT and HIIT modalities, combined with RT, in men living with T2D. Secondly, the study aimed to document acute exaggerated responses to participants undertaking such sessions so that CEPs wanting to progress their patients' programmes have an enhanced understanding of outcomes associated with introducing either a MICT or HIIT session. I hypothesised that the HIIT session would invoke greater acute physiological responses than MICT, while presenting with comparable acute exaggerated responses to MICT.

Methods

The study protocol was approved by the Auckland University of Technology Ethics Committee (AUTEC) (reference no. 14/396) and the study was performed in accordance with the Declaration of Helsinki.

Study participants

All middle-aged (aged 35 – 59 years) T2D men, referred by general practitioners to attend a clinical exercise physiology Health and Wellness Clinic (Palmerston North, New Zealand) to participate in a 12-week supervised exercise intervention programme were considered for inclusion. General practitioners diagnosed their patient as having T2D and provided written clearance for participation in supervised PA. The staggered nature of one or two referrals per fortnight, coupled with the number of eligible SPs required for the study, resulted in an 18-month enrolment period. Potential participants underwent a two-part screening process. Initially, the referral forms were screened for the following exclusion criteria: serious cardiac, respiratory or musculoskeletal pathologies, neurological disorders, unstable proliferative retinopathy, end-stage renal disease and/or uncontrolled hypertension. Due to a weight limitation of the cycle ergometer participants exceeding 170 kg were also excluded. Thereafter potential participants were invited to an individual consultation session in which the purpose, risks and benefits of the study were explained. Twenty-three SPs provided their informed consent and enroled in the study (Figure 4.1).

Referral note details and initial consultation. During the initial consultation, the medical history and referral note details of age, T2D duration, ethnicity, neuropathic pain and current medications were confirmed (Appendix E). Current levels of PA were monitored using the International PA Questionnaire (IPAQ). The adult, long version was administered via interview (Appendix F). Total metabolic equivalent (MET) minutes per week (min/wk) were determined along with MET min/wk for each of the four domains (work, active transportation, domestic and garden, and leisure-time) and the four intensity levels (vigorous, moderate, walking, and total sitting hours per week) using the recommended guidelines for data processing and analysis of IPAQ (IPAQ Research Committee, 2005).

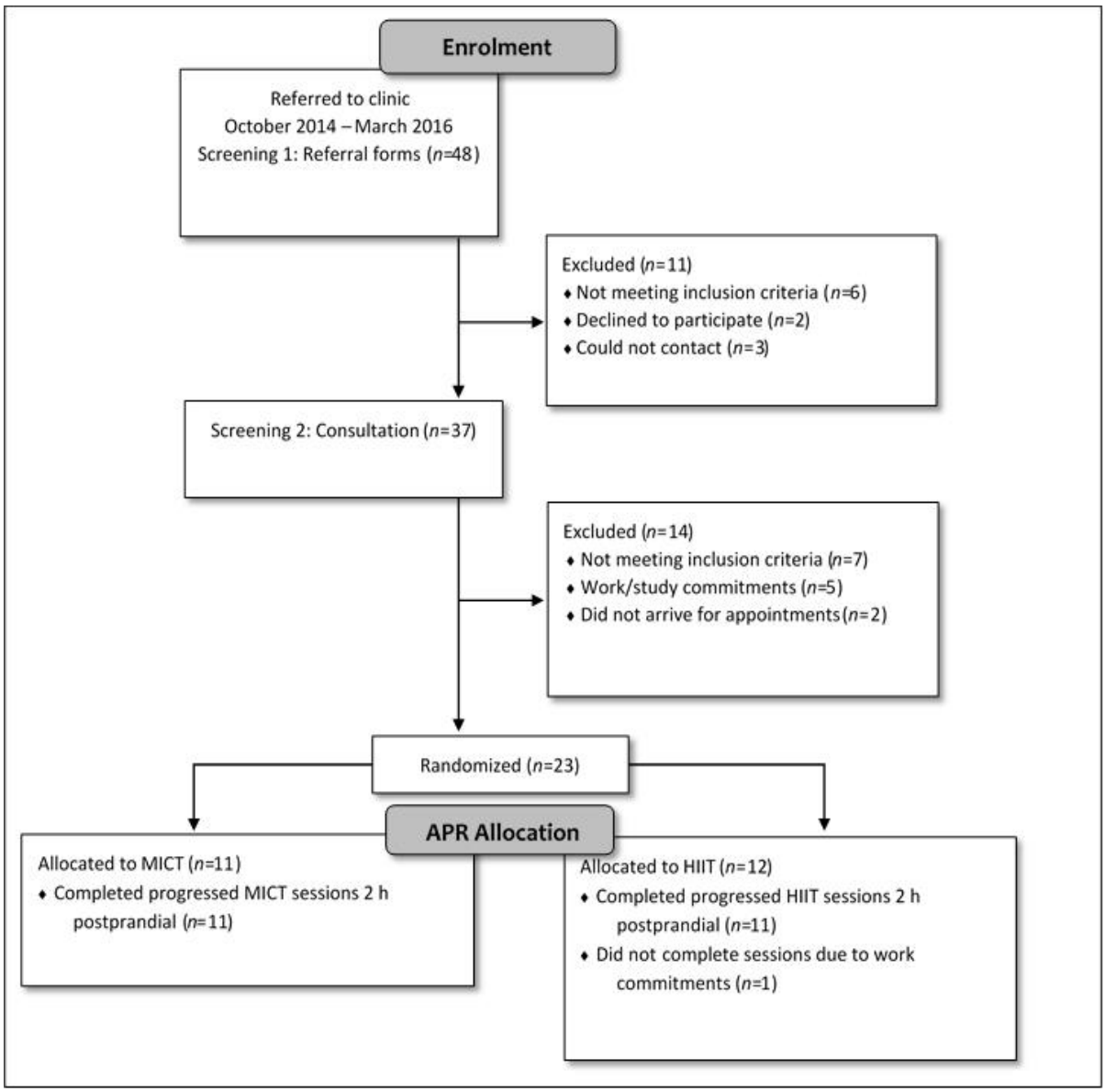

Figure 4.1: Consort diagram of study participant entry and randomisation to either a moderate-intensity continuous training (MICT) or high-intensity interval training (HIIT) acute physiological response (APR) session.

Blood samples. After the consultation and 48 hours before the baseline physiological assessments, overnight fasted (12 hours) blood and urine samples were given at the local hospital's laboratory. SPs arrived at the hospital by car, or public transport, and reported to the laboratory at 08:00 hours and a blood sample was collected from each SP's antecubital vein after which a spot urine sample was collected. HbA1c was measured on a Bio-Rad Haemoglobin Testing System (D-100™, Bio-Rad Laboratories, Inc., Hercules, CA) using high-performance liquid chromatography.

Physiological assessments (Session 1). Subsequent to the blood samples, SPs returned to the clinic for the first of two, 60-min assessments (separated by 48 hours) where they were instructed to continue taking their medications, to have a light meal based on usual intake, to avoid caffeine 2 hours before testing, and to abstain from exercise for the preceding 48 hours. The individual assessments (using a staggered structure of one or two SPs per fortnight – as per their referral to the clinic) were conducted, over a 15-month period, using the following protocols and sequence. Of note, other assessments were included during both the assessment sessions, but as they were exclusively used in the intervention study, the associated protocols are reported in Chapter Five.

Random blood glucose. A fingertip capillary blood sample was taken on each arrival to the clinic; assessments were postponed if blood glucose concentrations were <3.5 or >17 mmol/L. Of note, no SP arrived with a low blood glucose concentration (BG) for any of the assessments and one SP had a BG of 19.8 mmol/L, but the absence of ketones in his urine was confirmed before subsequent assessments were conducted.

BMI. Body mass was measured using the pre-calibrated HUR- force platform (ALU4, HUR Labs Oy, Tampere, Finland) with SPs standing, in short-pants, motionless on the platform. Body mass was recorded to the nearest 10 g. Height was measured using a wall-mounted stadiometer and recorded to the nearest 1.0 mm. BMI was calculated and reported as kg/m^2.

Resting BP. The participants lay supine on a plinth for 10-min after which BP was measured at the brachial artery using the auscultatory method at vertical height of the heart. Bicep circumference allowed correct selection of cuff size (large > 34.5 cm > extra-large). The first Korotkoff sound registered the systolic BP and the fifth Korotkoff sound was used to register the resting diastolic BP (Tan, Wei & Wang, 2012). The mean of two BP measurements obtained two minutes apart was recorded (Moe, Augestad, Åsvold & Flanders, 2011; Sigal et al., 2007).

Resting heart rate (HR_{rest}). The participants were prepared (chest hair shaven and electrode sites cleaned) and connected to a Custo-med (cardio 110, Müller & Sebastiani GmbH, Ottobrunn, Germany) 12-lead ECG. The HR_{rest} was recorded from the 10-sec ECG printout on completion of a further 1-min rest in the supine position.

Graded exercise test (GXT). The participants performed an incremental cycle ergometer test (Custo-med ergocontrol 3000, Müller & Sebastiani GmbH, Ottobrunn, Germany), monitored with a 12-lead ECG, to ~80% predicted maximum HR reserve (HRR) (i.e., (0.80 x [220-age] - HR_{rest}) + HR_{rest}) or a rate of perceived exertion (RPE) on Borg's 6-20 scale (Borg, 1982) of ~15 (i.e., "hard"). The cycle test consisted of a 1-min warm-up at 15 W followed by three 4-min stages (cycling at 60 revolutions per minute [rpm]). Based on information obtained during the consultation a starting load of 25-50 W was applied and which increased by 20-35 W for each stage. BP, HR and RPE were recorded for each stage and interpretation of symptom limits were used to optimise safe increments (Colberg et al., 2003). Subsequently, steady state HRs from the final two stages were extrapolated to the predicted maximum HR in order to estimate maximal workload (eWLmax) (Shaban et al., 2014). As the participants were from a clinical population, stage lengths of 4-min were used to help ensure a physiological steady state was met and by using extrapolated values maximal physiological responses are intentionally removed (Shaban et al., 2014). Data obtained from the SP's final two stages of the GXT was used to predict SP's aerobic capacity via maximal oxygen consumption (VO_2max) (Beekley et al., 2004). The gradient of the increase in SBP and DBP between resting and the GXT's final stage was recorded as SBP_{GXT} and DBP_{GXT}, respectively, and expressed as mmHg per Watt (mmHg/W).

Physiological assessments (Session 2).

Adiposity. Waist circumference was measured according to the International Society for the Advancement of Kinanthropometry (ISAK) guidelines (Stewart, Marfell-Jones, Olds & de Ridder, 2011) using a non-elastic measuring tape. With the participant standing in the anatomical zero position the waist circumference was measured in a horizontal plane midway between the last rib and the iliac crest. Subcutaneous adiposity was measured indirectly using skinfold thickness, according to ISAK at seven marked skinfold sites (triceps, subscapular, biceps, supraspinale, abdominal, front thigh and medial calf) using a Harpenden skinfold calliper (Baty International, West Sussex, England) and recorded to the nearest 0.1 mm. Subcutaneous adiposity was reported as the sum of the seven measurements.

Resting BP. As per the procedure previously described two BP measurements were repeated. The mean of the four recordings taken during the two assessment sessions was used for analysis.

Grouping

Data from the consultation and baseline physiological assessments were used to assign participants, via the method of minimization (on the basis of HbA1c, age, aerobic capacity, BMI and ethnicity), into the two intervention groups (Scott, McPherson, Ramsay & Campbell, 2002). Prior to the exercise intervention study, I provisionally paired the initial ten SPs as practically as possible (on the basis of HbA1c, age, aerobic capacity, BMI and ethnicity). Subsequently, a CEP blinded to the study randomly assigned these initial five pairs into the MICT and HIIT groups. Thereafter, as SPs joined the study during the next 12 months, they were allocated, by myself, to the alternate groups via the method of minimization ensuring comparable group characteristics.

Intervention exercise prescription

As this chapter focusses on the acute physiological responses to a single progressed session, the unabridged details of the 12-week intervention are presented in Chapter Five. Briefly, the intervention study was divided into three progressive stages in which a 3-week introductory stage was followed by a 4-week intermediate preparatory stage before the SPs commenced the 5-week advanced stage. This acute physiological response study was conducted during Week 7 (i.e., the final preparatory week) and used data collected from the first session that 100% emulated the advanced MICT or HIIT session (combined with RT). Baseline data were used for SP allocation and the results of the GXT were used to set the training intensities for both the introductory weeks and acute response session.

Cardiovascular training component. As demonstrated in Chapter Three, HIIT studies have no standardized training variables, so the duration of the study's intervention, and frequency and length of the training sessions were in alignment with both the operations of the exercise physiology clinic and the general training variables of the noted studies; specifically three scheduled 1-h sessions per week (i.e., Monday, Wednesday and Friday) for 12 weeks. Each

session was a combined CV and RT session separated by a BG check. In order to accommodate CV and RT into each session, the protocols of prior reported studies were emulated (Balducci et al., 2012; Tan et al., 2012), whereby shorter variations of both components (in comparison to alone training) were utilized.

As per the study design, one group had the CV component of the combined training intervention progress to longer duration MICT training, while the other group progressed to HIIT. Each intervention was designed to ensure equal energy expenditure during the CV component (i.e., isocaloric). During the 3-week introductory stage for both groups the CV component had moderate intensity (50% eWLmax) cycling of 10 min (flanked by a 2 min warm-up and 3 min cool-down of 40% eWLmax). During the 4-week intermediate preparatory stage the MICT group was progressed by increasing the training duration to 17:30 min (flanked by a 3 min warm-up and cool-down of 40% eWLmax) and increasing the training intensity to 55% eWLmax. During the same period the HIIT group progressed by including 3 bouts of 3:30 min duration at 75% eWLmax interspersed with similar duration recovery bouts at 45% eWLmax (flanked by a 1:30 min warm-up and 2 min cool-down of 30% and 45% eWLmax, respectively), based on prior reported protocols (Tjønna et al., 2008; Wisløff et al., 2007).

Resistance training component. Immediately after the CV component a water break and three static stretches (triceps, hamstring and chest) were performed, totalling 5 min, before confirming BG were >3.5 mmol/L in order to continue with the RT component. The RT component contained equal exercises and training variables for both groups and maintained a general strength focus with minimal progression or variation during the study intervention. Four compound exercises (seated low row, horizontal leg press, seated chest press and seated hamstring curls) and abdominal contractions were completed by the SPs using 2 sets of 15 repetitions at 66% of 1-repetition maximum (1RM) during the introductory stage, 3 sets of 10 repetitions at 75% of 1RM during the intermediate stage and a slightly condensed 2 sets of 12 repetitions at 75% of 1RM during the acute physiological response session.

TechnoGym cycle ergometers (Bike 700i, TechnoGym: The Wellness Company, Casena, Italy) and four TechnoGym isotonic machines (Selection Line with Isocontrol display, TechnoGym: The Wellness Company, Casena, Italy) were used by the SPs during their training and acute

physiological response sessions. The TechnoGym Wellness System™ (including TechnoGym/Polar T31 HR straps and individualized Wellness System™ Key) were used to control (i.e., time and wattage) and display each prescribed training session and then recorded training data. The training data were downloaded to the Wellness Expert ™ via the Wellness System™ Key on conclusion of each session.

To ensure the SPs' workload corresponded to the prescribed intensity and reflected any improved CV fitness, each SP had the CV component of their training session modified (during the Friday session of Week 4) by simulating the GXT of their assessment (i.e., three 4-min stages with each stage increasing by 20-35 W). These data were used to adjust each SP's workload. Similarly, to ensure that the resistance of the isotonic strength exercises were prescribed appropriately according to the strength levels of each SP during the progression phases, predicted 1RMs (Balducci et al., 2012) were tested and calculated for each exercise on two occasions (on the participants' first training day and the Monday of Week 5).

Supervision. To enhance safety, all participants were screened before the commencement of each training session, via a standardized 'pre-session monitoring procedure'. The lead researcher, assisted by three experienced CEPs measured SPs' physiological parameters of BG, HR and BP in the seated position and recorded these values alongside current feelings of wellbeing and confirmation that all medications for the day had been taken as prescribed. The assisting CEPs, not directly involved in the study design, received pre-intervention training to enhance their ability to capture reliable data pertaining to the requirements of this study. Additionally, the CEPs continually monitored each SP's training and recorded peak RPE, BP and HR on daily training sheets. Similar to the pre-session monitoring procedure, a post-session monitoring procedure was administered on conclusion of each SP's session.

Acute physiological response sessions

During the Wednesday session of Week 7 (i.e., the final week of preparatory training), a session of each SP's associated prescribed advanced programme was performed. Data from each SP's acute physiological response (APR) were used for analysis.

In order to standardise the time of the BG measurements for the APR each SP was required to eat their usual breakfast, mid-morning snacks and lunch at standardized times (i.e., lunch at 1200 h), to take and record all their prescribed medications and to measure and record their capillary BG (CareSens™N, i-SENS, Inc., Seoul, Korea) at standardised times during the course of the morning. On commencement of the supervised APR (1400 h; 2 h postprandial) and on conclusion of the CV session (1435 h) and RT session (1500 h) BG was recorded along with 10, 20, 30, 60 and 90 min post exercise. SPs were instructed not to consume or drink anything (besides water) until after their final BG recording (90 min post exercise), unless they had a low BG (< 3.5 mmol/L) and/or felt symptoms of hypoglycaemia.

For the APR, the SPs had to perform either a MICT or HIIT (each combined with RT) session, under the supervision of the lead researcher. The 32 min cycle ergometer MICT session included a training duration of 26 min at 55% eWLmax with a target RPE of ~13 (flanked by a 3 min warm-up and cool-down of 40% eWLmax) (Figure 4.2a). The 28 min cycle ergometer HIIT session included twelve 1-min bouts at 95% eWLmax interspersed with 1 min recovery bouts at 40% eWLmax, emulating the Little et al. (2011) and Gillen et al. (2012) studies, with a target RPE of ~17 (flanked by a 2:30 min warm-up and cool-down of 60% and 40% eWLmax, respectively) (Figure 4.2b).

As per the pre- and post-session monitoring procedure a seated BP (one auscultatory reading) and HR (using an Omron HCG-801 Portable ECG Monitor) were recorded. Midway during the CV component HR and BP were monitored. Moreover, to ensure due care to each participant the talk test was administered during the CV component and, only when deemed appropriate (factoring in HR, BP, verbal and non-verbal responses), respite was provided by the supervising CEP by reducing cycling duration or intensity. During the latter stages (i.e., the last minute and last bout for the MICT and HIIT, respectively) peak exercise HR and BP (auscultatory method) were recorded.

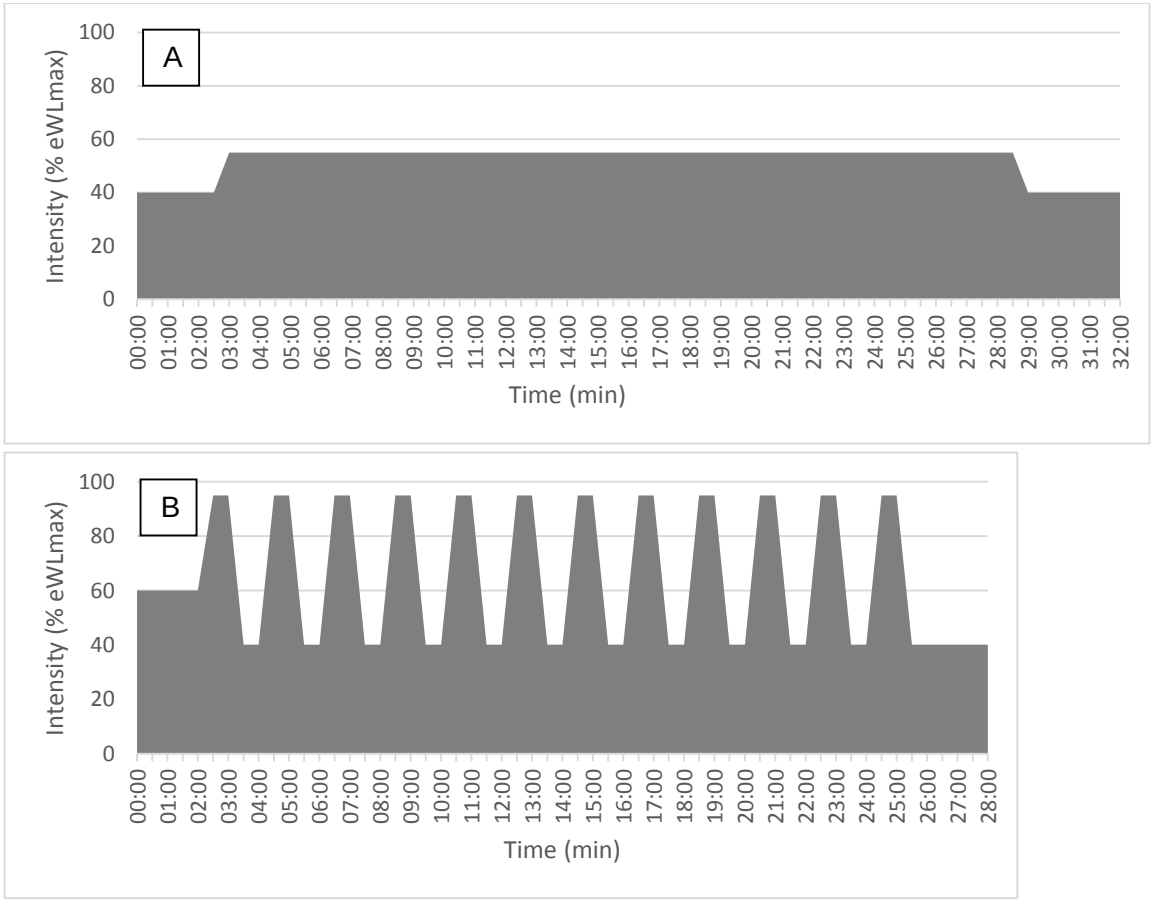

Figure 4.2: Acute physiological response sessions. The MICT session included 26 min of continuous training (A), and the HIIT session included twelve 1-min bouts of intense training (B).

Acute exaggerated responses. To reduce the risk of significant adverse events, indications for terminating exercise testing (ACSM, 2014) were used to define exaggerated responses during the sessions (e.g., exercise blood pressure approaching 250 mm Hg [SBP] or 115 mm Hg [DBP], exercise-induced angina, exercise-induced musculoskeletal strain) along with post-session exaggerated responses (e.g., hypoglycaemia [<3.5 mmol/L or feeling symptoms of hypoglycaemia] or post-session hypertension [≤90 mm Hg or ≤60 mm Hg for SBP and DBP, respectively], with feelings of pre-syncope).

Statistical analyses

Data were analysed using the SPSS (IBM SPSS Statistics for Windows v24.0, 2016 Armonk, NY: IBM Corp.) with statistical significance being accepted at $p < 0.05$. Normality was assessed using the Q-Q plots and the Shapiro-Wilk test. Data are presented as means ± SD where normality of distribution was confirmed. Alternatively, data were presented as median and interquartile range. The SPs' medical history, medication usage, ethnicity, were recorded for

descriptive purposes only and were not included in any analyses. To determine differences between groups during the alternate APR sessions, independent-sample t-tests (parametric analysis) and the Mann-Whitney U Test (non-parametric analysis) were used. A one-way analysis of variance (ANOVA) with post-hoc testing (Tukey) was used to determine the significance of change during acute sessions. Spearman's rho was used to determine the correlation between pre-exercise BG and magnitude of BG change post CV session. A Chi-square test for independence (with Yates Continuity Correction) was used to indicate the association between session type and incidence of acute exaggerated responses. Power and sample size calculations were based on a predicted difference in BG of 1.0 mmol/L with a SD of effect of 0.75 mmol/L, $\alpha = 0.05$, $1- \beta = 0.80$ and an expected dropout rate of 10%. The calculation yielded 11 participants per group (Chan, 2003). Due to these low sample size numbers, univariate scatterplots were also presented so that readers can critically evaluate the data and view individual changes during the alternate sessions (Weissgerber, Milic, Winham & Garovic, 2015).

Results

Baseline parameters two exercise groups are presented inTables 4.1 & 4.2. One SP in the HIIT group was excluded from this study as he was not able to attend the APR session due to unexpected work commitments (Figure 4.1). Similar to the T2D participants of previous acute studies (Gordon et al., 2013; Hordern et al., 2011; Gillen et al., 2012; Karstoft et al., 2014; Lima et al., 2008; Mackenzie et al., 2012; Mendes et al., 2013; Oguri et al., 2009; Terada et al., 2016) the SPs were middle-aged, borderline hypertensive with suboptimal glucose control (HbA1c), sedentary and unfit. However, this study was the only study with a mean BMI for SPs being classified as class II obesity (BMI ≥ 35.0 kg/m^2)(Table 4.1), and although MICT studies have included SPs using exogenous insulin this, to my knowledge, was the first acute study to include exogenous insulin users for HIIT (Table 4.2).

Table 4.1: Baseline characteristics and acute physiological response data of the 22 male T2D study participants

	MICT (*n* = 11)	HIIT (*n* = 11)	*P* value
Baseline characteristics			
Age (y)	53.7 (51.4, 57.0)	54.9 (52.3, 57.9)	
T2D duration (y)	8.0 ± 6.0	8.2 ± 4.7	
HbA1c (mmol/mol)	60.6 ± 10.8	60.3 ± 9.5	
Total (MET min/week)	1725 (527, 2235)	1440 (846, 2937)	
Sitting time (h/week)	83.2 (62.3, 93.8)	76.8 (63.3, 99.8)	
Resting heart rate (bpm)	75.3 ± 8.2	68.9 ± 8.4	
Resting SBP (mm Hg)	134.9 ± 9.7	129.4 ± 17.0	
Resting DBP (mm Hg)	86.3 ± 4.8	82.6 ± 7.3	
Weight (kg)	115.3 ± 25.5	117.1 ± 28.0	
BMI (kg/m^2)	35.0 ± 6.1	37.5 ± 7.3	
Waist girth (cm)	121.5 ± 14.9	125.0 ± 19.6	
Peak wattage during GXT (W)	106.8 ± 21.2	97.7 ± 23.3	
GXT eWLmax (W)	159.0 ± 33.8	142.9 ± 38.3	
Predicted VO_2max (mL/kg/min)	22.8 (17.9, 24.5)	18.3 (17.5, 28.4)	
APR session			
Peak wattage during APR (W)	96.6 ± 16.8	145.1 ± 32.4	0.001***
Peak RPE during APR	14.6 ± 1.4	17.1 ± 1.4	0.001***
APR heart rate (bpm): Pre session	84.7 ± 10.8	80.3 ± 10.7	0.34
APR heart rate (bpm): Peak	136.9 ± 14.6†††	151.6 ± 16.3†††	0.04*
APR heart rate (bpm): Post session	100.5 ± 11.6†	98.9 ± 11.8††	0.76
CV kcal expenditure	244.4 ± 50.1	237.5 ± 25.6	0.69
RT kcal expenditure	203.1 ± 67.5	231.4 ± 26.8	0.22
Total kcal expenditure	447.6 ± 117.4	468.8 ± 67.1	0.47

Data are presented as means ± standard deviation or as median (interquartile range).
Statistical significance is reported as follows: * $P<0.05$, ** $P<0.01$, *** $P<0.001$ difference between MICT and HIIT group; † $P<0.05$, †† $P<0.01$, ††† $P<0.001$, within group difference with pre value.
APR, acute physiological response; BMI, body mass index; CV, cardiovascular component; DBP, diastolic blood pressure; eWLmax, estimated maximum workload; GXT, graded exercise test at baseline; HbA1c, glycated haemoglobin; HIIT, high-intensity interval training; kcal, kilocalories; MET, metabolic equivalents; MICT, moderate-intensity continuous training; RPE, rate of perceived exertion (6-20); RT, resistance training component; SBP, systolic blood pressure; T2D, type 2 diabetes mellitus; VO_2max, maximum aerobic capacity; W, Watts.

Table 4.2: Baseline health history, medication usage and ethnicity of the study participants

		MICT (*n* = 11)	HIIT (*n* = 11)
Health history	Personal history of MI	2 (18.2%)	2 (18.2%)
	Atrial fibrillation	0	1 (9.1)
	Family history of MI	6 (54.6%)	4 (36.4%)
	Ex-smokers (>2 y)	5 (45.5%)	5 (45.5%)
	OSA requiring CPAP	3 (27.3%)	2 (18.2%)
Medication			
Antihyperglycaemia	Biguanide (Metformin)	9 (81.8%)	11 (100%)
	Sulfonylureas	5 (45.5%)	2 (18.2%)
	Exogenous insulin	4 (36.4%)	5 (45.5%)
Antihypertension	ACE inhibitors	4 (36.4%)	9 (81.8%)
	Non ACE inhibitors	7 (63.6%)	2 (18.2%)
	Diuretic	0	2 (18.2%)
Other Cardiac	Statins	4 (36.4%)	8 (72.7%)
	Anticoagulants	5 (45.5%)	6 (54.6%)
	Beta blockers	3 (27.3%)	2 (18.2%)
Respiratory	Bronchodilators	1 (9.1%)	2 (18.2%)
	Antihistamines	0	2 (18.2%)
	Reflux	1 (9.1%)	0
Other	Anti-depressants	2 (18.2%)	3 (27.3%)
Ethnicity	New Zealand European	9 (81.8%)	9 (81.8%)
	New Zealand Māori	1 (9.1%)	1 (9.1%)
	Asian	1 (9.1%)	1 (9.1%)

Data are presented as number of participants (sample %).
ACE, angiotensin-converting enzyme; CPAP, continuous positive airway pressure; HIIT, high-intensity interval training; MI, myocardial infarction; MICT, moderate-intensity continuous training; OSA, obstructive sleep apnoea.

As displayed in Table 4.1 the mean peak HR, peak wattage and peak RPE were significantly higher in the HIIT group (due to the intentional programme prescription differences), while the energy expenditure for the CV, RT and total session remained equal. Additionally, there were no dropouts during the APR, but for safety concerns respite was required during both MICT and HIIT and will be discussed further in this chapter. Of note was the variability in the individual physiological responses to both groups of participants, particularly for BG and DBP (Figure 4.3a & 4.3c). The MICT group experienced no statistically significant decreases to BG, although one SP (a non-insulin user) in the MICT group had to consume food between 60- and 90-min post session due to feelings of hypoglycaemia and, as such, a final BG was not included for that analysis. However, the HIIT group, in relation to the pre-session BG, had a significant reduction in BG for the remainder of the APR. DBP at peak intensity during the CV component increased (>10 mm Hg) for five SPs (45.5%) during MICT, while DBP at peak intensity only increased for two SPs (18.2%) during HIIT.

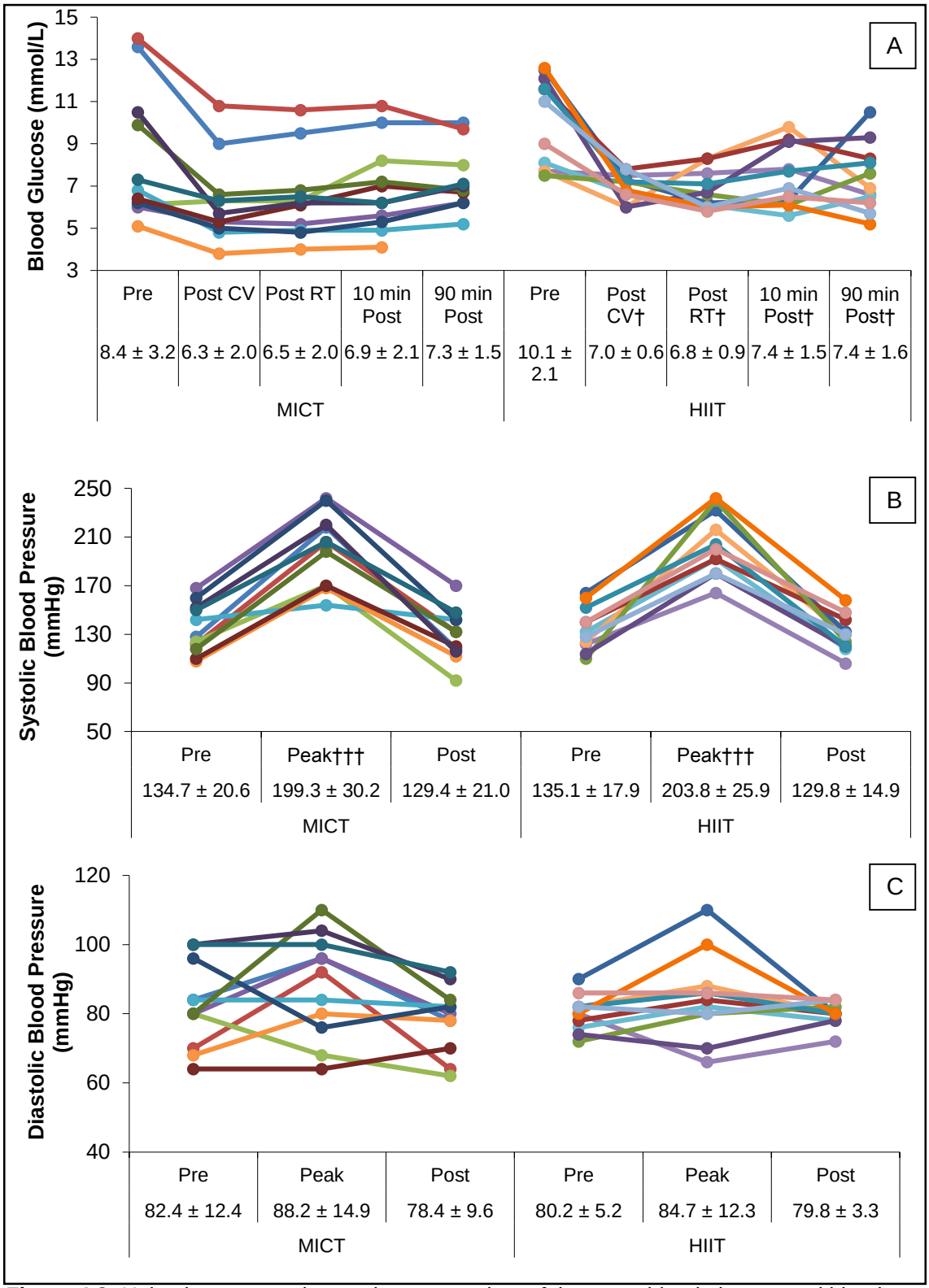

Figure 4.3: Univariate scatterplots and summary data of the acute blood glucose and blood pressure responses to the MICT and HIIT acute physiological response sessions. Statistical significance is reported as follows: *p<0.05, **p<0.01, ***p<0.001 difference between MICT and HIIT group; †p<0.05, ††p<0.01, †††p<0.001, within group difference with pre value.

Discussion

The key finding of this study was that the two different APRs elicited very similar acute physiological responses in T2D men, and for the first time, the level of precautionary respite required in such sessions has been detailed.

Acute exaggerated responses

During the completion of the APRs there were no major acute adverse events, but a similar amount (P = 0.39) of acute negative exaggerated responses were recorded in both groups with seven (63.6%) and four (36.3%) SPs in the MICT and HIIT, respectively. During the latter stages of the CV components, respite (decreases of 15-20%) had to be implemented by reducing intensity for one SP in each group due to exaggerated SBP and DBP hypertension and one SP in the MICT for SBP hypertension. Similarly, due to overexertion one MICT (RPE of 16) and three HIIT (RPE of 19) SPs required intensity reductions and two MICT SPs required duration reductions. Furthermore, two MICT SPs presented with post-exercise exaggerated responses, with one reporting pre-syncope feelings due to hypotension and the other with low BG and feelings of hypoglycaemia. Of note, the RT component required no alterations during the APR session. Due to the respite given during the CV component, Table 4.1 displays data with the peak values being possibly lower than would have been if the precautionary reductions were not implemented. However, the summary data in this table masks the individual responses (Figure 4.3) that are required by CEPs to better understand the BG and BP effects of intense acute exercise sessions.

To date, precautionary respite has not been reported in acute studies involving T2D and HIIT and the reasons may be due to the stringent inclusion criteria, pre-enrolment physiological assessments, qualified supervision and/or the suboptimal explicit reporting of such respite. The only acute study to use a similar HIIT protocol to that used in the current study, Gillen et al. (2012), did not report any respite to their seven elderly SPs who were sedentary and obese but who were not using insulin. Nonetheless, in the present study, respite was not unique to HIIT and was also needed, to a comparable extent, during the currently recommended MICT modality sessions (Colberg et al., 2010). Similarly, Gordon et al. (2013) reported that two of their eight (25.0%) male insulin-treated SPs could not complete the 30-min MICT session without frequent rest periods.

The reason for the noteworthy amount of precautionary respite in the current study could be due to the characteristics of the SPs. Being sedentary and presenting with class II obesity could contribute to exercise intolerance and the complications of T2D (e.g., elevated HbA1c and resting BP) along with the amount of medications taken (including insulin, statins and antidepressants) (Table 4.2) potentially affecting exercise ability. Further, although aligned to previously reported protocols, the exercise may have been too challenging for such a study sample and/or the preparatory period too short.

Blood glucose

The between group BG at each of the time points during the APR, and 90-min post, were similar with a significant within-group reduction in BG for HIIT evident (Figure 4.3a). However, elevated pre-exercise BG correlated to the magnitude of BG reduction post CV component for both MICT (-0.72; $p = 0.013$) and HIIT (-0.94; $p < 0.01$), similar to the BG reductions reported in other short-term studies (Hordern et al., 2008; Terada et al., 2013b). As such, this result must be interpreted with caution as the mean pre-exercise BG in the HIIT group was 10.1 ± 2.1 mmol/L compared to the MICT group's 8.4 ± 3.2 mmol/L. Nonetheless, when viewing the univariate scatter plots, the inconsistent variations within both group's individual SPs become more apparent. As glucose is an important fuel for contracting skeletal muscle during PA and with higher exercise intensities recruiting a greater amount of fast-twitch muscle fibers and carbohydrates (glucose) becoming the preferred substrate for adenosine-triphosphate (ATP) regeneration, individual variations in muscle fiber distributions may explain, in part, the individual variations observed. Additionally, the regulation of glucose uptake into skeletal muscle cells relies on numerous physiological factors, including the delivery of glucose (increases in skeletal muscle blood flow and capillary recruitment), glucose transport (GLUT4) proteins (expression and translocation into cell membranes) and glucose metabolism (mitochondrial capacity) (Richter & Hargreaves, 2013), that are different among individuals (particularly those with varying age, T2D duration, and baseline fitness) may have also contributed to the observed variations. Finally, it is possible that following an intense exercise session, the balance between increased catecholamine levels (promoting glycogenoylsis) (Adams, 2013) and the increased peripheral uptake of glucose (to replenish stores) is not consistent between individuals.

Blood pressure

The summary SBP and DBP responses within the MICT and HIIT sessions for the APR (Figure 4.3b & 4.3c) were both commensurate to the intensity of the training session (as seen in the HR and RPE data in Table 4.1) and comparable to results reported by Lima et al. (2008) of participants who performed a MICT session at 110% of anaerobic threshold. Furthermore, the univariate scatterplots revealed one MICT SP whose SBP reduction (marked post exercise hypotension with feelings of pre-syncope) to the APR were not evident in the summary data. Additionally, the large individual variations in DBP are only clear when viewing each appropriate scatterplot. The individual DBP variations suggest that physiological responses, including endothelial-dependent vasodilation (Mitranun et al., 2014) are not consistent between T2D men.

Limitations. Due to the nature of supervision required, blinding of session type was not possible and a lack of standardised meals across all SPs for the preceding dinner, breakfast and lunch may have confounded comparative analyses. Additionally, predicting eWLmax from a submaximal GXT may have led to inaccurate training intensities for some of the SPs, and using a motion-tolerant BP monitor may have enhanced the accuracy of the exercise BP measurements. As the respite was precautionary, knowing if actual adverse events (e.g., MI, stroke) would have occurred in the SPs remains unclear. Finally, the sample size was low and all SPs underwent pre-exercise screening thereby limiting the inference of acute exaggerated responses to the wider T2D population.

Strengths. The groups used in this study both received fully-supervised exercise interventions. Moreover, both groups included SPs with moderately-advanced T2D and those using multiple medications including exogenous insulin. The study was conducted in a real-world setting with findings possibly having strong external validity and clinical relevance.

Future research. Future studies should be conducted to report whether the effects at different times of the day would be similar. Additionally, studies that investigate the abstinence of all antihyperglycaemic medications (for 24-48 h before an APR session), different HIIT protocols or exercise modalities (e.g., running/swimming) and SPs only on oral medication compared to SPs using exogenous insulin would provide additional information to CEPs. Also, comparing the acute effects of such interventions in study samples with and without beta-blocker usage.

Conclusion

The MICT and HIIT, in the T2D men of this study, elicited similar acute HR, BP and BG responses, with acute exaggerated responses occurring during the combined (CV and RT) sessions, and in the 90 minutes following the sessions. But pre-exercise screening, individualised programme prescription, exposure to progressed preparatory training and, most importantly, respite (by reducing CV intensity/duration) were required to enhance the safety of the sessions. Furthermore, individual responses during both the MICT and HIIT modalities were not consistent, supporting the need for individually prescribed exercise programmes (O'Hagan et al., 2013). The findings of this study have clinical importance and will assist in helping healthcare professionals enhance their management of individuals living with T2D, via improved knowledge of the individual physiological responses of exercise sessions as experienced by the men who volunteered for this study. Qualified supervision was required when introducing an intense exercise session to such a study sample. This applied equally to both MICT and HIIT sessions, even after participants had undergone preparatory training.

CHAPTER FIVE

High-intensity interval training is equivalent to moderate intensity continuous training for short- and medium-term outcomes of macro- and microvascular complication markers in men with type 2 diabetes

This chapter comprises a paper in preparation for peer-review in the Frontiers in Endocrinology – Diabetes journal.

Abstract

The study sought to determine the efficacy of 12 weeks high-intensity interval training (HIIT), compared to moderate-intensity continuous training (MICT) on glucose control and macro- and microvascular complication markers in men living with type 2 diabetes (T2D). Both modalities were combined with resistance training (RT). Additionally, the study aimed to determine the medium-term durability of effects. After a 12-week, thrice weekly, training intervention incorporating either MICT+RT (n=11) or HIIT+RT (n=12), the study concluded with a 6-month follow-up analysis. The middle-aged study participants were obese, had moderate duration T2D and were taking multiple medications including insulin, statins and beta-blockers. Participants, randomised via the method of minimisation, performed MICT (progressing to 26-min at 55% maximum estimated workload [eWLmax]) or HIIT (progressing to two variations in which twelve 1-min bouts at 95% eWLmax interspersed with 1-min recovery bouts, alternated with eight 30-sec bouts at 120% eWLmax interspersed with 2:15 min recovery bouts) under supervision at an exercise physiology facility. To account for fixed and random effects within the study sample, mixed-effect models were used to determine the significance of change following the intervention and follow-up phases and to evaluate group*time interactions. Beyond improvements in aerobic capacity ($P<0.001$) for both groups, both training modalities elicited similar group*time interactions ($P>0.05$) while experiencing benefits for glycated haemoglobin (HbA1c; $P=0.01$), subcutaneous adiposity ($P<0.001$) and heart rate variability ($P=0.02$) during the 12-week intervention. Adiposity ($P<0.001$) and aerobic capacity ($P<0.001$) were significantly maintained in both groups at the 6-month follow-up. In addition, during the intervention, SPs in both MICT+RT and HIIT+RT experienced favourable reductions in their medication usage. The

study reported the inter-individual variability of change within both groups, the exaggerated acute physiological responses (using exercise termination indicators) that occurred during the interventions as well as the incidence of precautionary respite afforded in such a study sample. To reduce hyperglycaemia, and prevent further deterioration of macro- and microvascular complication markers (in both the short- and medium-term), future strategies that integrate the adoption and maintenance of physical activity as a cornerstone in the treatment of T2M for men should (cognisant of appropriate supervision) include either structured MICT+RT, or HIIT+RT.

Keywords: macrovascular, microvascular, moderate-intensity continuous training (MICT), high-intensity interval training (HIIT), resistance training, training durability, type 2 diabetes.

Clinical Trials Registration Number: ACTRN12617000582358

http://www.anzctr.org.au/default.aspx

Introduction

The burden of diabetes is reflected not only in the increasing numbers of people with T2D, but also in the growing number of premature deaths due to diabetes (IDF, 2015) with poor glycaemic control being a major source of morbidity and mortality (Fowler, 2008; Inzucchi et al., 2012). Diabetes alone increases cardiovascular disease, but in the presence of the macrovascular complication markers of hypertension, dyslipidaemia, adiposity and systemic inflammation, the risk of cardiovascular events (i.e., stroke, myocardial infarction) is significantly increased (Fowler, 2008). Furthermore, long-term follow-up studies on people living with T2D (The ACCORD study, 2016; Zoungas et al., 2014), in which participants received education and lifestyle advice, in conjunction with antihyperglycaemic medication, to either maintain or to intensify glycaemic control reported that long-term intensive glycaemic control did not lead to further long-term benefits with respect to mortality or macrovascular events. Similarly, Wing et al. (2016) reporting on the Look AHEAD project, in which participants accumulated ~3 hours of moderate-intensity physical activity each week (coupled with a calorie-restricted diet) for a year, concluded that intensive lifestyle interventions focusing on weight loss, counselling and increased physical activity did not reduce the cardiovascular events across all the participating adults with T2D. Nonetheless, in the latest position statement of the American Diabetes Association (ADA), the adoption and maintenance of physical activity still remains a vital component in the management of overall health in individuals with T2D (Colberg et al., 2016). Moreover, structured interventions in which participants engage in planned, individualized, and supervised/monitored programmes (Umpierre et al., 2011), such as MICT, have been associated with a reduced risk of all-cause mortality in people with T2D (Blomster et al., 2013; Dixit, Maiya & Shastry, 2014). More recently, the prescription of structured HIIT has been reported as an alternate therapy in affecting cardiometabolic health (Cassidy et al. 2017; Grace, Chan, Giallauria, Graham & Smart, 2017; Ramos et al. 2015). Likewise, combined training (MICT and RT) has been reported as both comparable to MICT alone (Chudyk & Petrella, 2011; Hayashino, Jackson, Fukumori, Nakamura & Fukuhara, 2012; Umpierre et al., 2011), and as possessing additional cardiometabolic benefits (Church et al., 2010; Colberg et al, 2016; Oliveira, Simões, Carvalho & Ribeiro, 2012; Schwingshackl, Missbach, Dias, König & Hoffmann, 2014). However, only three studies to date have combined resistance exercises with HIIT in people with T2D (Cassidy et al., 2015b; Francois et al., 2017; Praet et al., 2008); but none of these three studies included a MICT comparative group. In addition, the durability of HIIT-

derived benefits is unknown as only one pilot study has reported data beyond the intervention phase (Hollekim-Strand et al., 2014). Hence, the primary objective of this study was to determine the efficacy of 12-week HIIT combined with RT (HIIT+RT), compared to combined MICT and RT (MICT+RT) on HbA1c in men living with T2D. Secondary objectives of the study were to compare the efficacy of the two training modalities on macrovascular complication markers of resting blood pressure, adiposity, HDL, TG and hs-CRP and microvascular complication markers of HRV, distal tactile sensation, postural stability, isokinetic ankle strength and uACR. The final objective was to determine whether any effects achieved for both training modalities were sustained after a 6-month follow-up phase.

Determining both the short- and medium-term effects on glycaemic control and macro- and microvascular complication markers for two alternate exercise modalities for men with T2D will provide CEPs with a better understanding of exercise prescription which will assist with their goal of optimising patient care. It was hypothesised that HIIT+RT would be more effective than MICT+RT in reducing HbA1c during a 12-week supervised intervention in men with T2D.

Methods

Study participants

The SPs of this intervention study were the same SPs that completed the baseline assessments of Chapter Four. Sample size calculations were based on a smallest meaningful difference in HbA1c of 3.0 mmol/mol with a SD of effect of 2.5 mmol/mol, $\alpha = 0.05$, $1- \beta = 0.80$ with the calculation yielding 11-12 participants per group. Recruitment aimed to enrol an additional participant per group to account for a predicted ~10% dropout. Chapter Four contains the details of SP enrolment, initial consultation details (including the IPAQ) and the protocols of the baseline assessments for HbA1c, BMI, subcutaneous adiposity, HR_{rest}, BP_{rest} and of the GXT used in this chapter. Additionally, within the consultation and over the two individual assessment sessions the following measurements were conducted.

Baseline assessments

Initial consultation. In addition to the IPAQ, the questionnaires to document physical activity enjoyment (Physical Activity Enjoyment Scale [PACES]) (Motl et al., 2011) (Appendix G), and habitual nutrition were administered. Although it is conceivable that only those individuals who had an affinity to exercise enrolled in the study, the purpose of the PACES was to monitor the magnitude of change in physical activity enjoyment during the study. SPs were explained the purpose of PACES and were instructed to complete the form independently and in relation to physical activity in general and not a particular training modality.

Nutrition habits. Current "best practice" national nutritional management for diabetes in New Zealand (NZ) constitutes the Ministry of Health's (MoH) Eating and Activity Guidelines (MoH, 2015); which are to consume a diet moderate-to-high in carbohydrate and low in dietary fat. These guidelines are currently being challenged in the nutrition-related academic and practice arena (Feinman et al., 2015), with the counter, contemporary argument in favour of carbohydrate restriction, with a greater emphasis on dietary fat. This controversy about what constitutes "best practice" in nutrition is an area of debate that needs to be recognised, but as it is outside the scope of this study, the findings from this study will be interpreted in alignment with the Eating and Activity Guidelines.

Nutrition habits pertaining to the previous four weeks, were obtained using the 2008/09 NZ Adult Nutrition Survey (NZANS) Questionnaire (MoH, 2011). The questionnaire, which establishes the frequency with which various foods and food groups are consumed, was explained to each participant and a blank copy given to participants to independently complete (Appendix H). To objectively record responses of various nutrition aspects, a novel approach was applied in which the NZANS responses were grouped into five domains (Appendix I). The novel scoring system was applied as follows: Penalty points were allocated to responses that were contrary to the guidelines (with higher penalty points being allocated to responses further away from the guidelines). The general premise of the NZANS is that Check-box 1 represents never (or seldom) with the successive Check-boxes increasing in frequency. Of note, question 24a was added to ascertain the amount of teaspoons of sugar added to hot beverages daily. SPs fully adhering to the guidelines thus received zero penalty points. The domains of General

Food Quality, Fast Foods, Refined Carbohydrates, Smoking and Alcohol Consumption received maximum penalties of 60, 30, 50, 30 and 30, respectively.

Blood and urine samples. In addition to the HbA1c measurement, TC, HDL, LDL, and TG were determined using the enzymatic colorimetric method measured on a cobas® 8000 (cobas c702 [AU1], Roche Diagnostics International Ltd, Rotkreuz, Switzerland) chemistry module.
The measurement of hs-CRP was performed with a particle enhanced immunoturbidimetric assay measured on a cobas® 8000 (cobas c702 [AU1], Roche Diagnostics International Ltd, Rotkreuz, Switzerland) chemistry module, with hs-CRP estimation by latex turbidimetric method. Urine albumin-to-creatinine ratio (uACR) was measured with a spot urine sample and micro-albuminuria, for men, was defined as 2.5 ≤ uACR < 25 mg/mmol (Guo, Ekelund, Griffin & Simmons, 2016). The urinary microalbumin was measured on a cobas® 8000 (cobas c502 [AU2], Roche Diagnostics International Ltd, Rotkreuz, Switzerland) chemistry module using an immunoturbidimetric assay.

Physiological assessments (Session 1).

Monofilament test. SPs were assessed for sensation loss, a marker of DPN (McNamara, Vinik, Barrentine & De Vol, 2016), by their ability to register a sensation of a monofilament when applied, at 10 sites on the soles of both feet, with sufficient pressure to buckle the 10 g filament (Singh, Armstrong & Lipsky, 2005). The sequence and tempo of the measurements was varied to avoid a predictable pattern. Sensation was recorded as a score out of 20.

Postural stability. The stabiliometry assessment was performed while the participant maintained a quiet barefoot stance on the HUR Labs iBalance+ platform (ALU4, HUR Labs Oy, Tampere, Finland). The software received information (sample rate: 100 Hz) about centre of pressure motion in the anterior-posterior and medio-lateral directions and the resultant posturogram provided data on trace length (TL) (mm), C90 (90% confidence ellipse) area (mm^2) and the standard deviation of the velocity (mm/s). Postural stability was conducted, after calibration checks according to manufacturer's guidelines, for an eyes open (familiarisation) and eyes closed (analysis) condition. For each condition SPs stood as stable as possible, for 35-sec, with only the last 30-sec being recorded (Scoppa, Capra, Gallamini & Shiffer, 2013), with their feet in a joined parallel position and arms relaxed at their sides.

Deep-breathing HRV. HRV using the inspiration-to-expiration ratio of the cardiac rhythm's R-R interval was used as a marker of autonomic function. To complete the testing procedure, SPs (still resting in the supine position) were connected to the ECG and coached to perform deep breathing (six breaths per minute) for a full minute. HR variance was recorded using the longest R-R interval (in milliseconds) during expiration divided by the shortest R-R interval during inspiration. The mean of six of these individual ratios were recorded as the final ratio (Colberg et al., 2003).

Physiological assessments (Session 2).

Postural stability. As per the procedures previously described the postural stability tests was repeated in order to enhance reliability. The mean of each of the variables was used for analysis.

Isokinetic ankle strength testing. Before the isokinetic testing to assess distal muscle atrophy (a marker of DPN), SPs were instructed to warm-up with a 5-min cycle on an ergometer maintaining 60 rpm at a comfortable resistance. To conclude the warm-up 30-sec ankle plantar and dorsi-flexion stretches were performed. Strength assessments were conducted on a Humac NORM (Computer Sports Medicine Inc., Stoughton, MA) isokinetic dynamometer. The dynamometer was pre-calibrated for speed, weight and position following the instructions of the manufacturer. Peak torque and work recordings, assessing the ankle joint (of the dominant leg) through full plantar-dorsiflexion range, for the concentric action were obtained (Tan et al., 2012). Absolute isokinetic torque values (gravity-corrected) were recorded as Newton-meters (Nm). The assessment protocol was standardised with respect to patient set-up, familiarisation (1 set of 6 progressive repetitions for the 60°/s trials and 1 set of 3 progressive repetitions for the 30°/s trial), rest intervals (30-sec after the familiarisation trial repetitions and 60-sec between the test repetitions) and test repetitions (2 sets of 3 repetitions). The maximum values obtained during the two sets (reciprocal-contractions) at both 30- and 60°/s were recorded (Tan et al., 2012). SPs were assessed in the supine position with a chair back angle of 20° and the knee joint fully extended. Thigh straps were used for leg stabilisation and SPs were instructed to hold the handles while being verbally encouraged to exert maximal effort during the test.

Additionally, Chapter Four details how the participants were randomised, the 'pre-session monitoring procedure', the RT prescription and explained the acute exaggerated response indicators that were used in this intervention study. The study protocol was approved by the Auckland University of Technology Ethics Committee (reference no. 14/396), registered as a clinical trial (ACTRN 12617000 582358) and the study was performed following the tenets of the Declaration of Helsinki.

Study design

Over the 18-month period (using a staggered structure of one or two potential participants per fortnight – as per their referral to the clinic) individual consultations were conducted. My study was divided into two phases in which all SPs were to undergo a 12-week progressive training intervention phase incorporating either MICT+RT or HIIT+RT, after which all SPs would complete a 6-month follow-up phase. A *priori* power calculation indicated that n = 12 in each exercise training group would be sufficient to detect a significant interaction effect in glycaemic control, but after an initial 12-month enrolment period only 15 SPs had been randomised into the two intervention groups (Figure 5.1). Similar to prior studies reporting low enrolment rates, as discussed in Chapter Three, many of my potential participants did not meet study inclusion criteria (n = 12). To meet the planned sample size, the enrolment period was extended by six months, only enrolling an additional eight SPs. The final study sample consisted of 23 participants (MICT+RT, n = 11; HIIT+RT, n = 12).

Baseline data

The following data were obtained and used in the intervention phase to randomly allocate SPs to groups and were used to guide the initial individualised programme prescription: Referral note details and initial consultation data, physical activity habits, nutrition habits, and the baseline physiological assessments of blood samples, BMI, adiposity, resting BP and the GXT. Additionally, all SPs were instructed not to alter their usual dietary intake and to not alter their current physical activity habits outside of the study. All changes to medications during the study phases were recorded.

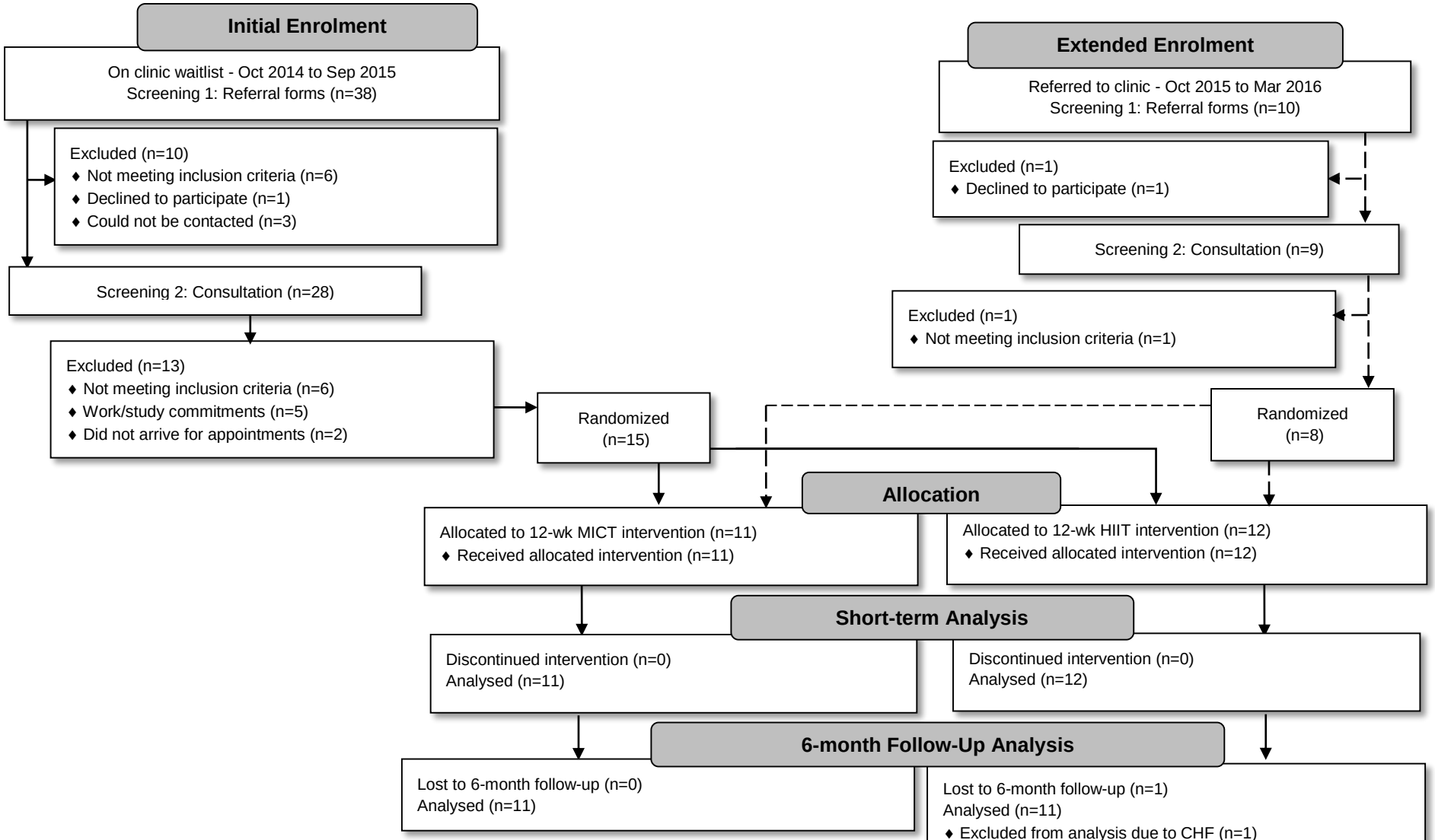

Figure 5.1: Consort diagram of study participant flow from initial enrolment to medium-term follow-up

The study phases

Intervention phase. As HIIT studies have no standardized training variables (as discussed in Chapter Three), the intervention duration, and frequency and length of the training sessions were in alignment with both the operations of the exercise physiology clinic and the general training variables of the noted studies; specifically three scheduled 1-h sessions per week (Monday, Wednesday and Friday) for 12 weeks. Each session was a combined CV and RT session separated by a BG check. In order to accommodate CV and RT into each session, the protocols of prior studies were emulated (Balducci et al., 2012; Tan et al., 2012), whereby shorter variations of both components (in comparison to alone training) were utilized.

As per the study design, one group had the CV component of the combined training intervention progress to longer duration MICT training, while the other group progressed to HIIT. Each intervention was designed to ensure equal energy expenditure during the CV component (i.e., isocaloric). Additionally, weekly foot inspections were conducted and as exercise-induced fat reduction was pursued during the study, weekly body mass measurements were graphically recorded on each SP's weight-loss chart.

Introductory stage. During the 3-week introductory stage the CV component for both groups had 10-min MICT cycling (50% eWLmax, flanked by a 2-min warm-up and 3-min cool-down of 40% eWLmax) with a target RPE of ~13.

Intermediate stage. During the 4-week intermediate stage the MICT+RT group was progressed by increasing the MICT duration to 17:30 min (flanked by a 3-min warm-up and cool-down of 40% eWLmax) and increasing the training intensity to 55% eWLmax; maintaining the target RPE of ~13. During the same intermediate stage the HIIT+RT group progressed to include 3 bouts of 3:30 min at 75% eWLmax, with a target RPE of ~16, interspersed with similar duration recovery bouts at 45% eWLmax (flanked by a 1:30 min warm-up and 2-min cool-down of 30% and 45% eWLmax, respectively) based on prior reported AIT protocols (Tjønna et al., 2008; Wisløff et al., 2007).

Advanced stage. For the final 5-week advanced stage, the 32-min MICT sessions included training for 26-min at 55% eWLmax with a target peak RPE of ~14 (flanked by a 3-min warm-up and cool-down of 40% eWLmax). As there is no consensus on an optimal HIIT protocol (Chapter Three), the advanced HIIT stage applied one of two variations alternately with each session requiring 28 min to complete. The first variation included twelve 1-min bouts at 95% eWLmax interspersed with 1-min recovery bouts at 40% eWLmax, aligned to the protocols of Little et al. (2011) and Gillen et al. (2012), with a target peak RPE of ~18 (flanked by a 2:30 min warm-up and cool-down of 60% and 40% eWLmax, respectively). The second variation, a SIT session similar to the Tabata et al. (1997) protocol, included eight 30-sec bouts at 120% eWLmax interspersed with 2:15 min recovery bouts at 30% eWLmax (flanked by a 2:30 min warm-up and cool-down of 40% and 25% eWLmax, respectively).

Resistance training. As reported in Chapter Four, the RT component contained equal exercises and training variables for both groups and maintained a general strength focus with minimal progression or variation during the study intervention. Four compound exercises and abdominal contractions were completed by the SPs using 2 sets of 15 repetitions at 67% of 1RM during the introductory stage, 3 sets of 10 repetitions at 75% of 1RM during the intermediate stage and 2 sets of 12 repetitions at 75% of 1RM during the advanced stage. Of note, strength and balance exercises for the ankles were intentionally omitted so as to not confound DPN variables.

To ensure the SPs' workload corresponded to the prescribed intensity and reflected any improved aerobic capacity, each SP had the CV component of their training session modified (during the Friday session of Week 4 and Week 8) by simulating the GXT of their assessment (i.e., three 4-min levels with each level increasing by 20-35 W). These data were used to adjust each SP's workload. Similarly, to ensure that the resistance of the isotonic strength exercises were prescribed appropriately according to the strength progressions of each SP, predicted 1RMs (Balducci et al., 2012) were tested and calculated regularly (on the participants' first and last training day and the Monday of Week 5 and 9). On conclusion of this intervention phase (Friday of Week 12) SPs repeated the baseline assessments and questionnaires, commencing with blood tests no sooner than the subsequent Monday morning and no later than the following morning (Tuesday).

Intervention phase supervision. To enhance safety, all participants were screened before the commencement of each training session, via a standardized 'pre-session monitoring procedure'. The lead researcher, assisted by three experienced CEPs measured SPs' physiological parameters of BG, HR and BP and recorded these values alongside current feelings of wellbeing and confirmation that medications for the day had been taken as prescribed. The assisting CEPs (having relevant post-graduate qualifications), not directly involved in the study design, received pre-intervention training to enhance their ability to capture reliable data pertaining to the requirements of the study. Additionally, the CEPs continually monitored each SP's training and recorded RPE, BP and HR during the latter stages of peak intensity on daily training sheets. Midway during the CV component HR and BP were monitored. Moreover, to ensure due care to each participant the talk test was administered during the CV component and, only when deemed appropriate (factoring in HR, BP, verbal and non-verbal responses), precautionary respite was provided by the supervising CEP by reducing cycling duration or intensity by 5-10% of cycling time or by 10-20 W, respectively, for MICT. Precautionary respite for HIIT involved reducing the 1-min bout durations by 50-100% for 1-2 of the twelve bouts. Similar to the pre-session monitoring procedure, a post-session monitoring procedure was administered on conclusion of each SP's combined training session.

Follow-up phase

On completion of the 12-week intervention phase all SPs were informed that they would be contacted in six months' time to confirm their follow-up assessments. In a real-world setting, upon completion of an exercise intervention, people living with T2D are typically advised to continue their training independently. Hence, the purpose of the follow-up phase was to determine the effects of unmonitored, independent training on HbA1c and the markers of macro- and microvascular complications. Study participants were advised to continue with their training modality only (i.e., MICT group to continue with MICT and HIIT group to continue with HIIT) and to include RT into their sessions. To this end, SPs were advised to join a local commercial training facility or adapt regular free living cardiovascular activities to replicate their training modality. Additionally, for the RT component, those SPs choosing not to join a commercial facility were provided with a home-based RT programme (Appendix J). During this phase SPs were independent and could choose to continue their mode of training at an external facility or environment, and received no further support or supervision from myself. At the end of

this 6-month phase SPs returned to the clinic and completed the baseline assessments and questionnaires. Additional to the study questionnaires, SPs were asked to discuss the regularity of maintaining their training during the 6-month independent training phase. A score of 2 was allocated when a month of training was adequately completed (i.e., 2-3 combined sessions per week for 4 weeks), a score of 1 for partial completion and a score of 0 when no training was done that month. Thus, the score range was between 0 (no training done for 6 months) and 12 (6 months of continued training).

Statistical analyses

The SP's medical history and ethnicity were recorded and descriptive analyses carried out. Normality of data were appraised using Shapiro-Wilk tests. Data are presented as means ± SD where normality of distribution was confirmed. Alternatively, data are presented as median and interquartile range when not normally distributed. To account for fixed and random effects within the clinical study sample, mixed-effect models were used to determine the significance of change (P = 0.05) following the intervention and follow-up phases as well as to evaluate the group*time interaction effect. Linear models were conducted for normally distributed data. Alternatively, generalised linear mixed models were conducted. Between-group training variables were compared using unpaired, two-tailed student t-tests. Data were analysed using Stata® (Release 14, College Station, TX: StataCorp LLC). The one drop-out during follow-up was left out of the final analysis and not replaced or imputed. Univariate scatterplots (Weissgerber et al., 2015) have been presented for some data to detail individual nuance.

Results

In general, the SPs were middle-aged (MICT+RT = 52.5 ± 7.0; HIIT+RT = 52.2 ± 7.1 years) with moderate-duration T2D (MICT+RT = 8.0 ± 6.0; HIIT+RT = 8.5 ± 4.7 years) using multiple medications, and were comparable for all measured variables at baseline, including HbA1c (poor control), BMI (class II obesity), and VO_2max levels (unfit). Referral information, including health history, medication usage and ethnicity, of the male SPs are presented in Table 5.1 with the data for habitual physical activity and nutrition, PACES, and VO_2max presented in Table 5.2. Despite the instruction to SPs to not alter their habitual physical activity and nutrition, both these showed improvements during the course of the study. However, these improvements occurred

in both groups to a comparatively similar extent (Table 5.2). Of note, both groups begun the study having a positive attitude towards physical activity (PACES) which significantly improved during the intervention phase and was sustained at follow-up. Both groups experienced similar significant VO_2max improvements (> 3.9 mL/kg/min) during the intervention which were also significantly sustained at follow-up.

Table 5.1: Health history, baseline medications and ethnicity of the study participants after randomisation

		MICT+RT (n = 11)	HIIT+RT (n = 12)
Health history	Personal history of MI	2 (18.2%)	2 (16.7%)
	Ex-Smokers (>2 yrs)	5 (45.5%)	5 (41.7%)
	Smoking (currently)	0	0
	Family history of MI	6 (54.6%)	5 (41.7%)
	Atrial fibrillation	0	1 (8.3%)
	Neuropathic Pain	0	0
	Mild retinopathy	1 (9.1%)	1 (8.3%)
	OSA requiring CPAP	3 (27.3%)	2 (16.7%)
	Arthritis	1 (9.1%)	1 (8.3%)
	Gout	2 (18.2%)	0
	Total hip replacement	1 (9.1%)	0
Medications			
Antihyperglycaemia	Biguanide (Metformin)	9 (81.8%)	12 (100%)
	Sulfonylureas	5 (45.5%)	3 (25.0%)
	Exogenous Insulin	4 (36.4%)	5 (41.7%)
Hypertension	ACE Inhibitors	4 (36.4%)	10 (83.3%)
	Non ACE Inhibitors	7 (63.6%)	2 (16.7%)
	Diuretic	0	2 (16.7%)
Other Cardiac	Statins	5 (45.5%)	9 (75.0%)
	Anticoagulants	5 (45.5%)	6 (50.0%)
	Beta Blockers	3 (27.3%)	2 (16.7%)
Respiratory	Bronchodilators	1 (9.1%)	2 (16.7%)
	Antihistamines	0	2 (16.7%)
	Reflux suppressors	1 (9.1%)	0
Other	Anti-depressants	2 (18.2%)	3 (25.0%)
	Gout	2 (18.2%)	0
	Erectile dysfunction	0	1 (8.3%)
	NSAID	0	1 (8.3%)
	Analgesics	0	1 (8.3%)
Ethnicity	European	9 (81.8%)	9 (75.0%)
	Māori	1 (9.1%)	2 (16.7%)
	Asian	1 (9.1%)	1 (8.3%)

Data are number of participants (percentage).
ACE, angiotensin converting enzyme; CPAP, continuous positive airway pressure; HIIT, high-intensity interval training; MI, myocardial infarction; MICT, moderate-intensity continuous training; NSAID, non-steroidal anti-inflammatory drug; OSA, obstructive sleep apnoea; RT, resistance training.

With regards to adherence, of the possible 36 sessions, the mean number of sessions attended by the MICT+RT and HIIT+RT groups were similar (P = 0.82) at 32.5 ± 2.5 (90.4 ± 6.8 %) and 32.8 ± 3.6 (91.2 ± 9.9 %), respectively, and the mean energy expenditure per combined (CV and RT) session per participant was similar (P = 0.90) with each SP, on average, having expended ~1040 kcal per week.

The assessment results at baseline, on the conclusion of the supervised interventions and the follow-up phase as well as the associated mixed-effects model coefficients, for HbA1c and the macrovascular complication markers for BP, adiposity, lipidaemia and hs-CRP are presented in Table 5.3. Detailed model coefficients of the mixed-effects model for HbA1c are presented in Table 5.4. The results of the interventions on microvascular complication markers for CAN, DPN and nephropathy are presented in Table 5.5. Large inter-individual variations during the study phases were evident with Figures 5.2 & 5.3 displaying the univariate scatterplots for select macro- (HbA1c, DBP and subcutaneous adiposity) and microvascular complication markers (HRV, isokinetic dorsiflexion strength and uACR), respectively.

Glycaemic control and macrovascular complication markers

Both training progressions produced comparable improvements in HbA1c after the 12-week supervised intervention (P < 0.01). However, these improvements were not significantly sustained at the 6-month follow-up (Table 5.3) (Figure 5.2a). Of note, SP age, T2D duration, hypertension and statin medication usage, or being enrolled during the extended enrolment period did not significantly contribute to the training effect on HbA1c (Table 5.4). Additionally, the model was repeated to evaluate the effect of background improvements in physical activity and nutrition. Neither the changes to background physical activity (moderate MET min/week) nor nutrition changes (total NZANS penalty score) significantly impacted the findings for HbA1c (P = 0.30 and P = 0.22, respectively).

Similarly, for waist girth and subcutaneous adiposity there was no between group difference in the significant reductions experienced by both training modalities during the supervised intervention. SP age, T2D duration, hypertension and statin medication usage, or being enrolled during the extended enrolment period did not significantly contribute to the training effect on subcutaneous adiposity. Again, changes to background physical activity (moderate MET

Table 5.2: Baseline, 12-week intervention and 6-month follow-up comparisons for habitual physical activity (IPAQ), nutrition (NZANS), physical activity enjoyment (PACES) and aerobic capacity (VO_2max)

	MICT+RT (n=11)	HIIT+RT (n=12)	β	SE β	Z statistic	P	β Confidence interval
Mod METmin/wk - Baseline	480 (290, 1435)	690 (380, 1234)					
12-week intervention	1185 (320, 2520)	1023 (473, 1474)	435.80	498.44	0.87	0.382	-541.12 – 1412.72
6-month follow-up	1650 (960, 3095)	1620 (420, 2050)[a]	1395.48	503.08	2.77	0.006**	409.46 – 2381.50
Group*Time interaction			-312.10	665.97	-0.47	0.639	-1617.37 – 993.18
Total METmin/wk - Baseline	1632 ± 1017	1808 ± 1315					
12-week intervention	2435 ± 1816	2371 ± 1850	802.85	480.32	1.67	0.095	-138.57 – 1744.26
6-month follow-up	2951 ± 2478	2763 ± 2591 [a]	1399.65	487.19	2.87	0.004**	444.76 – 2354.53
Group*Time interaction			-363.46	733.54	-0.50	0.620	-1801.18 – 1074.25
Sitting hours - Baseline	76.4 ± 24.1	80.1 ± 21.4					
12-week intervention	75.4 ± 26.4	70.7 ± 24.5	-1.03	4.75	-0.22	0.829	-10.33 – 8.28
6-month follow-up	72.2 ± 28.8	68.2 ± 23.9 [a]	-5.14	4.88	-1.05	0.293	-14.7 – 4.43
Group*Time interaction			6.26	12.55	0.50	0.618	-18.34 – 30.86
Ref CHO (/50) - Baseline	10.0 (4.5, 15.5)	6.0 (1.5, 10.5)					
12-week intervention	8.0 (2.0, 12.0)	6.0 (3.5, 8.0)	-3.55	1.62	-2.19	0.029*	-6.72 – -0.37
6-month follow-up	10.0 (3.5, 12.0)	6.0 (4.0, 9.0) [a]	-1.07	1.66	-0.65	0.518	-4.32 – 2.18
Group*Time interaction			-5.32	3.25	-1.64	0.102	-11.70 – 1.05
Total NZANS (/200) - Baseline	52.1 ± 14.6	47.0 ± 16.2					
12-week intervention	44.6 ± 15.4	41.8 ± 14.3	-7.48	2.20	-3.41	0.001**	-11.79 – -3.18
6-month follow-up	47.4 ± 15.0	42.4 ± 10.9 [a]	-4.95	2.26	-2.19	0.029*	-9.39 – -0.51
Group*Time interaction			-7.43	7.06	-1.05	0.293	-21.26 – 6.40
PACES (/80) - Baseline	64.0 (63.5, 72.5)	65.5 (59.0, 77.3)					
12-week intervention	72.0 (69.0, 75.5)	76.5 (73.0, 78.3)	5.27	1.90	2.78	0.006**	1.55 – 9.00
6-month follow-up	71.0 (67.5, 75.5)	70.0 63.0, 76.5) [a]	3.96	1.95	2.03	0.042*	0.14 – 7.79
Group*Time interaction			-3.11	4.74	-0.66	0.512	-12.41 – 6.19

	MICT+RT (n=11)	HIIT+RT (n=12)	β	SE β	Z statistic	P	β Confidence interval
VO_2max - Baseline	22.7 ± 5.3	20.4 ± 6.6					
12-week intervention	27.3 ± 5.5	24.3 ± 6.3	4.64	0.74	6.30	<0.001***	3.19 – 6.08
6-month follow-up	25.5 ± 5.1	23.2 ± 6.8 [a]	3.31	0.76	4.35	<0.001***	1.82 – 4.80
Group*Time interaction			-3.85	3.16	-1.22	0.224	-10.05 – 2.35

Data are median (interquartile range), means ± standard deviation. [a] n = 11

Statistical significance is reported as follows: * *P*<0.05, ** *P*<0.01, *** *P*<0.001 for within group analysis.

CHO, carbohydrates; HIIT, high-intensity interval training; IPAQ, International Physical Activity Questionnaire; MET, metabolic equivalent; min/wk, minutes per week; MICT, moderate-intensity continuous training; NZANS, New Zealand Adult Nutrition Survey; PACES, Physical Activity Enjoyment Scale; RT, resistance training; VO_2max, maximum aerobic capacity (mL/kg/min); (/50), possible 50 maximum; (/80), possible 80 maximum; (/200), possible 200 maximum.

Table 5.3: Baseline, 12-week intervention and 6-month follow-up comparisons for HbA1c and macrovascular complication markers

	MICT+RT (n=11)	HIIT+RT (n=12)	β	SE β	Z statistic	P	β Confidence interval
HbA1c - Baseline	58.0 (54.5, 68.5)	62.5 (55.5, 66.5)					
12-week intervention	50.0 (47.0, 58.0)	57.5 (55.8, 65.5)	-6.27	2.47	-2.54	0.011*	-11.11 – -1.44
6-month follow-up	55.0 (51.0, 57.0)	63.0 (56.5, 71.5)[a]	-3.60	2.54	-1.42	0.156	-8.59 – 1.38
Group*Time interaction			0.42	7.41	0.06	0.955	-14.11 – 14.95
SBP - Baseline	134.8 ± 9.7	133.1 ± 20.9					
12-week intervention	133.2 ± 17.0	133.4 ± 18.1	-1.64	2.92	-0.56	0.576	-7.37 – 4.10
6-month follow-up	133.4 ± 18.8	131.8 ± 19.6[a]	-2.15	3.00	-0.72	0.474	-8.04 – 3.74
Group*Time interaction			-6.41	7.14	-0.90	0.369	-20.39 – 7.58
DBP - Baseline	86.2 ± 5.0	83.7 ± 7.9					
12-week intervention	83.4 ± 9.5	83.6 ± 9.6	-2.82	1.92	-1.47	0.142	-6.58 – 0.94
6-month follow-up	83.9 ± 9.4	84.1 ± 9.6[a]	-2.56	1.95	-1.31	0.190	-6.39 – 1.27
Group*Time interaction			-5.69	3.32	-1.72	0.086	-12.22 – 0.81
BMI - Baseline	35.0 ± 6.1	39.2 ± 9.4					
12-week intervention	34.4 ± 5.5	39.0 ± 9.2	-0.63	0.33	-1.92	0.055	-1.27 – 0.01
6-month follow-up	34.0 ± 4.6	38.9 ± 9.9[a]	-1.00	0.34	-2.94	0.003**	-1.66 – -0.33
Group*Time interaction			6.23	4.16	1.50	0.134	-1.92 – 14.38
Waist - Baseline	121.5 ± 15.0	127.4 ± 20.5					
12-week intervention	119.5 ± 14.3	126.9 ± 19.6	-2.02	0.77	-2.63	0.008**	-3.52 – -0.52
6-month follow-up	119.0 ± 12.6	126.1 ± 21.1[a]	-2.67	0.79	-3.36	0.001**	-4.22 – -1.11
Group*Time interaction			14.79	9.39	1.58	0.115	-3.61 – 33.18
Skinfolds - Baseline	239 ± 95	274 ± 123					
12-week intervention	210 ± 79	249 ± 110	-19.31	7.41	-3.96	<0.001***	-43.83 – -14.79
6-month follow-up	209 ± 71	241 ± 117[a]	-30.98	7.67	-4.04	<0.001***	-46.02 – -15.94
Group*Time interaction			71.48	53.33	1.34	0.180	-33.05 – 176.00

	MICT+RT (n=11)	HIIT+RT (n=12)	β	SE β	Z statistic	P	β Confidence interval
HDL - Baseline	1.02 ± 0.26	1.08 ± 0.21					
12-week intervention	1.03 ± 0.25	1.13 ± 0.27	0.01	0.03	0.29	0.768	-0.05 – 0.07
6-month follow-up	1.01 ± 0.34	1.05 ± 0.22[a]	-0.04	0.03	-1.41	0.158	-0.11 – 0.02
Group*Time interaction			-0.21	0.11	-1.90	0.057	-0.43 – 0.01
TG - Baseline	1.7 (1.5, 3.2)	2.2 (1.7, 2.9)					
12-week intervention	1.4 (1.3, 2.0)	1.8 (1.4, 2.4)	-0.79	0.41	-1.92	0.055	-1.61 – 0.02
6-month follow-up	1.5 (1.2, 3.2)	2.1 (1.4, 2.4)[a]	-0.60	0.41	-1.46	0.144	-1.41 – 0.21
Group*Time interaction			-0.11	2.27	-0.05	0.962	-4.55 – 4.33
hs-CRP - Baseline	2.1 (1.6, 5.0)	1.8 (1.3, 3.2)					
12-week intervention	2.6 (1.3, 5.4)	1.8 (1.0, 3.0)	-0.74	0.69	-1.07	0.287	-2.09 – 0.62
6-month follow-up	3.0 (1.3, 6.6)	2.3 (1.6, 5.5)[a]	-0.60	0.71	-0.84	0.402	-2.00 – 0.80
Group*Time interaction			-3.47	2.91	-1.19	0.233	-9.18 – 2.24

Data are means ± standard deviation, median (interquartile range). [a] n = 11

Statistical significance is reported as follows: * $P<0.05$, ** $P<0.01$, *** $P<0.001$ for within group analysis.

BMI, body mass index (kg/m^2); DBP, diastolic blood pressure (mm Hg); HbA1c, glycated haemoglobin (mmol/mol); HDL, high-density lipoprotein (mmol/L); HIIT, high-intensity interval training; hs-CRP, high sensitivity C-reactive protein (mg/L); MICT, moderate-intensity continuous training; RT, resistance training; SBP, systolic blood pressure (mm Hg); TG, triglycerides (mmol/L).

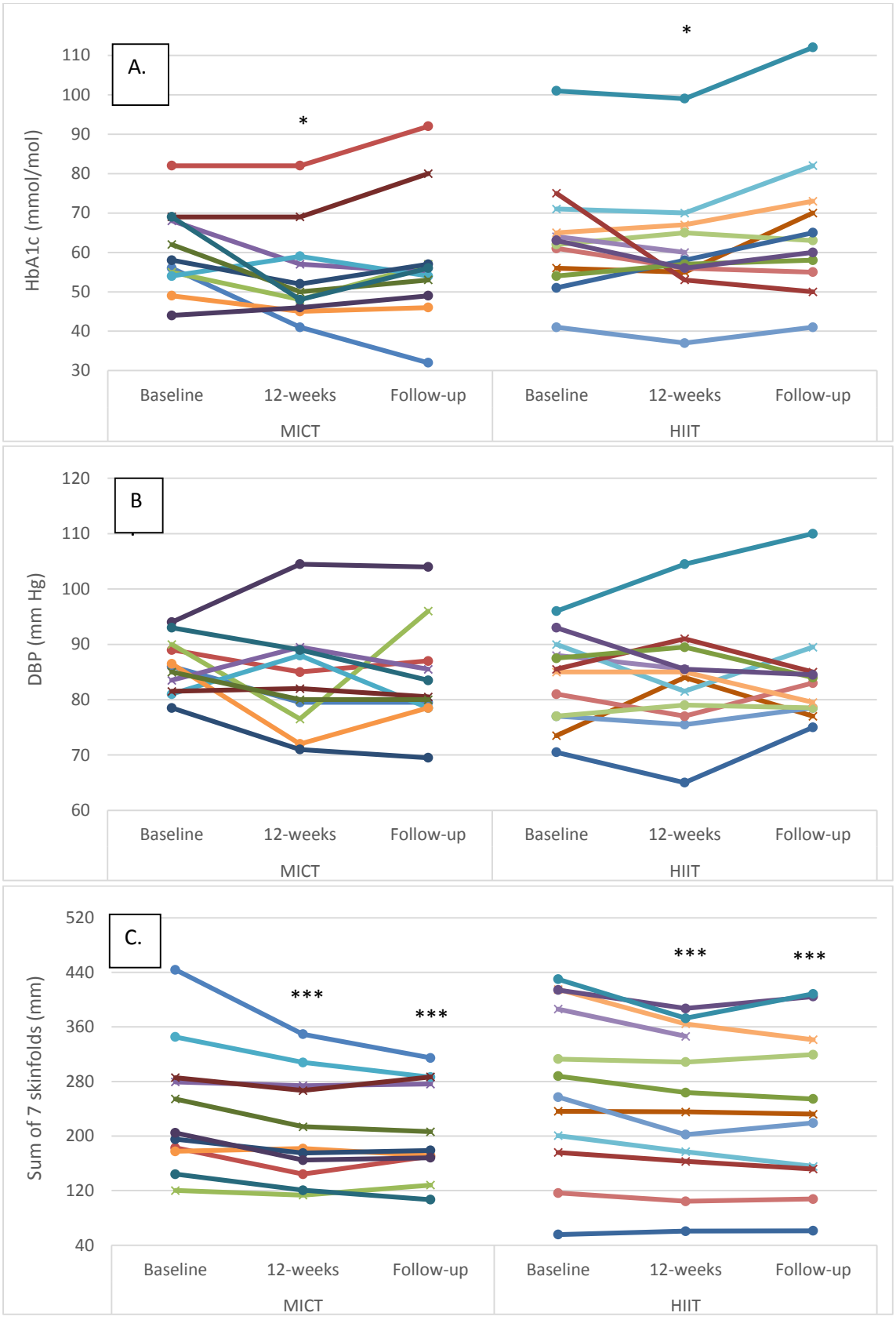

Figure 5.2: Univariate scatterplots for A. glycated haemoglobin (HbA1c), B. diastolic blood pressure (DBP), and C. subcutaneous adiposity (sum of 7 skinfolds) changes during the study period. MICT, moderate-intensity continuous training; HIIT, high-intensity interval training. (o = participants using oral antihyperglycaemic medication, x = participants using exogenous insulin).

min/week) and nutrition changes (total NZANS penalty score) did not significantly impact the findings for subcutaneous adiposity (P = 0.47 and P = 0.67, respectively). Importantly however, the reductions to adiposity were the only macrovascular complication markers still sustained at the 6-month follow-up (Table 5.3).

Table 5.4: Effect of training group, time point (TP), age, diabetes duration, ACE inhibitors, use of non-ACE inhibitors, statin use and those study participants that commenced the study during the extended enrolment period on HbA1c.

HbA1c	β	SE β	Z statistic	P value	Confidence interval
Training group	0.42	7.41	0.06	0.955	-14.11 – 14.95
TP1: Post 12 wk	-6.27	2.47	-2.54	0.011*	-11.11 – -1.44
TP2: Post 6 mo	-3.60	2.54	-1.42	0.156	-8.59 – 1.38
Age	-0.42	0.43	-0.98	0.328	-1.26 – 0.42
T2D duration	0.05	0.54	0.10	0.923	-1.01 – 1.12
ACE	10.49	6.48	1.62	0.105	-2.21 – 23.19
Non-ACE	3.42	7.87	0.44	0.663	-12.00 – 18.84
Statins	0.06	5.75	0.01	0.992	-11.22 – 11.34
Extended	8.13	5.68	1.43	0.152	-3.01 – 19.26
Random-effects Parameters	Estimate	SE			Confidence interval
Subject: Identity Var (Cons)	134.68	42.32			72.76 – 249.33
Var (HbA1c)	33.48	7.12			22.07 – 50.79

Statistical significance is reported as follows: * *P*<0.05, ** *P*<0.01, *** *P*<0.001.
ACE, angiotensin converting enzyme inhibitor; Cons, constant; HbA1c, glycated haemoglobin; mo, months; SE, standard error; TP, time point; T2D, type 2 diabetes mellitus; Var, Variable; wk, weeks.

Of note, T2D duration (P = 0.001) and the extended enrolment period (P = <0.001) did impact the effects of training on DBP. Training modality almost contributed to a significant difference in HDL responses - in favour of HIIT+RT (P = 0.06) (Table 5.3) with SP age (P = 0.02), T2D duration (P = <0.001), non-ACE inhibitors (P = 0.02) and statin therapy (P = 0.003) also contributing to the effects of training on HDL. SP age (P = 0.02) and statin therapy (P < 0.05) were contributing factors to the effects of training on TG and changes to background physical activity and nutrition changes did not significantly impact our findings for TG (P = 0.15 and P = 0.23, respectively).

Table 5.5: Baseline, 12-week intervention and 6-month follow-up comparisons for the microvascular complication markers

	MICT+RT (n=11)	HIIT+RT (n=12)	β	SE β	Z statistic	P	β Confidence interval
HRV - Baseline	1.11 (1.07, 1.15)	1.11 (1.04, 1.21) [a]					
12-week intervention	1.17 (1.08, 1.21)	1.09 (1.06, 1.17) [a]	0.05	0.02	2.30	0.021*	0.01 – 0.08
6-month follow-up	1.12 (1.08, 1.15)	1.11 (1.05, 1.18) [a]	0.01	0.02	0.42	0.671	-0.03 – 0.05
Group*Time interaction			-0.03	0.05	-0.61	0.539	-0.13 – 0.07
MFT (/20) - Baseline	18.0 (17.0, 19.5)	18.0 (14.8, 19.3)					
12-week intervention	19.0 (17.0, 19.5)	17.5 (14.5, 20.0)	1.73	0.90	1.93	0.054	-0.03 – 3.48
6-month follow-up	19.0 (18.0, 20.0)	18.0 (15.0, 20.0) [a]	2.17	0.91	2.38	0.018*	0.38 – 3.96
Group*Time interaction			0.32	1.45	0.22	0.823	-2.51 – 3.16
Balance (TL) - Baseline	982 (776, 1140)	855 (718, 1021)					
12-week intervention	847 (810, 1036)	835 (682, 1041)	-54.34	39.23	-1.39	0.166	-131.23 – 22.56
6-month follow-up	895 (864, 1083)	956 (653, 1157) [a]	-0.70	40.57	-0.02	0.986	-80.21 – 78.80
Group*Time interaction			-127.50	166.04	-0.77	0.443	-452.93 – 197.93
Dorsi (PT) - Baseline	30.9 ± 9.1	26.2 ± 5.9					
12-week intervention	27.2 ± 6.5	23.8 ± 5.5	-3.72	1.95	-1.91	0.056	-7.56 – 0.10
6-month follow-up	27.1 ± 7.0	26.4 ± 7.7 [a]	-3.94	1.97	-2.00	0.046*	-7.80 – -0.07
Group*Time interaction			1.61	2.69	0.60	0.549	-3.66 – 6.88
uACR - Baseline	1.1 (0.6, 2.0)	1.5 (0.5, 19.9)					
12-week intervention	1.0 (0.7, 1.9)	0.9 (0.5, 16.0) [††]	0.06	2.54	0.03	0.980	-4.92 – 5.05
6-month follow-up	0.9 (0.7, 1.3)	0.7 (0.5, 2.6) [††b]	-0.49	2.63	0.03	0.851	-5.64 – 4.65
Group*Time interaction			26.28	9.94	2.64	0.008[††]	6.79 – 45.76

Data are means ± standard deviation, median (interquartile range). [a] n=11, [b] n=10.

Statistical significance is reported as follows: * $P<0.05$, ** $P<0.01$, *** $P<0.001$ for within group analysis; [†] $P<0.05$, [††] $P<0.01$, [†††] $P<0.001$ for group*time interaction

CAN, cardiac autonomic neuropathy; Dorsi, ankle dorsi-flexion; DPN, diabetic peripheral neuropathy; HIIT, high-intensity interval training; HRV, heart rate variability; MFT, 10g monofilament test; MICT, moderate-intensity continuous training; PT, absolute peak torque (Nm); TL, trace length (mm); (/20), possible 20 maximum; uACR, urine albumin: creatinine ratio (mg/mmol).

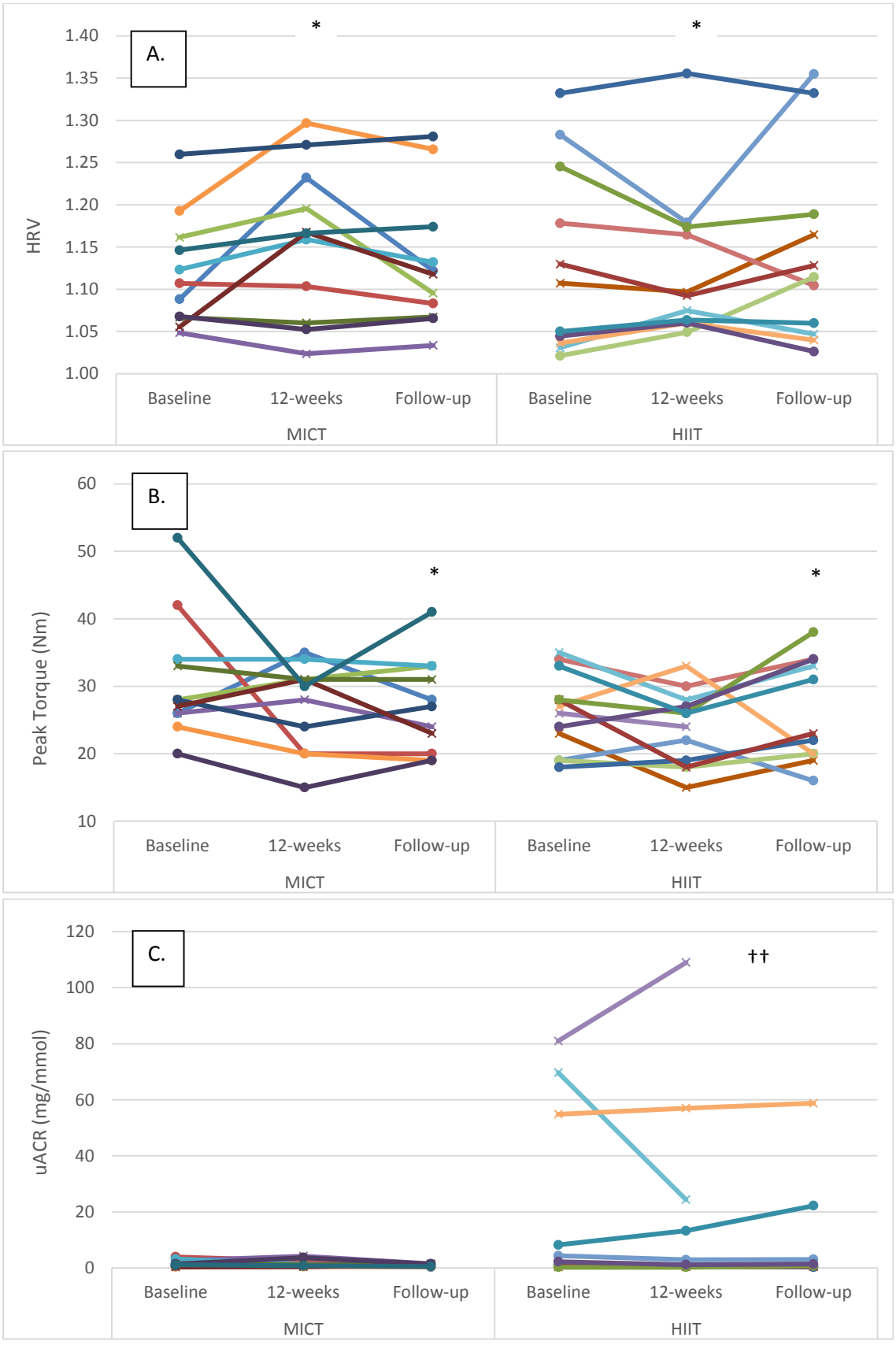

Figure 5.3: Univariate scatterplots for A. heart rate variability (HRV), B. isokinetic peak torque (dorsiflexion) and C. urine albumin-to-creatinine ratio (uACR) changes during the study period. MICT, moderate-intensity continuous training; HIIT, high-intensity interval training. (o = participants using oral antihyperglycaemic medication, x = participants using exogenous insulin).

Microvascular complication markers

There was no difference in HRV with respect to MICT+RT or HIIT+RT, with both training modalities producing comparable improvements after the 12-week supervised intervention ($P = 0.05$). However, these improvements were not significantly sustained at the 6-month follow-up (Table 5.5) (Figure 5.3a). Of note, SP age, T2D duration, hypertension and statin medication usage, or being enrolled during the extended enrolment period did not significantly contribute to the training effect on HRV. Similarly, for the 10g MFT there was no difference in the significant improvements experienced by both training modalities during the supervised intervention. SP age, hypertension and statin medication usage did not significantly contribute to the training effect on 10g MFT. T2D duration ($P = 0.03$) and the extended enrolment period ($P < 0.01$) did impact the training effect, and the improvements in this peripheral neuropathy marker were still sustained at the 6-month follow-up (Table 5.5).

Isokinetic dorsiflexion strength decreased almost significantly ($P = 0.06$), to a comparable extent in both groups, during the supervised intervention. This weakness reached significance ($P < 0.05$) at the follow-up assessment. Of note, SP age ($P = 0.02$), T2D duration ($P < 0.001$), non-ACE inhibitor use ($P < 0.01$) and statin therapy ($P < 0.001$) were contributing factors to the effects of training.

Acute exaggerated responses

During the completion of the intervention phase there were no major acute adverse events, but a number of acute negative exaggerated responses were recorded in both groups. During the introduction stage (both groups performed low volume MICT prior to that session's RT) precautionary respite had to be administered during 13 of the 184 sessions (7.1%). The cycling intensity had to be reduced once due to elevated exercise BP and five times due to SPs experiencing overexertion (RPE >15). Similarly, the cycling duration had to be reduced twice for overexertion while RT was omitted four times due to low BG readings and once for post-exercise (MICT) hypotension.

During the intermediate stage precautionary respite had to be administered during 14 of the 121 MICT sessions (11.6%) and during 17 of the 132 AIT sessions (12.9%). In the MICT group

cycling intensity was reduced seven times for elevated BP, cycling duration and cycling intensity had to be reduced five times and once, respectively, for overexertion (RPE >15), while RT had to be omitted once due to post-exercise hypotension. In the HIIT group cycling intensity had be reduced thrice for elevated BP, thrice for moderate levels of angina, twice for musculoskeletal discomfort (hamstring strain) and nine times for overexertion (RPE ≥17). Additionally, RT had be omitted twice, once for a low BG reading and once for a SP being too 'tired' after the cycling.

During the advanced stage of training, precautionary respite had to be administered during 26 of the 165 MICT sessions (15.8%) and during 19 of the 180 HIIT sessions (10.6%). In the MICT group cycling intensity was reduced five times for elevated BP, cycling duration and cycling intensity had to be reduced seven and eight times, respectively, for overexertion, while RT had to be omitted twice for a SP being too tired after the cycling. In the HIIT group cycling intensity had be reduced four times for elevated BP, thrice for moderate levels of angina and 12 times for overexertion (RPE ≥19). Of note, the respite was similar for both groups during the intermediate stage (P = 0.75) and advanced stage (P = 0.15).

Discussion

The imperative to enhance glycaemic control is compelling as poor control affects the macro and microvascular systems and is a major source of morbidity and mortality in diabetes (Fowler, 2008; Inzucchi et al., 2012). The present study was designed to determine the glucose control (HbA1c) and markers of macro- and microvascular complication changes induced by a 12-week training programme that progressed either to HIIT+RT or MICT+RT. Moreover, the study included a 6-month follow-up phase to monitor the durability of change.

The improvements in aerobic capacity (>3.9 mL/kg/min) of my SPs are on parity with prior reported improvements in VO_2max that ranged from 1.9 mL/kg/min (Ruffino et al., 2017) to 6.1 mL/kg/min (Mitranun et al., 2014) for HIIT. However, unlike my study's MICT+RT improvement of 4.6 mL/kg/min, the prior studies have generally reported lower improvements for MICT ranging from 0.2 mL/kg/min (Ruffino et al., 2017) to 3.3 mL/kg/min (Mitranun et al., 2014).

Whereas three previous studies have, using T2D participants, combined HIIT with RT (Cassidy et al., 2015b; Francois et al., 2017; Praet et al., 2008), only Praet et al. (2008) reported on 1-RM strength and their male-only participants (with clinical signs of neuropathy) experienced significant improvements in upper and lower body strength. Similarly, in my study in which both intervention groups performed the same RT exercises employing the same training variables, significant improvements in the predicted 1-RM strength were achieved in all four isotonic exercises ($P < 0.01$) that were comparable between both groups.

Intervention phase effects

My study resulted in a significant reduction in HbA1c that, following the supervised intervention, was similar for both MICT+RT and HIIT+RT groups (Table 5.3). This finding is akin to seven of the eight prior HIIT and MICT comparison studies that reported similar improvements in HbA1c for both their intervention groups (Backx et al., 2011; Hollekim-Strand et al., 2014; Karstoft et al., 2013; Maillard et al., 2017; Mitranun et al., 2014; Ruffino et al., 2017; Terada et al., 2013). The remaining comparison study (Støa et al., 2017) reported a greater significant change in HbA1c for HIIT, however, the authors did report that the greater effect may have been due to the significantly higher HbA1c level in their HIIT group ($P = 0.02$) at baseline.

***Macrovascular complication markers*.** Beyond the positive effects on HbA1c, aerobic capacity and strength, my study determined the efficacy of MICT+RT and HIIT+RT on the macrovascular complication markers of hypertension, adiposity, dyslipidaemia and inflammation in men with T2D.

In my study there was no interaction effect for either SBP ($P = 0.37$) or DBP ($P = 0.09$) (Table 5.3), and similar to the large individual variations evident in the univariate scatterplot for DBP (Figure 5.2b), SBP changes in my study also had disparate changes within the intervention groups. Although prior studies have reported positive results for HIIT's efficacy on BP (Alvarez et al., 2016; Fex et al., 2015; Francois et al., 2017; Madsen et al., 2015, Mitranun et al., 2014; Parpa et al., 2009; Ruffino et al., 2017), no study has reported superior benefits over MICT. Interestingly, the only other HIIT combined with RT study to report BP change (Praet et al., 2008) also included only male participants with moderate-duration T2D with similar HbA1c as

my SPs (but with lower levels of baseline obesity and all using exogenous insulin). As with my study, these authors reported no significant changes to either SBP or DBP. The specific mechanisms responsible for the lack of improvements in BP in my study are not obvious, but possibly the modest weight loss of the obese participants and the impact of their moderate duration of diabetes along with elevated HbA1c could already be contributing to arterial remodeling and stiffening (Henry et al., 2003). Importantly however, the mean SBP and DBP of both groups did not deteriorate during the nine month study period.

Although both MICT+RT and HIIT+RT resulted in a significant, yet modest, reduction in subcutaneous adiposity the interaction effect in my study was not significant for both waist girth (P = 0.11) and sum of seven skinfolds (P = 0.18). In two prior, slightly longer 16-week studies that compared HIIT to MICT (Karstoft et al., 2013; Maillard et al., 2016), both studies reported statistically superior adiposity benefits for HIIT. However, in the 12-week interventions similar in length to my study (Backx et al., 2011; Hollekim-Strand et al., 2014; Mitranun et al., 2014; Støa et al., 2017; Terada et al., 2013), no changes within the groups were reported as being statistically superior. The importance of these initial, although modest, improvement in adiposity following a 12-week intervention must not be overlooked as a post-hoc analysis of the Look AHEAD study (Look AHEAD Research Group, 2016) reported that the overweight and obese T2D participants in their intensive lifestyle intervention group who lost 10% body weight in the first year of the study, had a 20% lower risk of their study's primary outcome (a composite of death from cardiovascular causes, non-fatal acute MI, non-fatal stroke or admission to hospital for angina). Of note, in their post-hoc analysis, improvements in fitness, by as much as two metabolic equivalents (7.0 mL/kg/min) in the first year of the study, were not associated with decreases in the risk of the primary outcome. Fat loss addresses the root causes of insulin resistance and is an essential goal for all patients with ectopic lipid deposition, insulin resistance and T2D (Samuel and Shulman, 2016; Stokes et al, 2018). Recently, in a 4-week study of the effects of MICT and HIIT on non-alcoholic fatty liver disease (in obese adults without T2D) significant reductions in intrahepatic liver content were achieved with only small non-significant changes to body mass (Winn et al., 2018). As weight loss needs to be significantly higher (closer to 20% of an individual's weight [Lim et al., 2011]) in people living with T2D wanting to achieve remission, strategies to improve the magnitude of sustained weight loss are needed.

My study demonstrated that fat loss was achieved and maintained in both groups following a 12-week supervised intervention.

In my study both exercise groups, presenting with the characteristic dyslipidaemia of T2D at baseline (consisting of elevated TG [≥ 1.7 mmol/L] and reduced HDL [≤ 1.3 mmol/L] concentrations [Fowler, 2008; Schofield, Liu, Rao-Balakrishna, Malik & Soran, 2016]), experienced similar, almost significant improvements in TG (P = 0.055) (Table 5.3). Whereas Alvarez et al. (2016) and Mitranun et al. (2014) were the only HIIT studies using T2D participants to report significant improvements in HDL, the interaction effect between my study groups was almost significant (P = 0.057) in support of HIIT+RT for improving HDL concentrations. However, SP age, T2D duration and the use of non-ACE inhibitors and statin medication influenced our finding. Importantly, the lipid profile of both groups were maintained during the nine month study period.

Akin to a recent review on exercise and inflammatory markers in people with T2D (Melo et al., 2017), the effectiveness of my study's interventions to modify systemic levels of inflammatory markers (e.g., hs-CRP), remains unclear. In parity with my study, the only two studies (Hollekim-Strand et al., 2014; Praet et al., 2008) reporting hs-CRP changes through HIIT in T2D also used participants with normal levels of hs-CRP (<5 mg/L) at baseline. As inflammatory processes are involved in the pathogenesis of diabetes, and hyperglycaemia itself contributes to the generation of pro-inflammatory factors (Goldberg, 2009; Melo et al., 2017; Patil & Ganu, 2014), more studies are needed, particularly using participants with elevated hs-CRP, to determine the efficacy of various exercise modalities on systemic inflammation.

***Microvascular complication markers*.** This present study was the first to report on the efficacy of MICT+RT and HIIT+RT on microvascular complication markers in men with T2D. Although associated with high morbidity and mortality rates, in its early stages CAN may be completely asymptomatic but can be detected by a decreased HRV with deep breathing (Boulton et al., 2005). Reduction in HRV is the earliest indicator of CAN (Maser & Lenhard, 2005), with the Sundkvist, Almér and Lilja (1979) study being one of the first to report that a reduced variation in the expiration: inspiration ratio of 1.10 (i.e., only a 10% variation) was indicative of autonomic dysfunction. In this early study, people without diabetes (control group), people with diabetes,

but without sensory neuropathy, and those with both diabetes and sensory neuropathy had waning ratios of 1.33, 1.27 and 1.16, respectively. In my study both groups significantly improved their HRV during the intervention period (Table 5.5). The DPN group of the Morrison, Colberg, Parson and Vinik (2014) study in which their participants had similar baseline HRV (1.13 ± 0.20) to my study, and performed MICT (alone) thrice weekly for 12 weeks, reported non-significant improvements in HRV and HbA1c. Parpa et al. (2009) did not report on HbA1c, but their participants experienced a significant improvement in HRV following a HIIT pilot study. Restoration of autonomic balance may have clinical importance in preventing adverse cardiovascular events in people with T2D, a concept supported by Vinik et al. (2013), who reported that autonomic dysfunction was associated with cardiovascular risk and sudden death and that increased physical activity positively impacts this autonomic imbalance.

DPN is the leading cause of non-traumatic lower-limb amputations (IDF, 2015) and both training groups almost improved significantly (P = 0.054) in the 10g monofilament test, suggesting a possible increase in peripheral sensation. However, concomitantly, both groups experienced an almost significant (P = 0.056) counter-intuitive reduction in isokinetic dorsiflexion strength and neither group experienced any change in postural stability (Table 5.5). T2D duration almost had an influential impact (P = 0.051) on the 10g monofilament findings. Furthermore, SP age, T2D duration and the use of non-ACE inhibitor and statin medications had a significant impact on my findings for dorsiflexion strength. Of note, my intervention intentionally excluded proprioception and lower limb RT in an attempt to limit confounding factors on the DPN findings. Hence, future studies, incorporating such balance and strength exercises are warranted to determine their impact on DPN.

No previous HIIT study has reported on nephropathy measures in participants with T2D. While training modality reportedly contributed to a significant difference in uACR responses, it must be noted that the HIIT group was the only group that contained SPs with elevated readings at baseline (Figure 5.3c) and, as such, this finding must be interpreted with caution.

Although the scope of microvascular complications seems vast, not all cell populations are prone to complications with those affected being limited to vascular endothelia, renal mesangial and proximal tubular cells, glomerular epithelial cells, neurons and glial cells. In these tissues,

facilitated diffusion of glucose occurs in an insulin-independent manner via the glucose transporter 1 (GLUT1) with the resultant intracellular hyperglycaemia possibly a key initiating factor in the development of diabetic complications (Russell & Cooper, 2015). Even though my study did not directly measure these complex mechanisms, the enhanced reduction in overall systemic hyperglycaemia, in which the frequent metabolic demands within the skeletal muscles possibly enhanced glucose transporter 4 (GLUT4) expression, potentially deceased the diffusion of glucose via GLUT1 into the microvascular complication prone cells, thereby resulting in the favourable effects in HRV and the 10g monofilament test. Further research is however warranted to elucidate the precise mechanism affected by various modes of exercise.

***Medication changes*.** As medication, along with habitual physical activity and nutrition changes, confound exercise's efficacy on HbA1c, it is worthwhile to highlight the medication changes that occurred during the study. During the 12-week intervention, both MICT+RT and HIIT+RT groups had changes to medication usage with the majority being antihyperglycaemic decreases. MICT+RT had one SP no longer on any antihyperglycaemic medication (partial remission), two SPs made minor reductions (~2.0 units) to insulin, one SP took 50% less metformin and sulfonylurea and one SP reduced his BP medication. Similarly, with HIIT+RT all five SPs on insulin made reductions (~4.2 units), four SPs each took one less metformin with a meal, one SP stopped taking sulfonylureas while one SP increased his sulfonylurea dose. These reductions in medication usage (including insulin) experienced in both training groups are an important finding of my study and, although these reductions confound the comparison of MICT+RT with HIIT+RT, they demonstrate the benefit of regular structured exercise.

Training variables. Although my study was the first RCT to determine the efficacy of modalities that combined RT with either HIIT or MICT, in order to minimise confounding factors between the HIIT and MICT group, the RT variables in both groups were equivalent. Notwithstanding the RT component, my study was similar to prior studies comparing HIIT and MICT in people with T2D with regards to the 12-week intervention duration (Backx et al., 2011; Hollekim-Strand et al., 2014; Mitranun et al., 2014; Støa et al., 2017) and the frequency of three HIIT sessions per week (Backx et al., 2011; Hollekim-Strand et al., 2014; Mitranun et al., 2014; Ruffino et al., 2017; Støa et al., 2017). Although the diverse application of the HIIT variables (i.e., intensity, duration and number of bouts) across all studies limit direct comparisons, my study's HIIT

variables were comparable. However, apart from the 10 min SIT session of Ruffino et al. (2017) incorporating two 20-sec sprints, and the 20 min SIT session of Maillard et al. (2016) incorporating sixty 8-sec sprints, my study's progressed 28 min sessions were shorter than the progressed AIT sessions that were either 40 min (Hollekim-Strand et al., 2014; Mitranun et al., 2014), 50 min (Støa et al., 2017) or 60 min (Backx et al., 2011; Karstoft et al., 2013; Terada et al., 2013) in duration. The durations of the AIT sessions of prior studies are substantially longer than my study and may contribute to the findings reported in these HIIT studies. However, with regards to MICT, only Maillard et al. (2016) reported that MICT was conducted exclusively on a cycle-ergometer and while Terada et al. (2013) reported alternating between cycle-ergometry and treadmill walking, the remaining studies either did not report a specific MICT mode (Backx et al., 2011; Hollekim-Strand et al., 2014) or reported MICT being conducted via a walking mode (Karstoft et al., 2013; Mitranun et al., 2014; Ruffino et al., 2017; Støa et al., 2017). Notably in my study, SPs reported a mean RPE during the progressed MICT of 13.6 ± 0.9, whereas in the walking MICT group of Ruffino et al. (2017), the only comparative study to report RPE, their participants reported their RPE as 12 ± 1. Of note, as per my study's design, the mean RPE of the HIIT group during the progressed stage (15.2 ± 1.2) was significantly higher than the MICT group ($P = 0.003$). Interestingly, the SPs in the HIIT group reported a higher RPE ($P = 0.009$) following the twelve 1-min bout variation (16.0 ± 1.5) compared to the eight 30-sec higher intensity bouts (14.4 ± 1.2).

Physiologically, during exercise, the coordinated increases in skeletal muscle blood flow, capillary recruitment and GLUT4 translocation (from their intracellular sites to the sarcolemma and T-tubules) and regulation of AMP-activated protein kinase and liver kinase B1 (Stanford & Goodyear, 2014), enhance glucose uptake and oxidation (Richter & Hargreaves, 2013). Moreover, the latest position statement by the ADA (Colberg et al., 2016) reports that the increases in insulin sensitivity and improved glycaemic control, for both MICT and HIIT, are related to the increased muscle capillary density and increased skeletal muscle oxidative function achieved through the improvements in aerobic capacity. Additionally, regular exercise training improves muscle capillary density, lipid metabolism (Colberg et al., 2016), mitochondrial function, increases mitochondrial biogenesis and increases the expression of GLUT4 (Stanford & Goodyear, 2014). However, total training volume per se, contributes to the training-induced glycaemic benefits in participants with T2D (Laughlin, 2016; Umpierre et al., 2013).

Skeletal muscle is a highly dynamic tissue which is composed of individual muscle fibres with a dynamic range of chemical, biomechanical and physiological properties. The presence of diverse fibre types with distinct ranges of adaptability reflects muscle plasticity to various metabolic and functional demands (Duan, Li, Tan, Yao & Yin, 2017; Qaisar, Bhaskaran, & van Remmen, 2016). In people with T2D there is an increased proportion of fast glycolytic fibres (type IIb) and a reduced proportion of slow oxidative fibres (type I) and is the reason people with T2D present with a diminished oxidative capacity (Oberbach et al., 2006). Whereas the amount of respite administered for overexertion in all study phases of my present study may be due to the indirect estimation of eWLmax, exercise intolerance of this study sample may also have been a factor. Typically, in healthy individuals during MICT, type I fibres are predominantly recruited and during more intense training (i.e., RT and HIIT) the recruitment is predominantly type II fibres. Recent studies have examined the alterations in muscle fibre proportions following medium-term training using MICT, HIIT and/or RT, but such interventions have been conducted in non-diabetic populations (Kazior et al., 2016; MacInnis et al., 2016; Stuart et al., 2017). Although Roberts et al. (2017) reported that exercise-stimulated skeletal muscle fibre-type alters from type IIb to type I and type IIa (intermediate fibres), without further study the precise effect of MICT, HIIT and/or RT on muscle fibre recruitment, and subsequent adaptation, in people living with T2D will remain speculative.

Inter-individual variability. For each dependent variable there were unique SP responses within each group (Figures 5.2 & 5.3). Although the underlying molecular pathomechanics for sub-optimal responsiveness following various interventions are not yet known, a possible explanation for such individuality in responsiveness could, in part, be genetic susceptibility (Stephens & Sparks, 2015; Böhm, Weigert, Staiger & Häring, 2016), the complex pathology of the disease itself (Russell & Cooper, 2015), pre-training muscle fibre characteristics (Stuart et al., 2017) and/or the side effects of the multiple medications, including insulin, statins, antihypertensive and antidepressant agents (Larsen, Skaaby, Helge & Dela, 2015). However, of note, after the preparatory phases of the study design, the progressed sessions were only administered for five weeks and, as such, the responsiveness within SPs may have been limited and future studies could consider longer intervention durations (e.g., 18 weeks). In addition, limiting the combined sessions to three 1-hr sessions per week (as common in many commercial CEP settings) may have impacted SP responsiveness as both the CV and RT

component were limited to ~30-min and ~20-min, respectively. Increasing training frequency and/or training time for either, or both, training components may result in enhanced SP responsiveness. Anecdotally, and encouragingly, there seemed to be no visual differences in overall changes for the SPs who were exogenous insulin users compared to those only on oral antihyperglycaemic medications (Figures 5.2 & 5.3). Additionally, inspection of individual SP data indicated that unresponsiveness was not consistent across variables. For example, the four SPs in the MICT+RT group (and four SPs in HIIT+RT) that either had no change, or deteriorated in HbA1c, all achieved improvements in subcutaneous adiposity, but obtained mixed results for DBP changes. Furthermore**,** of the four SPs in the MICT+RT group that experienced limited HbA1c change, each achieved improvements in other microvascular complication markers (one for postural stability, one for HRV and two for uACR). However, of the seven SPs in the HIIT+RT group that either had no change, or deteriorated in HbA1c, five remained unresponsive or deteriorated further in the microvascular complication markers. However, it must be noted that within such a study sample (i.e., morbidly obese men with moderate duration T2D), the maintenance of a function/marker can be considered as a favourable intervention outcome and should not be purely interpreted as 'unresponsive'.

Six month follow-up assessment

In comparison to baseline, both groups significantly improved their habitual physical activity during the 6-month follow-up phase (Table 5.2). During the follow-up assessment SPs were scored on their adherence to regularly maintaining their training during the 6-month phase. While the MICT+RT adherence score was not significantly different to the HIIT+RT adherence score (P = 0.19), the MICT+RT group's mean score was 8.3 ± 3.7 (with one SP [9.1%] not continuing with any further training) and the HIIT+RT group's score 5.7 ± 5.4 (with five SPs [45.5%] not continuing with any further training). Nevertheless, both groups maintained their VO_2max improvements achieved during the 12-week intervention. Although further study incorporating more regular and objective measures, which limit the impact of affecting external validity, are warranted, the medium-term durability of improved fitness is noteworthy in such a study sample.

During the 6-month follow-up, while both groups were able to maintain their overall habitual nutrition changes, both groups failed to maintain their refined carbohydrate score (Table 5.2). Additionally, both groups had changes to antihyperglycaemic medication usage. To elaborate, the MICT+RT group had one SP increase his daily insulin by 5.0 units, however two SPs decreased by 4.0 and 2.0 units, respectively. Further, one MICT+RT SP was placed on Metformin and another had his sulfonylurea (Gliclazide) increased, but, of note, the MICT+RT SP who achieved partial remission remained as such. However, in the HIIT+RT group one SP was placed on Metformin and four SPs using insulin had their daily dosage increased by an average of 9.5 units.

Importantly, at follow-up both MICT+RT and HIIT+RT groups significantly maintained the adiposity improvements of waist girth (Table 5.3) and subcutaneous adiposity (Figure 5.2c). However, both groups failed to experience significant durability in their intervention achievements of improved HbA1c and HRV. On completion of the follow-up phase, both BMI and 10g monofilament testing in both groups had reached significant change beyond baseline (Table 5.3 & 5.5, respectively), though BP, TG, HDL, hs-CRP and postural stability remained indifferent to baseline values. The reduction in uACR was further compounded by the withdrawal of the SP diagnosed with congestive heart failure and a urine result that was not returned from the local hospital (both SPs having elevated concentrations at baseline).

Comparisons of effect durability to prior HIIT studies in people with T2D are limited as the only study to report a follow-up analysis was the pilot study by Hollekim-Strand et al. (2014). At a 9-month follow-up (successive to a 12-week structured HIIT but unsupervised MICT intervention) the primary finding related to diastolic function (early diastolic tissue velocity) maintained an improvement for HIIT, but for MICT regressed during their follow-up period. Their interventions' initial small, yet significant, waist circumference improvements were retained for HIIT but diminished for MICT, and while the significant improvement in VO_2peak for HIIT was sustained, the improvement in HbA1c for HIIT was not sustained (while the follow-up measure of HbA1c for MICT was not reported).

As my study only determined the short- and medium-term efficacy of either MICT+RT or HIIT+RT on markers of diabetic complications and not on hard clinical end-points (e.g.,

myocardial infarction, lower limb amputations), studies with substantially longer follow-up periods are required to compare the impact of such interventions.

Summary

Both training modalities significantly improved HbA1c, subcutaneous adiposity, HRV and aerobic capacity during the 12-week intervention in the study's middle-aged obese men with moderate-duration T2D. Furthermore, adiposity and aerobic capacity were significantly maintained in both groups at the 6-month follow-up. As such, combined CV and RT training that progresses the CV component to either MICT or HIIT provides men living with T2D comparable glycaemic, macro- and microvascular complication marker benefits following a supervised exercise intervention.

Limitations. Both exercise groups had participants being prescribed multiple medications including metformin, beta-blockers and statins. For example, the HIIT+RT group had nine SPs (75%) and the MICT+RT group five SPs (46%) on statin medication. Until well-designed clinical trials can determine the effect of statin therapy on muscle damage and reduced aerobic fitness benefits (Panza, Taylor & Thompson, 2016), the full extent to which statins, and other common medications, impact cardiometabolic responses in people living with T2D particularly, will be unknown. All SPs underwent pre-exercise screening thereby limiting the inference of responses to the wider T2D population. During the nine month study period, general practitioners' care for each SP resulted in antihyperglycaemic medication modifications in both groups. Although the changes in medication and habitual diet and physical activity were monitored, the extent to which these, alone or in combination, impacted my study's finding remains unclear. BP was measured manually, so the mean reading of four measures, over two non-consecutive days, was recorded for analysis in order to enhance reliability. During my 12-week progressive intervention, the advanced stage was only applied for five weeks which may have limited the impact of the training stimuli. As each participant only experienced one type of CV modality, the PACES score can only be interpreted as affinity to exercise in general, and not as a preference to any one particular modality. In my study no blinding was possible as I conducted all the assessments (except for the blood samples), supervised all the intervention sessions and captured and interpreted the data. In addition, due to nature of MICT and HIIT sessions, both

participants and assisting CEPs, were aware of the intervention modality. Although there was no attrition during the intervention phase, during the follow-up phase the one SP with pre-existing atrial fibrillation was diagnosed with congestive heart failure and withdrew from the study. Quantitative monitoring of SP adherence and compliance of training during the 6-month independent training phase was intentionally omitted so as to enhance external validity, but non-invasive monitoring technologies are required to observe, more quantitatively and qualitatively, the adoption of physical activity by SPs after the introduction of an exercise intervention.

Strengths. My study included men more advanced in their T2D pathology (as indicated by their moderate-duration T2D, higher degree of obesity and medication usage) than those involved in previous studies. My study provided a head-to-head comparison of a HIIT+RT modality to a modality recommended by multiple guidelines (i.e., MICT+RT) proposed by several expert groups (Bertoluci et al., 2014; Colberg et al., 2016). The level of supervision by qualified CEPs to both groups throughout the intervention stages allowed for intensity goals to be safely met within each session. Employing the method of minimisation after both enrolment periods (Figure 5.1) assisted in enhancing internal validity and, notwithstanding the low sample size, the results of our study are relevant to all CEPs working with men living with T2D in commercial settings, as such patients typically present with co-morbidities and multiple prescribed medications. My study documented the exaggerated responses and precautionary respite employed. Data was provided at both group and SP level leading to a warning against classifying individuals simply as a 'non-responder' to exercise without being specific about the nature of the specific response of interest. Additionally, my study included a 6-month follow-up assessment essential to establishing the potential for the sustained benefits of exercise.

***Future research*.** Additional studies, using adequately powered designs incorporating increased training variables (i.e., intervention duration, training frequency and/or session length), are required to determine the associations between baseline values and changes in diabetic complications and to determine whether magnitude of change in general health and fitness parameters (VO_2max, strength and adiposity) are related to specific macro- and microvascular function outcomes.

Conclusions

My study hypothesis of HIIT+RT affecting greater HbA1c reductions than MICT+RT in men was rejected. Beyond improvements in aerobic capacity, both training modalities elicited similar benefits on HbA1c, adiposity and HRV in men living with T2D. In addition, during the intervention, SPs in both MICT+RT and HIIT+RT experienced favourable reductions to their hyperglycaemic medication use. Furthermore, my study reported the inter-individual variability of change evident in both groups, the exaggerated acute physiological responses that occurred during both interventions as well as the incidence of precautionary respite afforded in such a study sample. Health practitioners have a greater understanding of the impact of two exercise modalities on diabetic complication markers in men with moderate duration T2D. In order to reduce hyperglycaemia, and prevent further deterioration of macro- and microvascular function (in the short- and medium-term), future strategies that integrate the adoption and maintenance of physical activity as a cornerstone in the optimal treatment of T2M for men should include either structured MICT, or HIIT, combined with RT.

CHAPTER SIX

Study Conclusion

Increased physical activity, along with changes to nutrition habits, and the progressive use of medications have long been touted as cornerstones in the management of T2D. However, the fight against T2D and its insidious complications is being lost with one adult death every six seconds across the world being due to diabetic complications (IDF, 2015). Notwithstanding the potential benefits of sound nutrition and regularly-reviewed medication, my thesis focussed on structured exercise typically advocated by CEPs (namely combined training). The overarching aim of my study was to conduct a cohesive investigation to compare the effects of MICT+RT and HIIT+RT in a group of men living with T2D.

This thesis draws from, and adds knowledge to, the limited body of work regarding HIIT and its efficacy on overall health in people already living with T2D.

Research summary

This thesis makes a substantial contribution to the field of clinical exercise physiology and the health of men with T2D through, firstly, a review of all the HIIT studies conducted on people with T2D, and then, a cohesive quantitative study on the acute effects and then the, short- and medium-term diabetic health benefits in a group of men with T2D.

The narrative review in Chapter Three included a table that presented a concise summary of the central characteristic of HIIT used in all the studies (beyond the limited RCT studies) in people with T2D. Additionally, five separate tables reported the efficacy of the various HIIT interventions, and their comparative groups, for metabolic control, body composition, aerobic capacity (VO_2max), BP and lipidaemia. However, the heterogeneity of participants (broad ranges in age, T2D duration, level of glycaemic control, diabetic complication presence and medication usage), coupled with substantial variations in HIIT application (session length and intervention duration, type of HIIT protocol used, inclusion of MICT sessions, adherence rates

and extent of supervision provided) limited my ability to make direct comparisons among studies. Moreover, the low numbers of participants in each of the studies highlight the low numbers of participants with T2D who initially volunteer for exercise interventions, the high logistic requirements for supervised HIIT interventions and/or the comorbidities associated with T2D that exclude many potential volunteers.

Nevertheless, all 14 studies included in my review (as well as the four studies since my publication) demonstrated that HIIT was effective in adults with T2D for improving multiple cardiometabolic risk factors and, regardless of the precise parameters employed, could be considered a suitable option for pursuing such improvements in middle-aged/elderly individuals with T2D who present with reasonably controlled hyperglycaemia. Although no study reported mean baseline BMI values greater than 35.0 kg/m^2, modest improvements in body composition were achieved using medium-term HIIT. Additionally, HIIT was beneficial for aerobic fitness and seemed to positively impact hypertension and lipidaemia. However, in comparison to MICT, there was no evidence of HIIT being significantly superior for glycaemic control, BP, lipidaemia and body composition improvements, except for one study, employing a 60-min intervention five days a week for 16 weeks, reporting a greater reduction in body mass (Karstoft et al., 2013). However, my review only included full-text English articles, and the number of participants included in the studies were understandably small, thus contributing to diminished statistical power within the individual studies. My review concluded by highlighting that until further RCTs have been conducted, knowing whether HIIT was of more benefit when compared to MICT in people with T2D would remain unclear. Hence, the requirement of a cohesive RCT to add to the limited body of work was established.

Chapter Four presented a detailed profile inclusive of health history, medication usage and habitual PA and nutrition within two groups of middle-aged T2D men about to commence exercise interventions in a real-world commercial setting. The reported baseline data of these groups will be of comparative interest to CEPs working in research and/or commercial environments. Additionally, Chapter Four reported the methodology for the baseline (pre-exercsie screening) assessments and diabetic complications markers emulating the process of a typical patient assessment by a CEP.

Quantitatively recording habitual PA and nutrition, not only provided new and valuable information in themselves that can assist to guide CEPs in identifying areas where possible lifestyle change may be required. To this end, a component of my study included the use of a novel scoring system for the NZANS which results in obtaining individual objective nutrition habit 'scores' for adults. This scoring system is not limited to CEP use and can be used by all healthcare professionals. As such, the use of such a questionnaire is encouraged, particularly prior to pre-exercise screening.

The objective of Chapter Four was however concerned with comparing the acute physiological responses of HR, BP and BG between the MICT+RT and HIIT+RT modalities in men living with T2D. In addition, the acute exaggerated responses of the participants and the precautionary respite provided to my T2D participants undertaking such sessions were documented so that CEPs wanting to progress their patients' programmes have an enhanced understanding of outcomes associated with introducing either an advanced MICT or HIIT session.

In Chapter Four the methodologies for participant randomisation, intervention exercise prescription, supervision (including exaggerated responses), and the details for the acute physiological response sessions were provided. The key finding of Chapter Four was that even though SPs had completed a preparatory training phase towards their respective modality, both "unaccustomed" HIIT trialled for the first time and a progressed MICT session elicited similar acute physiological responses in men with T2D. Furthermore, for the first time in people with T2D, the amount of the precautionary respite required following a MICT and HIIT session were detailed. The reason for the noteworthy amount of precautionary respite in my study could be due to the characteristics of the SPs. Being sedentary, presenting with class II obesity and other complications of T2D, and using a combination of medications could have affected exercise ability. Thus, although aligned to previously reported protocols, supervision was required for such a study sample even though a 7-week preparatory period was completed prior to the APR session. Of note, pre-study screening limits the inference of acute exaggerated responses to the wider T2D population. Nonetheless, as the groups used in this study comprised middle-aged, males and the study was conducted in a real-world setting, the findings potentially have strong external validity and clinical relevance in as much that for men with T2D, as in this study, MICT+RT and HIIT+RT elicited similar acute HR, BP and BG responses, with acute

exaggerated responses occurring during the CV component of both groups, and to a lesser degree, in the 90 minutes following the sessions. Furthermore, individual responses during both the MICT and HIIT modalities were not consistent. These findings will assist in helping healthcare professionals enhance their management of individuals living with T2D, via improved knowledge of the individual physiological responses and precautionary respite requirements when introducing an intense exercise session, such as advanced MICT+RT or HIIT+RT to obese middle-aged men living with T2D for a moderate duration.

Chapter Five addressed the central research question of my study which was to determine whether HIIT or MICT (both combined with RT) would be of greater benefit to men with T2D. Concurrently within Chapter Five reporting the efficacy of the 12-week interventions on cardiometabolic control (inclusive of both glucose control and macrovascular complication markers), the chapter also reported the efficacy on microvascular complication markers. In addition, the chapter reported the durability of effects following a medium-term 6-month follow-up period. In Chapter Five the methodologies for the follow-up phase were presented.

As a product of my randomisation both groups were comparable at baseline across all cardiometabolic and microvascular complications markers as well as for health history, medication usage, exercise enjoyment, fitness, and habitual PA and nutrition. During the intervention and follow-up there were reported within-group changes for the cornerstones of medication usage, fitness, and habitual PA and nutrition, but changes were similar in both the MICT+RT and HIIT+RT groups, and analysis demonstrated that both groups were similar in these cornerstone variables at completion of the short-term 12-week intervention and the medium-term 6-month follow-up.

Through addressing the overarching research question, '**Do structured interventions in middle-aged men with T2D that progress to HIIT, combined with RT, produce more pronounced acute physiological responses as well as greater short- and medium-term effects on cardiometabolic and microvascular complication markers, than combined MICT training?**, the changes within the cardiometabolic and microvascular complication markers, for both exercise groups, were not statistically different after the short-and medium-term. The research did not support my hypothesis that the inclusion of a progressed HIIT

component would elicit greater benefits than a progressed MICT component in men living with T2D. As such, it does not appear that the inclusion of the cardiovascular HIIT component is superior.

In my study the SPs were more advanvced in their T2D pathology (as indicated by their moderate-duration T2D, higher degree of obesity and medication usage) than those involved in previous studies making the finding relevant to a broader range of patients. Furthermore, the follow-up data is esential for establishing the potential for the sustained benefits of exercsie. A summary of the resultant benefits are presented in Table 6.1,

Table 6.1: Summary of the improvements ($P < 0.05$) experienced by the T2D male participants on completion of the short-term intervention and medium-term follow-up analyses

	12-week Intervention	6-month Follow-up
Habitual lifestyle changes		
Moderate METmin/week		< 0.01
Weekly sitting hours		
Refined carbohydrate score	0.03	
Total NZANS score	< 0.01	0.03
PACES	< 0.01	0.04
Cardiometabolic complication markers		
Aerobic capacity (VO_2max)	< 0.001	< 0.001
Glycated haemoglobin	0.01	
Systolic blood pressure		
Diastolic blood pressure		
Body mass index		< 0.01
Subcutaneous adiposity	< 0.001	< 0.001
High-density lipoproteins		
Triglycerides		
Microvascular complication markers		
Heart rate variability	0.02	
10g monofilament test		0.02
Postural stability		
Ankle strength (dorsi-flexion)		0.05[a]

[a] Restoration of function lost during the 12-week intervention.
HIIT, high-intensity interval training; MET, metabolic equivalent; MICT, moderate-intensity continuous training; NZANS, New Zealand Adult Nutrition Score; PACES, Physical Activity Enjoyment Score; RT, resistance training.

Furthermore, the findings of my study were that such men with moderate T2D had idiosyncratic responses to the exercise interventions and precautionary respite was required from the commencement of the study, through the introductory and intermediate phases and into the advanced progressed phase. Of note, such respite was required to a comparable extent in both groups.

Taken together ,the exercise-induced improvements in T2D were not necessarily reflected in the common marker of glycated haemoglobin. As such, in a clinical context, it means that exercise should not be dismissed purely because there is no statistaically significant improvement in glucose control, but more importantly in a research context, it demonstrates the need to augment glucocentric outcome measures with others related to the pathophysiology of T2D.

Study learnings

During this study I got to consider that T2D education should not be glucocentric even though the initial insult on diabetic complications may be triggered by hyperglycaemia. So, in addition to glucose control monitoring, people living with T2D should be made aware of the broader markers of “diabetic control” in order to develop a comprehensive understanding of their condition and the rate of progression/reversal of the macro- and microvascular complication risk. Analogous to broadening the focus of attention from only the iceberg, after it has stuck the boat, to include interpretation of the damage (or repair) being done to both the “structures” and “instrumentation” of the boat.

This study has taught me that the completion a supervised 12-week intervention is not an isolated remedy that immediately reduces obesity and sets all people with T2D into remission, but rather that the 12-week period should be the platform to instil confidence and to assist in putting people with T2D on the right path (with the required self-management skills) to, over time, improve their condition. Moreover, the study highlighted the challenges with reversing the complication markers associated with T2D (e.g., significantly reducing body weight, blood pressure, hyperlipidaemia while improving lower limb function in such a study sample) and that to achieve full remission the extent of weight loss, for example, is likely to be much greater than conventionally advised and more aggressive, holistic approaches may be warranted.

Future research

The findings of my study gives rise to a need for three major investigations. Firstly, determining whether the adoption of regular exercise and the durability of effects are sustained for a long-term period following such structured interventions. Directly associated with the long-term

benefits would be the financial impact of the training intervention on the local healthcare system. Secondly, to determine the optimal comprehensive, multi-faceted intervention, future research must include investigations that alongside structured training, analyse the effects of alternate nutritional advice (i.e., significantly reducing caloric intake and advising alternate macronutritient components) and holistic educational resources (e.g., diabetes related pathophysiology, medication and stress management information) on both a broader array of diabetic complication markers and clinical hard-endpoints (e.g., the development of end-stage disease). Thirdly, to prevent people progressing towards T2D in the first instance, research needs to be conducted on the impact of exercise-professional monitored exercise interventions that progress towards advanced forms of structured training in individuals identified as being at-risk of developing T2D.

Conclusion

In a group of middle-aged obese men living with T2D for a moderate duration, the completion of a structured 12-week intervention combining RT with either MICT or HIIT indicated that HIIT+RT is not superior to MICT+RT for improving fitness, HbA1c, subcutaneous adiposity, HRV and distal foot sensation over the short and/or medium term. This indicates that the current guidelines are efficacious and exercise professionals can be confident including MICT+RT into their intervention strategies.

This study was the first RCT incorporating HIIT and MICT (both combined with RT) in people with T2D and was the first RCT to report the efficacy of HIIT+RT and MICT+RT on microvascular complications as well as being the first RCT to report on the medium-term durability of exercise intensity on diabetic control. In addition, this study reported the precautionary respite required during the interventions and reported that responsiveness was not consistent across individuals or variables.

Type 2 diabetes mellitus is a progressive and life-threatening disease that requires a concerted effort by all healthcare professionals to provide the individual with the most appropriate strategies to delay the progress of insidious complications. Clinical exercise physiology is a new profession in NZ and CEPs strive to ensure that optimal exercise interventions are prescribed to

their clients. Knowing the practical applications and the associated benefits achievable (at both the group and the individual participant level) with implementing MICT +RT and HIIT+RT interventions, coupled with an awareness of precautionary respite requirements, CEPs can now implement such sessions with greater confidence and safety to their clients presenting with similar characteristics as to the participants of my study.

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Appendices

Appendix A: Ethics approval

AUT UNIVERSITY
TE WĀNANGA ARONUI O TAMAKI MAKAU RAU

AUTEC SECRETARIAT

15 December 2014

Nigel Harris
Faculty of Health and Environmental Sciences

Dear Nigel

Re Ethics Application: **14/396 Exercise intensity and diabetic control.**

Thank you for providing evidence as requested, which satisfies the points raised by the Auckland University of Technology Ethics Committee (AUTEC).

Your ethics application has been approved for three years until 15 December 2017.

As part of the ethics approval process, you are required to submit the following to AUTEC:

- A brief annual progress report using form EA2, which is available online through http://www.aut.ac.nz/researchethics. When necessary this form may also be used to request an extension of the approval at least one month prior to its expiry on 15 December 2017;
- A brief report on the status of the project using form EA3, which is available online through http://www.aut.ac.nz/researchethics. This report is to be submitted either when the approval expires on 15 December 2017 or on completion of the project.

It is a condition of approval that AUTEC is notified of any adverse events or if the research does not commence. AUTEC approval needs to be sought for any alteration to the research, including any alteration of or addition to any documents that are provided to participants. You are responsible for ensuring that research undertaken under this approval occurs within the parameters outlined in the approved application.

AUTEC grants ethical approval only. If you require management approval from an institution or organisation for your research, then you will need to obtain this. If your research is undertaken within a jurisdiction outside New Zealand, you will need to make the arrangements necessary to meet the legal and ethical requirements that apply there.

To enable us to provide you with efficient service, please use the application number and study title in all correspondence with us. If you have any enquiries about this application, or anything else, please do contact us at ethics@aut.ac.nz.

All the very best with your research,

Kate O'Connor
Executive Secretary
Auckland University of Technology Ethics Committee

Cc: Shohn Wormgoor s.wormgoor@ucol.ac.nz

Appendix B: Participant information sheet

Participant Information Sheet

Date Information Sheet Produced: ***11 November 2014***

Project Title: ***Exercise Intensity and Diabetic Control***

An Invitation

Kia Ora.

My name is Shohn Wormgoor and I am a senior lecturer and Clinical Exercise Physiologist at U-Kinetics. Currently I am working towards my PhD qualification through Auckland University of Technology (AUT) and doing a research project that investigates the effects different exercise intensity has on people living with diabetes. (I will explain all this later in this letter.) Your participation in the research is entirely voluntary and you may withdraw at any time, even before all the data has been collected. If you withdraw, or choose not to participate, your referral to U-Kinetics will not be affected in any way. That is, you can still participate in the 12 week exercise training programme that your doctor referred you for and you can still learn about (and personally experience) the benefits of regular supervised training. All referred people to U-Kinetics are allowed to attend the clinic three times a week (for about an hour each time) all fully funded by UCOL and MidCentral DHB and each person participates on a voluntary basis.

My research will need male volunteers living with type 2 diabetes mellitus (T2DM), aged between 40 and 60, and who are able to train three times per week during the operational hours of the clinic (Monday, Wednesday & Friday: 8am – 5pm; Tuesday & Thursday 8am -12noon).

What is the purpose of this research?

The overall purpose of the research is to assist people living with diabetes by seeing if there are better ways of exercising so that diabetes (and its complications) are managed as best possible.

One component of the exercise that we use at U-kinetics is cycling on a stationary bike as this has shown to help people with diabetes (by lowering their blood sugar readings). The difficulty (also known as “intensity”) of the cycling is entirely based your fitness and will be designed to be at a comfortable level. Another component of the exercise is resistance training (gym machines) and this is also used by us to help people with diabetes. Both these exercise components are done under the safe supervision of Clinical Exercise Physiologists (CEPs) who will fully monitor you (e.g. heart rate, blood pressure and blood sugar levels).

Over the weeks as you get fitter and more confident we will make the cycling more challenging so that you continue to receive the benefits that this exercise has to offer. The main purpose of this research is to see which method of making it more challenging is better for people with T2DM. One option is to make the cycling last longer while the other option is to insert several bursts of higher intensity cycling (with an easy recovery after each burst).

Additionally, the research wants to see how your blood sugar levels react in the long-term to the exercises (and see if the benefits from exercises are kept after you have finished with your 12 weeks at U-Kinetics). You will also be invited back 6 months after you have finished to re-do the assessments.

As part of my qualification I will use the data obtained from your participation to write my thesis document, to write academic papers and give verbal presentations. I will not include your name in any of these documents/presentations - only the average results of the two exercise options.

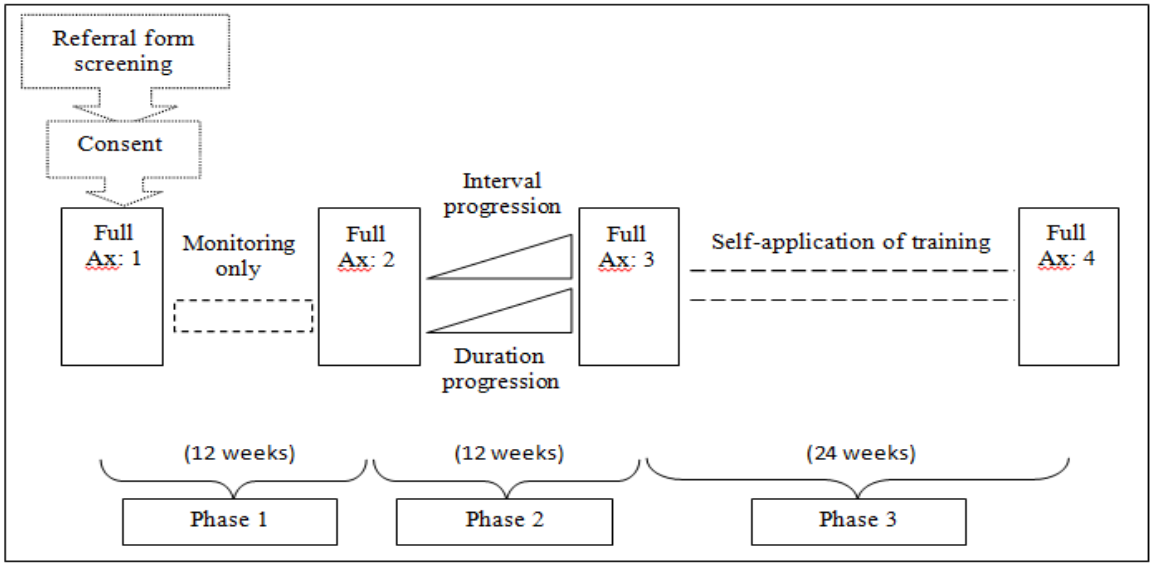
How was I identified and why am I being invited to participate in this research?

From the notes that your doctor sent on your behalf to U-Kinetics (to get you enrolled on the funded programme) were looked at by the person who deals with our referrals. They noticed that you meet the requirements of my study (e.g. male, 40-60 years of age and being diagnosed as having T2DM) and as such I want to invite you to attend a face-to-face meeting where we can meet each other and discuss the research further (and answer any questions you may have).

In order to ensure safety only participants who do not have serious heart problems (e.g. recent heart attack or recent bypass surgery), serious respiratory conditions (e.g. asthma or sleep apnoea), muscle or joint concerns (e.g. recent knee replacement) or who weigh more than 180 kg (the stationary bicycles I plan to use has weight limitations). Remember that if you are not able to participate in my research project you will still be able to train at U-Kinetics as per your referral.

What will happen in this research?

The picture below shows the 3 phases of my research. At the start and end of each phase there are assessments designed to see your progress (abbreviated as “Full Ax” in the picture).



You will be exercising under supervision at U-Kinetics (as per your referral) for the 12 weeks but the 3 phases of the study will involve you for a full year (in varying degrees of involvement).

As you may be aware, there is a relatively long waiting list at U-Kinetics and while participating in this research will not change your wait-time, we can use this time as a vital component of the study.

Phase 1 – Monitoring Only: At the beginning of the research project we will meet and discuss your health and if you are able and willing we will start by doing the tests a week or two later. During your wait-time you will first be part of what scientists call the control group. During this time I would like to see you once a week for about 10 minutes. In this visit to the clinic I will record your blood pressure, your blood sugar, your body weight and answer any questions you may have about your assessment results.

Phase 2 – Exercise: Here you will be randomly assigned into one of the two options. As you complete more sessions and get fitter you will notice me making the cycling more challenging (either by making it longer or by adding in some short bursts of faster cycling). At certain stages during these 12 weeks I will monitor your fitness (and strength) and make any necessary adjustments so that as you improve, you still train at the right level. If necessary, I will also make the exercises easier (or I may ask you not to exercise at all) on the days that you are not feeling well.

At the end of your training the assessments will be used to determine the size of the effects your exercising had on your diabetic health. This would be the end of your referral and the end of the supervised exercise training at U-Kinetics.

Phase 3 – Independent Training and Follow-up Assessment: You are welcome to continue training by yourself at your home or local gym and you may take your U-Kinetics programme with you if you want. You will be invited back six months later to complete the final assessment sessions to allow for the changes in your health to be compared.

What do the assessments involve?

The assessment sessions are conducted over 2 days (maximum of 1 hour each time) so that you do not get too tired. It will be of interest to see how much your results change during of a year. These tests include body composition (fatness), heart rate tests (ECG), blood pressure, fitness (a comfortable, highly monitored cycle test) and foot health tests. For your own records, you will receive a report at the completion of each of these assessments.

An important component of this research is to determine the effects of changes in your blood results. The timing of your regular blood checks (the ones that your doctor normally asks the laboratory to analyse) will be matched to your assessments. Remember that the laboratory does test all the samples “completely” (until there is no blood left) and as such no blood samples can be returned to you.

Please also remember that this research is voluntary and that your referral to U-Kinetics is not affected if you choose not to be a participant.

What are the discomforts and risks and how will they be alleviated?

The face-to-face meetings and assessment sessions take place in a private consultation room, but I may have a fourth-year student with me to help with the note-taking. All information is treated as confidential and information is recorded on documentation that will NOT have your name on it (just a research code). I will be asking you questions related to your medical conditions (reading what your doctor wrote in his referral letter), medications and activity levels - so that I get a better understanding of how diabetes is affecting you and your ability to exercise safely.

Most of the assessments are done with you in a relaxed state (e.g. height, weight, blood pressure, body fat). To obtain and accurate picture of your heart rhythm I may need to shave certain small areas of your chest (if very hairy) so that the electrodes stick better (and then not painful to pull them off afterwards).

However there are two tests that may place some stain on you, but these are necessary in order to determine your safe exercise limits and strength results. The first is a stationary cycling test which will start off very easy and I will regularly monitor your heart rate and rhythm (via the ECG images) and blood pressure. Only if you are safe to continue to the next level of the test, will I make it slightly more difficult. Your blood sugar level will be monitored after the cycling to see that it did not decrease too much. I will have sugar tablets handy, just in case, for you to chew.

The second test that may place strain on you is a test of your ankle strength where you will need to give a maximal push (and pull) with your foot.

The 12 week exercise programme I will design for you is based on assessment results and will be in line with international recommendations for people with diabetes and similar health conditions.

I have been safely helping people with exercise for the past 15 years, but just in case, all staff members and students of U-Kinetics are trained regularly in first-aid and resuscitation, and there is an AED (portable defibrillator) and oxygen cylinder on site - which gets checked daily.

What are the benefits?

The potential benefits to you include:

- improved glucose (blood sugar) control
- enhanced understanding of diabetic complications
- 12-week supervised and monitored individualized exercise programme
- regular blood pressure and blood glucose checks
- regular body mass monitoring (to help with weight loss motivation)
- better understanding the effects of exercise (immediate and long-term) on blood sugar levels
- knowledge, experience and confidence to continue exercising by yourself

This research will benefit me by providing me with:

- understanding of how glucose responds (within a training session) to the 2 options of exercise
- evidence of the effect the exercise options has on diabetic complications
- data for the completion of my PhD qualification

There is potential for a wider-community understanding to how exercise effects:

- the slowing down of the diabetic complications
- a reduction in future disease and death rates
- a reduction in the associated health care expenses

Additionally all student helpers will be exposed to how research is conducted so that they may, in future, build on this experience.

What compensation is available for injury or negligence?

In the unlikely event of a physical injury as a result of your participation in this study, rehabilitation and compensation for injury by accident may be available from the Accident Compensation Corporation, providing the incident details satisfy the requirements of the law and the Corporation's regulations.

What are the costs of participating in this research?

During phases 1 and 2 only travel and time costs will be your responsibility. All the assessments and supervised training is fully-funded by UCOL and the MidCentral DHB. The car parks at, and around, U-Kinetics are free.

During phase 3 (independent exercise) you may take your training programme with you and you can continue to exercise regularly (if you wish) either at home or in your community, but this will not be funded. You will be invited back for the final assessments which again will be funded by UCOL.

What opportunity do I have to consider this invitation?

You will be given a week from our first face-to-face meeting to talk to your whanau/family before needing to decide on accepting (or not) the invitation.

How do I agree to participate in this research?

At our first face-to-face meeting I will explain the process again, give you a tour of the assessment and training facilities and give you a consent form. Once you are satisfied I have answered all your questions relating to the research you can consider signing the form.

Will I receive feedback on the results of this research?

After each assessment week you will receive feedback on your results. At the completion of the research I will give a presentation at U-Kinetics to which all participants will be invited.

What do I do if I have concerns about this research?

Any concerns regarding the nature of this project should be notified in the first instance to the Project Supervisor, *Dr Nigel Harris, nigel.harris@aut.ac.nz,* (09) 921-9999 x 7301

Concerns regarding the conduct of the research should be notified to the Executive Secretary of AUTEC, Kate O'Connor, *ethics@aut.ac.nz*, 921 9999 ext. 6038.

Whom do I contact for further information about this research?

Please feel welcome to contact me, or my supervisor, should you have any questions:

Researcher contact details:

Shohn Wormgoor

U-Kinetics
(06) 952-7100

Project supervisor contact details:

Dr Nigel Harris

AUT
(09) 921-9999 x 7301

Approved by the Auckland University of Technology Ethics Committee on 15 December 2014 AUTEC Reference number: 14/396

Appendix C: Informed consent

Consent Form

Project title: ***Exercise Intensity and Diabetic Control***

Project Supervisor: ***Dr Nigel Harris***

Researcher: ***Shohn Wormgoor***

- ○ I have read and understood the information provided about this research project in the Information Sheet dated 11 November 2014
- ○ I have had an opportunity to ask questions and to have them answered.
- ○ I understand that I may withdraw myself or any information that I have provided for this project at any time prior to completion of data collection, without being disadvantaged in any way.
- ○ I understand that notes will be taken (by Shohn Wormgoor and/or fourth year students) during the interviews.
- ○ If I withdraw, I understand that all relevant information and transcripts, or parts thereof, will be destroyed.
- ○ I am not suffering from heart disease, uncontrolled high blood pressure, any respiratory condition (mild asthma excluded), sleep apnoea, any illness or injury that impairs my physical performance, or any infection.
- ○ I agree to provide blood samples and understand that the blood samples will be taken by the hospital's trained specialists (phlebotomists).
- ○ I understand that all the blood samples are analysed completely (to destruction) by the hospital's laboratories and therefore cannot be returned to me.
- ○ I agree to take part in this research.
- ○ I wish to receive a copy of the report from the research (please tick one): Yes ○ No ○

Participant's signature: .....

Participant's name: .....

Participant's contact details (if appropriate):

……..

……..

Date:

Approved by the Auckland University of Technology Ethics Committee on 15 December 2014 AUTEC Reference number: 14/396

Note: The Participant should retain a copy of this form.

Appendix D: Confidentiality agreement

Confidentiality Agreement

Project title: ***Exercise Intensity and Diabetic Control***

Project Supervisor: ***Dr Nigel Harris***

Researcher: ***Shohn Wormgoor***

- ○ I understand that all the material I will be asked to record is confidential.
- ○ I understand that the contents of the Consent Forms, questionnaires, interview notes and results of performance tests can only be discussed with the researchers.
- ○ I will not keep any copies of the information nor allow third parties access to them.

Intermediary's signature: .....

Intermediary's name:.....

Intermediary's contact details (if appropriate):

……..

……..

Date:

Project supervisor's contact details (if appropriate):

Dr Nigel Harris
AUT
nigel.harris@aut.ac.nz
(09) 921-9999 x 7301

Approved by the Auckland University of Technology Ethics Committee on 15 December 2014 AUTEC Reference number: 14/396

Note: The Intermediary should retain a copy of this form.

Appendix E: Consultation form

Consultation Form

Participant Code:_____

Ethnic identity:_____

Referring GP:_____

Assessed by: Shohn Wormgoor **Assistant:**_____

Medical Information

Have you ever had a graded exercise stress test? YES NO

Date and Place of Test: _____

Have you ever had any cardiological tests (e.g. ECG)? YES NO

Date and Place of Test: _____

HOSPITALISATION: Details of your recent hospitalisations

Year *Location* *Reason*

_____

_____

Have you ever had a heart attack? YES NO

If yes, when _____

Have you ever had a heart operation? YES NO

If yes, which procedure and where (and when) was it done?

Stents/ Bypass _____

Other _____

Have you been diagnosed with a heart condition? YES NO

If yes, which condition and when was it diagnosed?

_____

While resting, do you experience pain/discomfort in the chest, neck, jaw or arms? YES NO

During physical exercise do you experience any chest discomfort? YES NO

Do you experience unreasonable breathlessness (day or night)? YES NO

Do you ever get significant swelling of your feet (ankle oedema) YES NO

If yes to any of the above questions, please explain how often?

_____

_____

Smoking status: _____

33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60

Age at diagnosis: Yr__ Mo __ Duration of Diabetes: Yr___ Mo __ Current Age: Yr___ Mo __

How diagnosed: _____

What reason was provided: _____

How treated by GP: Diet advice __, Oral meds__, Exercise advice ___, Insulin (When?) ____

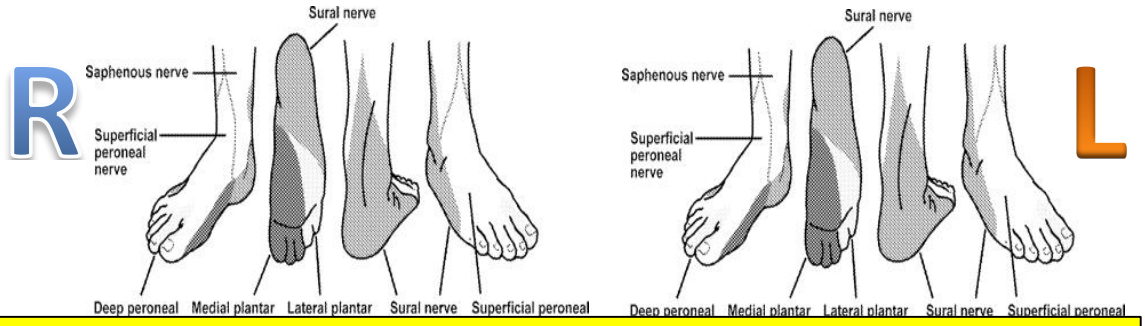
Have you attended any seminars/educational sessions to help manage/understand diabetes better?

When? _____Where?_____Effectiveness?_____

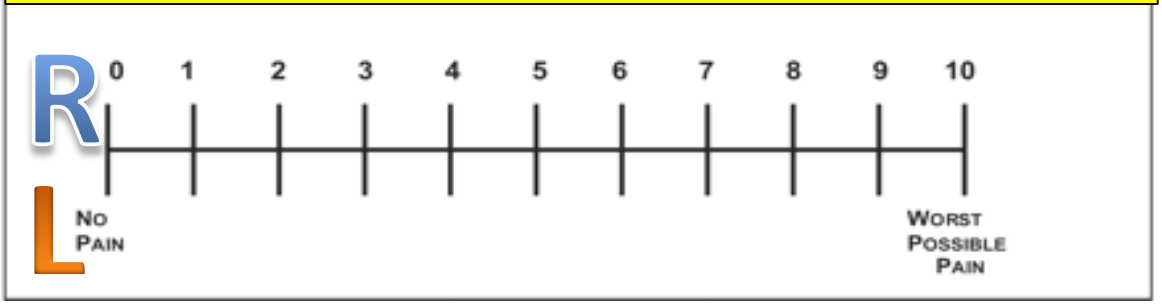
Any complications from diabetes: _____

_____

_____



11-Point Likert pain scale



Latest HbA1c: _____ Date:_____	How often measured: _____ Target Hb_{A1c}: 48-53 mmol/mol	Previous HbA1c's: ____ ____ ____ Dates: _____ _____ ____

How long have you had a Glucometer? _____ How many times per day do you check? ____

Highest ever reading? _____ When? _____ Lowest ever reading? _____ When? _____

What are your typical readings nowadays? _____

Hypo history?_____ Symptoms? _____

Do you get strange sensations in your lower legs when walking short distances? YES NO

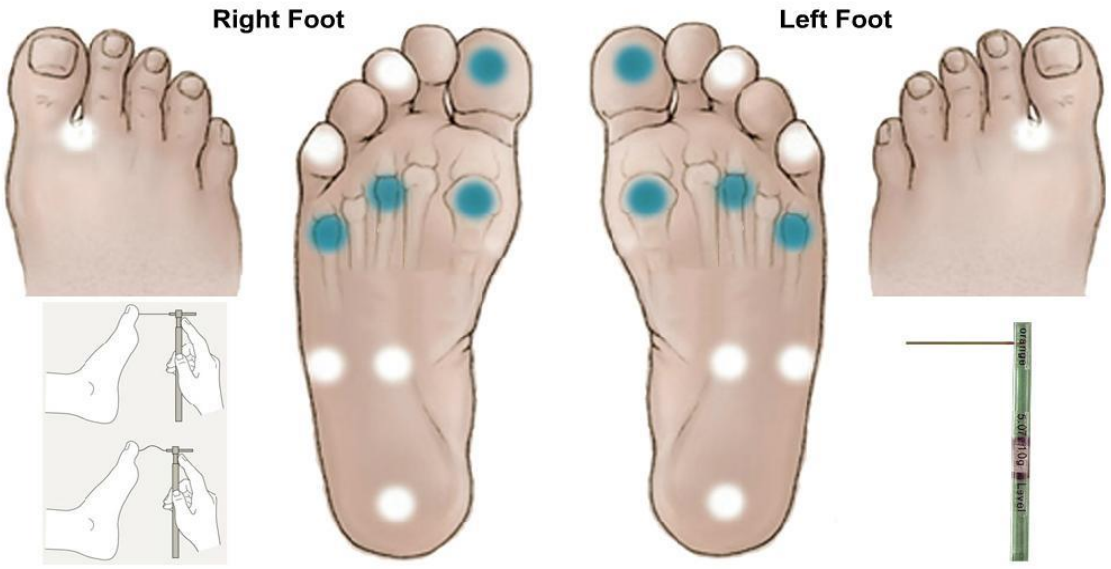
Do you ever experience any dizziness, fainting, or blackouts? YES NO

_____

_____

Musculoskeletal problems that limit your physical activity _____

10g Monofilament Test: _____



Current medications:

Name	Frequency	Dosage

Appendix F: International Physical Activity Questionnaire (IPAQ)

I would like to get an understanding of your current physical activity levels. This relates to a typical week that is indicative of your current (the last 7 days) physical activities.

	VIGOROUS ACTIVITY	MODERATE ACTIVITY	WALKING	SITTING
Working currently: *(Includes all activities outside the house e.g. paid jobs, farming, studying, volunteer work, unpaid work and looking for work)*	Heavy lifting, digging, climbing stairs, heavy construction work	Carrying light loads	Only at work (not walking to or from work)	Time spent on sedentary activities at work (confirm this is the remainder of the 8 / 9 hour workday): Y or N ?
Days/ week				
Hours/day				
(or total minutes/day)				
Active Transportation: *(Includes travel to work, shops, cinema)*		Cycling	Walking	Sitting in car, bus or train
Days/ week				
Hours/day				
(or total minutes/day)				
Garden and House: *(Includes all gardening, housework and caring for family members)*	In the YARD – Heavy lifting, chopping wood, digging	In the YARD - Carrying light loads, sweeping, raking, washing windows	INDOORS – Carrying light loads, sweeping, vacuuming,	
Days/ week				
Hours/day				
(or total minutes/day)				
Leisure: *(includes those activities solely for recreation, sport or exercise – not meal preparation)*	Aerobics, fast bicycling, running, fast swimming	Regular cycling, regular swimming, jogging, (U-Kinetics)	Walking for Leisure	Sitting as remainder of leisure time (after work and on weekends)
Days/ week				
Hours/day				
(or total minutes/day)				

What are your barriers to exercise?

Appendix G: Physical Activity Enjoyment Scale (PACES)

Physical Activity Enjoyment

Project title: ***Exercise Intensity and Diabetic Control***

Project Supervisor: ***Dr Nigel Harris***

Researcher: ***Shohn Wormgoor***

When I am active …	Disagree a lot	Disagree a little	Neutral	Agree a little	Agree a lot
I enjoy it					
I feel bored					
I dislike it					
I find it pleasurable					
It's no fun at all					
It gives me energy					
It makes me feel sad					
It's very pleasant					
My body feels good					
I get something out of it					
It's very exciting					
It frustrates me					
It's not at all interesting					
It gives me a strong feeling of success					
It feels good					
I feel as though I would rather be doing something else					

On completion of the exercise intervention phase:

What did you like about your exercise programme?

_____

_____

_____

_____

What aspects of the exercise programme did you NOT like and why?

_____

_____

_____

_____

How will you use this style of exercise in the future, if at all?

_____

_____

_____

_____

Appendix H: New Zealand Adult Nutrition Survey (NZANS)

U-KINETICS EXERCISE & WELLNESS CLINIC	**Nutrition Survey**	AUT UNIVERSITY TE WĀNANGA ARONUI O TAMAKI MAKAU RAU

Project title: ***Exercise Intensity and Diabetic Control***

Project Supervisor: ***Dr Nigel Harris***

Researcher: ***Shohn Wormgoor***

2008/09 New Zealand Adult Nutrition Survey Questionnaire

http://health.govt.nz/system/files/documents/publications/ans_questionnaire.pdf (07 October 2014)

Dietary Habits

The first section of this questionnaire is about your usual eating patterns. When answering these questions please think back over the **past 4 weeks**. Remember to think about all meals (that is breakfast, lunch and dinner) as well as snacks and times when you eat both at home and away from home.

01. How many days in an average week do you have something to eat for breakfast?
You may have eaten at home, in a car, at work or in a café.

[Includes both weekends & weekdays. Include breakfast drinks including smoothies and shakes. Breakfast is usually the first meal of the day, eaten within 2 hours of getting up]

☐ days per week (for the average of the past 4 weeks)

02. On average, how many slices of bread/toast OR bread rolls do you eat per day?

- ☐ None, I don't eat bread or toast
- ☐ Less than one per day
- ☐ 1-2 per day
- ☐ 3-4 per day
- ☐ 5-6 per day
- ☐ 7 or more per day
- ☐ Don't know

03. What type of bread, rolls or toast do you eat most of?

- White
- High fibre white
- Light grain bread (e.g. Molenberg, Freya's, Ploughmans, and MacKenzie High Country)
- Heavy grain bread (e.g. Vogels and Burgen)
- Other
- Don't know

04. In the past four weeks which of the following have you eaten at all?

- Red meat - such as beef, pork, mutton, lamb and goat
- Chicken - such as chicken breast, drumsticks, or whole chickens, but not chicken nuggets or chicken roll.
- Processed meats - such as ham, bacon, sausages, luncheon, canned corned beef, pastrami, and salami.
- Seafood - such as fish or shellfish
- None
- Don't know

05. How often do you eat red meat?

- Never
- Less than once per week
- 1-2 times per week
- 3-4 times per week
- 5-6 times per week
- 7 or more times per week
- Don't know

06. How often do you eat chicken?

- Never
- Less than once per week
- 1-2 times per week
- 3-4 times per week
- 5-6 times per week
- 7 or more times per week
- Don't know

07. How often do you remove excess fat from meat?
[Includes fat removed before or after cooking, but before eating.]

- Never
- Rarely
- Sometimes
- Regularly
- Always
- Don't know

08. How often do you remove the skin from chicken?

[Includes skin removed before or after cooking, but before eating. If you only buy skinless cuts, enter this as "always"]

- Never
- Rarely
- Sometimes
- Regularly
- Always
- Don't know

09. How often do you eat processed meat products? Processed meat includes ham, bacon, sausages, luncheon, canned corned beef, pastrami, and salami.

- Never
- Less than once per week
- 1-2 times per week
- 3-4 times per week
- 5-6 times per week
- 7 or more times per week
- Don't know

10. How often do you eat fresh or frozen fish or shellfish? Do not include battered / fried or canned fish or shellfish.

- Never
- Less than once per week
- 1-2 times per week
- 3-4 times per week
- 5-6 times per week
- 7 or more times per week
- Don't know

11. How often do you eat battered or fried fish or shellfish? This may include battered or deep fried fish bought from the 'Fish and Chip' shop.

- Never
- Less than once per week
- 1-2 times per week
- 3-4 times per week
- 5-6 times per week
- 7 or more times per week
- Don't know

12. How often do you eat canned fish or shellfish? Canned fish includes products such as tuna, salmon, and sardines.

- Never
- Less than once per week
- 1-2 times per week
- 3-4 times per week
- 5-6 times per week
- 7 or more times per week
- Don't know

13. On average how many servings of fruit - fresh, frozen, canned or stewed - do you eat per day? Do not include fruit juice or dried fruit.
A serving is the same as a medium piece of fruit such as an apple or two small pieces of fruit such as two apricots, or half a cup of stewed fruit.

- Never, I don't eat fruit
- Less than one serving per day
- 1 serving
- 2 servings
- 3 servings
- 4 or more servings
- Don't know

14. On average how many servings of vegetables - fresh, frozen or canned - do you eat per day? Do not include vegetable juices.
A serving is the same as one potato/kumara, half a cup of peas or a cup of salad. For example, 2 medium potatoes + ½ cup of peas = 3 servings

- Never, I don't eat vegetables
- Less than one serving per day
- 1 serving
- 2 servings
- 3 servings
- 4 or more servings

15. What type of milk do you use the most of?

- None, I don't use milk
- Whole or standard milk (Dark blue or silver)
- Reduced fat (light blue)
- Skim or Trim (Green or yellow)
- Soy milk
- Other (such as rice, goats milk)
- Don't know

16. What type of butter or margarine spread do you use the most of?

- None, I don't use butter or margarine as spread
- Butter (including semi soft)
- Butter and margarine blend
- Margarine - Full fat (e.g. Canola, Sunflower, and Olive oil based)
- Lite or reduced fat margarine (e.g. Canola, Sunflower, and Olive oil based)
- Plant sterol margarine - full and low fat varieties (e.g. Proactive or Logicol)
- Don't know

17. What type of fat or oil do you use most often when cooking?

- None, I don't use fat or oil
- Butter
- Margarine
- Butter blend
- Oil
- Dripping or Lard
- Other
- Don't know

18. How often do you add salt to your food after it has been cooked or prepared?

- Never
- Rarely
- Sometimes
- Regularly
- Always
- Don't know

Does your household use any "iodised salt"? (Not all salt is iodised, so it is best to view the container.) YES: _____ NO: _____ DON'T KNOW: _____

19. How often do you choose low or reduced fat varieties of foods instead of the standard variety?

- Never
- Rarely
- Sometimes
- Regularly
- Always
- Don't know

20. How often do you choose low or reduced salt varieties of foods instead of the standard variety?

- Never
- Rarely
- Sometimes
- Regularly
- Always
- Don't know

21. How often do you eat hot chips, French fries, wedges, or kumara chips? Think about lunch and dinner as well as snacks.

- Never
- Less than once per week
- 1-2 times per week
- 3-4 times per week
- 5-6 times per week
- 7 or more times per week
- Don't know

22. How often do you eat fast food or takeaways from places like McDonalds etc.? Think about breakfast, lunch, dinner and snacks. Do not include times when you have only purchased a drink/beverage.

- Never
- Less than once per week
- 1-2 times per week
- 3-4 times per week
- 5-6 times per week
- 7 or more times per week
- Don't know

23. How often do you drink fruit juices and drinks? Don’t include diet or diabetic varieties.
[Fruit juices and drinks include freshly squeezed varieties, and brands such as Just Juice, Fresh-up, Keri, Golden Circle, Ribena, Thextons, McCoy and Charlie's.
Excludes - 'diet varieties', soft drinks and energy drinks, flavoured waters (e.g. H2Go), and sports waters (e.g. Charlies Sports water, Mizone and Aqua-shot).]

- Never
- Less than once per week
- 1-2 times per week
- 3-4 times per week
- 5-6 times per week
- 7 or more times per week
- Don't know

24. How often do you drink soft drinks or energy drinks? Do not include diet varieties.
[Soft drinks are often carbonated or 'fizzy' and include Coca-Cola, Pepsi, Lemonade, Ginger beer, Energy drinks (e.g. 'V', Red Bull, Lift plus), PowerAde, E2 and G-force.
Excludes - 'diet varieties', fruit juices and drinks, flavoured waters (e.g. H2Go), and sports waters (e.g. Charlies Sports water, Mizone and Aqua-shot).]

- Never
- Less than once per week
- 1-2 times per week
- 3-4 times per week
- 5-6 times per week
- 7 or more times per week
- Don't know

24a. How many hot beverages (tea/coffee/milo etc.) do you drink on average per day and how many teaspoons of sugar do you add?

[ ] *hot drinks per day with* [ ] *teaspoons of sugar on average in each drink.*

25. How often do you eat lollies, sweets, chocolate and confectionary?

- Never
- Less than once per week
- 1-2 times per week
- 3-4 times per week
- 5-6 times per week
- 7 or more times per week
- Don't know

26. Now a few questions on dietary supplements. For these questions please think back over the past 12 months.

Did you take any supplements at any time during the last **12 months**?

- Yes
- No *(if ‘NO’ please proceed to question 30)*

27a. For each supplement taken we have a series of questions.
Which did you take? Can you please state the type OR do you still have the supplement container?

- Brand/product (taken directly from container will be most accurate)
- Multivitamin and multiminerals
- Multivitamins
- Multiminerals
- Single vitamin and/or single mineral
- Oil (please specify type:_____)
- Other supplement
- Unsure of classification

27ai. Please record all available information from the container which should include:

- brand name:_____
- product name:_____
- single vitamin (please specify type:_____)
- multi-vitamin (please specify type:_____)
- single mineral (please specify type:_____)
- multi-mineral (please specify type:_____)
- bar code (if no other information given): _____
- dosage/strength: _____

27b. Please specify any other supplements you are currently taking.

27c. Please specify if they are:

- Bran
- Lecithin
- LSA (linseed, sunflower and almond)
- Kelp
- Spirulina
- Glucosamine and/or chondroitin
- Echinachea
- Ginkgo
- Hypericum (St John's Wort)
- Sports supplement
- Other

28. Were these supplements prescribed to you by a doctor / nurse practitioner?

- Yes
- No

29. How often did you take the supplement in the last 12 months?

- Daily
- More than once per week
- Once per week
- Monthly
- Episodic (REGULAR use but for a limited time period)
- Infrequent and irregular use
- Other
- Don't know

Finally, a few questions on smoking and alcohol consumption.

30. Have you ever smoked a total of more than 100 cigarettes in your whole life?

- Yes
- No *(if 'NO' please proceed to question 34)*

31. How often do you currently smoke?

- I don't smoke now
- At least once a day
- At least once a week
- At least once a month
- Less often than once a month

32. How long ago did you stop smoking?

- Within the last month
- 1 month to 6 months ago
- 6 to 12 months ago
- 1 to 2 years ago
- 2 to 5 years ago
- Longer than 5 years ago

33. On average, how many cigarettes do you smoke a day?

[ ] cigarettes per day (for the average of the past 4 weeks)

34. In your entire life, have you had at least one alcoholic drink, not counting small tastes or sips?

- Yes
- No

35. Have you had a drink containing alcohol in the last 12 months?

- Yes
- No

36. How often do you have a drink containing alcohol?

- Monthly or less
- Up to 4 times per month
- Up to 3 times a week
- 4 or more times per week

37. How many drinks containing alcohol do you have on a typical day when you are drinking?

- One or two
- Three or Four
- Five or Six
- Seven to Nine
- Ten or more

Appendix I: The NZANS scoring system

The penalty point allocation per check-box response for the 2008/09 NZANS.

	Question No:	Guideline	Check-box: 1	Check-box: 2	Check-box: 3	Check-box: 4	Check-box: 5	Check-box 6	*Category Score*
Smoking			**Input number of cigarettes smoked per day**						**30**
Cigarettes per day	33	No smoking							
Alcoholic drinks per week			**Product of penalties from questions 36 and 37**						**30**
Drink frequency	36	Less often	0.5	1	3	4			
Drinks each occasion	37	Lower	1.5	3	4.5	6	7.5		
Fast-foods per week			**Sum of penalties from questions 11, 21 and 22**						**30**
Battered fish	11	Lower	0	2	4	6	8	10	
Hot chips	21	Lower	0	2	4	6	8	10	
Take-aways	22	Lower	0	2	4	6	8	10	
Refined carbohydrates			**Sum of penalties from questions 23 to 25**						**50**
Fruit juices	23	Lower	0	2	4	6	8	10	
Soft drinks	24	Lower	0	2	4	6	8	10	
Sugar via hot drinks	24a	Lower	Input number of teaspoons of sugar via hot beverages						
Lollies/candy	25	Lower	0	2	4	6	8	10	
General food quality			**Sum of penalties from the following questions**						**60**
Breakfast frequency	1	Higher	Input number of days breakfast skipped per week						
Slices of bread	2	Lower	0	0.5	1	3	5	7	
Bread's grain quality	3	Higher	4	3	2	1	1.5		
Eat Meat (unprocessed)	5	1-2 x / week	2	1	0	1	2	4	
Eat Chicken	6	2-4 x / week	2	1	0	0	1	2	
Eat Fish (not battered)	10	2-4 x / week	2	1	0	0	0.5	1	
Remove meat fat	7	More often	4	3	2	1	0		
Remove chicken skin	8	More often	4	3	2	1	0		
Eat processed meat	9	Less often	0	1	2	3	4	5	
Eat canned fish	12	More often	5	4	3	2	1	0	
Fruit consumption	13	More often	5	4	3	2	1	0	
Vegetable consumption	14	More often	5	4	3	2	1	0	
Salt adding	18	Less often	0	1	2	3	4		
Choose low fat option	19	More often	4	3	2	1	0		
Choose low salt option	20	More often	4	3	2	1	0		
TOTAL			**SUM OF THE FIVE DOMAINS**						**200**

Appendix J: Independent training

U-Kinetics

U·KINETICS EXERCISE & WELLNESS CLINIC

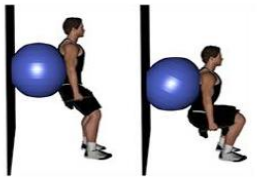
AUT UNIVERSITY

Independent Training Programme for T2D Study

Frequency: 2-3 times a week **Duration:** 45 - 50 minutes

Cardiovascular: Cycling, Jogging, Swimming, Elliptical or Walking
As per your knowledge/experience

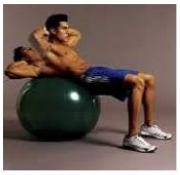
Strength: *Choose 1 exerise per row (3 x 10)*
Start on left side of page and progress towards right when ready















Cool-down Stretches: As per your knowledge/experience

Appendix K: Original 'Baseline Associations' chapter

Associations between select pre-exercise screening variables and markers of diabetic complications in a group of men with type 2 diabetes: Implications for exercise physiologists

Abstract

Type 2 diabetes mellitus (T2D) is a pandemic with hyperglycaemia contributing to progressive health complications. Knowledge of associations between pre-exercise screening variables and diabetic complications would enable CEPs to better understand the physiological implications of the disease and provide lifestyle advice to assist diabetes management. The study objective was to determine associations between pre-exercise screening variables of middle-aged T2D men and markers of diabetic complications. T2D men referred to attend supervised exercise intervention programmes were considered for inclusion. The magnitude of the correlations were determined using Pearson's correlation coefficients or Spearman's rho. Twenty-four men having moderate-duration T2D presented as sedentary, morbidly obese, and while taking medications had elevated HbA1c and pre-hypertension. This study presented a profile of a homogenous group of T2D men about to exercise in a real-world setting and determined associations between pre-exercise screening variables and macro- and microvascular complication markers. Associations between diabetic complications were not glucocentric and other readily obtained variables, such as those obtained during a pre-exercise screening (specifically diabetes duration, BMI, monofilament and heart rate variability) provide additional information to all healthcare professionals. Understanding these relationships can assist CEPs in providing enhanced pre-exercise screening and lifestyle education.

Introduction

T2D has become a global emergency with resultant hyperglycaemia contributing to the development of progressive, life-threatening health complications (IDF, 2015; Inzucchi et al., 2012; Russell & Cooper, 2015; Strasser & Pesta, 2013; Zhang et al., 2012). Hyperglycaemic readings, as measured by HbA1c three months post T2D diagnosis, have been positively associated with clinical end points such as myocardial infarction (MI), stroke, death from peripheral vascular disease, amputations and microvascular disease (Stratton et al., 2000). However, in those with a longer duration of diagnosed T2D, the association of HbA1c alone with diabetic complications are not as clear. Zoungas et al (2012) reported that for values above 48.0 - 53.0 mmol/mol, a higher HbA1c was significantly associated with higher risks of macrovascular and microvascular events, and death. In contrast, while van Munster, van der Grafff, de Valk, Visseren and Westerink (2016) noted no relationship between HbA1c and cardiovascular events, BMI and weight showed significant interaction for the relation between HbA1c and mortality. To add to the uncertainty Rodríguez-Vigil, Rodríguez-Chacón and Ruiz Valcarcel (2016) found that poor metabolic control along with male gender, longer duration of diabetes, and older age were associated with macrovascular complications and that cardiovascular disease was not associated with BMI.

It is the goal of all healthcare providers to positively influence the health outcomes of people living with T2D, and CEPs play an important role within this multi-disciplinary team by providing specialised screening, exercise testing and exercise interventions in conjunction with related lifestyle education (Clinical Exercise Physiology New Zealand [CEPNZ], 2014).

An enhanced knowledge of the association between pre-exercise screening variables and diabetic complication in people already living withT2D would enable CEPs to both better understand the physiological implications of the disease and provide optimal lifestyle advice to assist diabetes management. Thus, the primary aim of this study was to determine associations between pre-exercise screening variables of T2D men and markers of diabetic complications. Secondary aims were to profile various aspects (e.g., medications, PA, nutrition scores and physiological status) of these T2D men to better understand the inter- and intra-complication associations within T2D. Specifically, the research question includes determining the

association of referral note variables (e.g., HbA1c and T2D duration), habitual PA (including sitting hours), resting physiological variables and fitness, with markers of macro- and microvascular complications.

We hypothesised that strong relationships independently exist for HbA1c, PA, BMI and aerobic fitness with markers of macro- and micro- diabetic complications.

Methods

The study protocol was approved by the Auckland University of Technology Ethics Committee (AUTEC) (reference no. 14/396) and the study was performed in accordance with the Declaration of Helsinki.

Study participants

All middle-aged (aged 35 – 59 years) T2D men, referred by general practitioners to attend a clinical exercise physiology Health and Wellness Clinic (Palmerston North, New Zealand) to participate in a 12-week supervised exercise intervention programme were considered for inclusion. General practitioners diagnosed their patient as having T2D and provided written clearance for participation in supervised PA. The staggered nature of one or two referrals per fortnight, coupled with the number of eligible SPs required for the study, resulted in an 18-month enrolment period. Potential participants underwent a two-part screening process. Initially, the referral forms were screened for the following exclusion criteria: serious cardiac, respiratory or musculoskeletal pathologies, neurological disorders, unstable proliferative retinopathy, end-stage renal disease and/or uncontrolled hypertension. Due to a weight limitation of the cycle ergometer participants exceeding 170 kg were also excluded. Thereafter potential participants were invited to an individual consultation session in which the purpose, risks and benefits of the study were explained. Twenty-four SPs provided their informed consent and were included in the final analysis (Figure 2).

Blood samples. After the consultation and 48 hours before the baseline physiological assessments, an overnight fasted blood and urine sample was given at the local hospital's laboratory. SPs arrived at the hospital by car, or public transport, and reported to the laboratory

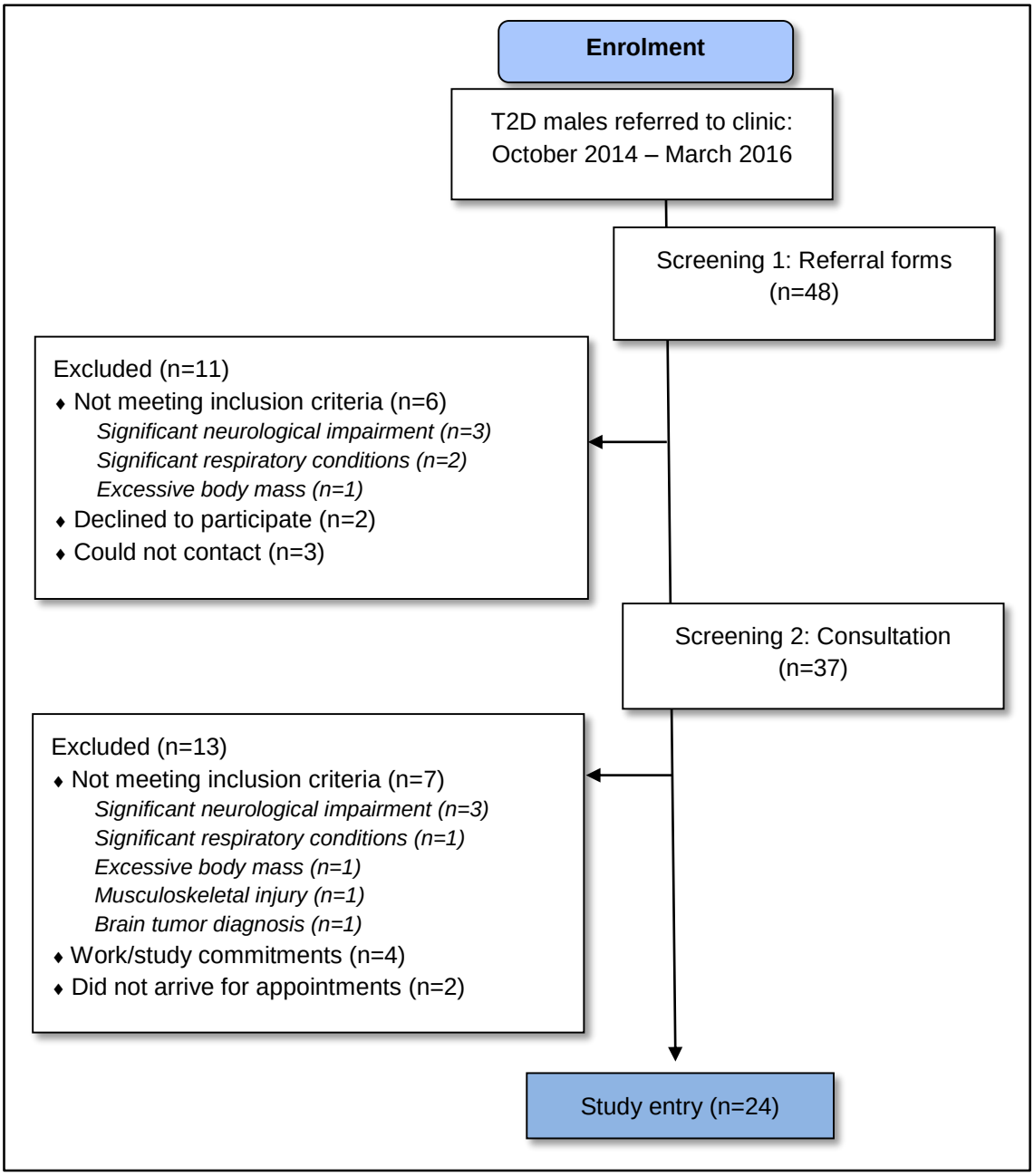


Figure 2: Consort diagram of study participant entry. During an 18-month enrolment period, the referral form of T2D men were screened for study eligibility before candidates were invited to attend a consultation. 24 participants were included to commence a supervised exercise intervention study.

at 08:00 hours and a blood sample was collected from each SP's antecubital vein after which a spot urine sample was collected.

HbA1c was measured on a Bio-Rad Haemoglobin Testing System (D-100™, Bio-Rad Laboratories, Inc., Hercules, CA) using high-performance liquid chromatography. TC, HDL, LDL, and TG were determined using the enzymatic colorimetric method measured on a cobas® 8000

(cobas c702 [AU1], Roche Diagnostics International Ltd, Rotkreuz, Switzerland) chemistry module. The measurement of hs-CRP was performed with a particle enhanced immunoturbidimetric assay measured on a cobas® 8000 (cobas c702 [AU1], Roche Diagnostics International Ltd, Rotkreuz, Switzerland) chemistry module, with hs-CRP estimation by latex turbidimetric method. Urine albumin-to-creatinine ratio (uACR) was measured with a spot urine sample and micro-albuminuria, for men, was defined as 2.5 ≤ uACR < 25 mg/mmol (Guo, Ekelund, Griffin & Simmons, 2016). The urinary microalbumin was measured on a cobas® 8000 (cobas c502 [AU2], Roche Diagnostics International Ltd, Rotkreuz, Switzerland) chemistry module using an immunoturbidimetric assay.

Referral Note Details and Initial Consultation. During the initial consultation, the medical history and referral note details of age, T2D duration, ethnicity, neuropathic pain and current medications were confirmed (Appendix E). Additionally, the questionnaires to document PA enjoyment (Physical Activity Enjoyment Scale [PACES]) (Motl et al., 2011) (Appendix F), and habitual PA and nutrition were administered. Although it is conceivable that only those individuals who had an affinity to exercise enrolled in the study, the purpose of the PACES was to monitor the magnitudes change in PA enjoyment during the study. SPs were explained the purpose of PACES and were instructed to complete the form independently and in relation to PA in general and not a particular training modality.

Physical activity. Current levels of PA were monitored using the International PA Questionnaire (IPAQ). The adult, long version (2005) was administered via interview (Appendix G). Total metabolic equivalent (MET) minutes per week (min/wk) were determined along with MET min/wk for each of the four domains (work, active transportation, domestic and garden, and leisure-time) and the four intensity levels (vigorous, moderate, walking, and total sitting hours per week) using the recommended guidelines for data processing and analysis of IPAQ (IPAQ Research Committee, 2005).

Nutrition habits. Current “best practice” national nutritional management for diabetes in New Zealand (NZ) constitutes the Ministry of Health’s (MoH) Eating and Activity Guidelines (MoH, 2015); which are to consume a diet moderate-to-high in carbohydrate and low in dietary fat. These guidelines are currently being challenged in the nutrition-related academic and practice

arena (Feinman et al., 2015), with the counter, contemporary argument in favour of carbohydrate restriction, with a greater emphasis on dietary fat. This controversy about what constitutes “best practice” in nutrition is an area of debate that needs to be recognised, but as it is outside the scope of this study, the findings from this study will be interpreted in alignment with the Eating and Activity Guidelines.

Nutrition habits pertaining to the previous four weeks, were obtained using the 2008/09 NZ Adult Nutrition Survey (NZANS) Questionnaire (MoH, 2011). The questionnaire, which establishes the frequency of which various foods and food groups are consumed, was explained to each participant and a blank copy given to participants to independently complete (Appendix H). To objectively record responses of various nutrition aspects, a novel approach was applied in which the NZANS responses were grouped into five domains (Appendix I). The novel scoring system was applied as follows: Penalty points were allocated to responses that were contrary to the guidelines (with higher penalty points being allocated to responses further away from the guidelines). The general premise of the NZANS is that Check-box 1 represents never (or seldom) with the successive Check-boxes increasing in frequency. Of note, question 24a was added to ascertain the amount of teaspoons of sugar added to hot beverages daily. SPs fully adhering to the guidelines thus received zero penalty points. The domains of General Food Quality, Fast Foods, Refined Carbohydrates, Smoking and Alcohol Consumption received maximum penalties of 60, 30, 50, 30 and 30, respectively.

Physiological assessments (Session 1). Subsequent to the blood samples, SPs returned to the clinic for the first of two, 60-min assessments (separated by 48 hours) where they were instructed to continue taking their medications, to have a light meal based on usual intake, to avoid caffeine 2 hours before testing, and to abstain from exercise for the preceding 48 hours. The individual assessments (using a staggered structure of one or two SPs per fortnight – as per their referral to the clinic) were conducted, over a 15-month period, using the following protocols and in the following sequence:

Random blood glucose. A fingertip capillary blood sample was taken on each arrival to the clinic; assessments were postponed if blood glucose concentrations were <3.5 or >17 mmol/L. Of note, no SP arrived with a low blood glucose concentration (BG) for any of the assessments

and one SP had a BG of 19.8 mmol/L, but the absence of ketones in his urine was confirmed before subsequent assessments were conducted.

BMI. Body mass was measured using the pre-calibrated HUR- force platform (ALU4, HUR Labs Oy, Tampere, Finland) with SPs standing, in short-pants, motionless on the platform. Body mass was recorded to the nearest 10 g. Height was measured using a wall-mounted stadiometer and recorded to the nearest 1.0 mm. BMI was calculated and reported as kg/m^2.

Monofilament test. SPs were assessed for sensation loss, a marker of diabetic peripheral neuropathy (DPN) (McNamara, Vinik, Barrentine & De Vol, 2016), by their ability to register a sensation of a monofilament when applied, at 10 sites on the soles of both feet, with sufficient pressure to buckle the 10 g filament (Singh, Armstrong & Lipsky, 2005). The sequence and tempo of the measurements was varied to avoid a predictable pattern. Sensation was recorded as a score out of 20.

Postural stability. The stabiliometry assessment was performed while the participant maintained a quiet barefoot stance on the HUR Labs iBalance$^+$ platform (ALU4, HUR Labs Oy, Tampere, Finland). The software received information (sample rate: 100 Hz) about centre of pressure motion in the anterior-posterior and medio-lateral directions and the resultant posturogram provided data on trace length (TL) (mm), C90 (90% confidence ellipse) area (mm^2) and the standard deviation of the velocity (mm/s). Postural stability was conducted, after calibration checks according to manufacturer's guidelines, for an eyes open (familiarisation) and eyes closed (analysis) condition. For each condition SPs stood as stable as possible, for 35-sec, with only the last 30-sec being recorded (Scoppa, Capra, Gallamini & Shiffer, 2013), with their feet in a joined parallel position and arms relaxed at their sides.

Resting BP. The participants lay supine on a plinth for 10-min after which BP was measured at the brachial artery using the auscultatory method at vertical height of the heart. Bicep circumference allowed correct selection of cuff size (large > 34.5 cm > extra-large). The first Korotkoff sound registered the systolic BP and the fifth Korotkoff sound was used to register the resting diastolic BP (Tan, Wei & Wang, 2012). The mean of two BP measurements obtained two minutes apart was recorded (Moe, Augestad, Åsvold & Flanders, 2011; Sigal et al., 2007).

Resting heart rate (HR_{rest}). The participants were prepared (chest hair shaven and electrode sites cleaned) and connected to a Custo-med (cardio 110, Müller & Sebastiani GmbH, Ottobrunn, Germany) 12-lead ECG. The HR_{rest} was recorded from the 10-sec ECG printout on completion of a further 1-min rest in the supine position.

Deep-breathing HRV. HRV using the inspiration-to-expiration ratio of the cardiac rhythm's R-R interval was used as a marker of autonomic function. To complete the testing procedure, SPs (still resting in the supine position) were connected to the ECG and coached to perform deep breathing (six breaths per minute) for a full minute. HR variance was recorded using the longest R-R interval (in milliseconds) during expiration divided by the shortest R-R interval during inspiration. The mean of six of these individual ratios were recorded as the final ratio (Colberg, Swain & Vinik, 2003).

Graded exercise test (GXT). The participants performed an incremental cycle ergometer test (Custo-med ergocontrol 3000, Müller & Sebastiani GmbH, Ottobrunn, Germany), monitored with a 12-lead ECG, to ~80% predicted maximum HR reserve (HRR) (i.e., (0.80 x [220-age] - HR_{rest}) + HR_{rest}) or a rate of perceived exertion (RPE) on Borg's 6-20 scale (Borg, 1982) of ~15 (i.e., "hard"). The cycle test consisted of a 1-min warm-up at 15 W followed by three 4-min stages (cycling at 60 revolutions per minute [rpm]). Based on information obtained during the consultation a starting load of 25-50 W was applied and which increased by 20-35 W for each stage. BP, HR and RPE were recorded for each stage and interpretation of symptom limits were used to optimise safe increments (Colberg et al., 2003). Subsequently, steady state HRs from the final two stages were extrapolated to the predicted maximum HR in order to estimate maximal workload (eWLmax) (Shaban et al., 2014). As the participants were from a clinical population, stage lengths of 4-min were used to help ensure a physiological steady state was met and by using extrapolated values maximal physiological responses are intentionally removed (Shaban et al., 2014). Data obtained from the SP's final two stages of the GXT was used to predict SP's aerobic capacity via maximal oxygen consumption (VO_2max) (Beekley et al., 2004). The gradient of the increase in SBP and DBP between resting and the GXT's final stage was recorded as SBP_{GXT} and DBP_{GXT}, respectively, and expressed as mmHg per Watt (mmHg/W).

Physiological assessments (Session 2).

Adiposity. Waist circumference was measured according to the International Society for the Advancement of Kinanthropometry (ISAK) guidelines (Stewart, Marfell-Jones, Olds & de Ridder, 2011) using a non-elastic measuring tape. With the participant standing in the anatomical zero position the waist circumference was measured in a horizontal plane midway between the last rib and the iliac crest. Subcutaneous adiposity was measured indirectly using skinfold thickness, according to ISAK at seven marked skinfold sites (triceps, subscapular, biceps, supraspinale, abdominal, front thigh and medial calf) using a Harpenden skinfold calliper (Baty International, West Sussex, England) and recorded to the nearest 0.1 mm. Subcutaneous adiposity was reported as the sum of the seven measurements.

Postural stability. As per the procedures previously described the postural stability tests was repeated in order to enhance reliability. The mean of each of the variables was used for analysis.

Resting BP. As per the procedure previously described two BP measurements were repeated. The mean of the four recordings taken during the two assessment sessions was used for analysis. Mean arterial pressure (MAP) was calculated by adding a third of the pulse pressure to DBP (MAP = DBP + [0.33 x [SBP – DBP]]).

Orthostatic tolerance test (OTT). During this test, an additional marker of autonomic function (Russell & Cooper, 2015), a standing BP was taken immediately upon rising from the supine position.

Isokinetic ankle strength testing. Before the isokinetic testing to assess distal muscle atrophy (a marker of DPN), SPs were instructed to warm-up with a 5-min cycle on an ergometer maintaining 60 rpm at a comfortable resistance. To conclude the warm-up 30-sec ankle plantar and dorsi-flexion stretches were performed. Strength assessments were conducted on a Humac NORM (Computer Sports Medicine Inc., Stoughton, MA) isokinetic dynamometer. The dynamometer was pre-calibrated for speed, weight and position following the instructions of the manufacturer. Peak torque and work recordings, assessing the ankle joint (of the dominant leg) through full plantar-dorsiflexion range, for the concentric action were obtained (Tan et al., 2012).

Absolute isokinetic torque values (gravity-corrected) were recorded as Newton-meters (Nm). The assessment protocol was standardised with respect to patient set-up, familiarisation (1 set of 6 progressive repetitions for the 60°/s trials and 1 set of 3 progressive repetitions for the 30°/s trial), rest intervals (30-sec after the familiarisation trial repetitions and 60-sec between the test repetitions) and test repetitions (2 sets of 3 repetitions). The maximum values obtained during the two sets (reciprocal-contractions) at both 30- and 60°/s were recorded (Tan et al., 2012). SPs were assessed in the supine position with a chair back angle of 20° and the knee joint fully extended. Thigh straps were used for leg stabilisation and SPs were instructed to hold the handles while being verbally encouraged to exert maximal effort during the test.

Statistical analyses

Data were analysed using the Statistical Package for the Social Sciences (SPSS) (IBM SPSS Statistics for Windows v24.0, 2016 Armonk, NY: IBM Corp.). Normality was assessed using the Q-Q plots and the Shapiro-Wilk test. Data are presented as means ± standard deviation (SD) where normality of distribution was confirmed. Alternatively, data are presented as median and interquartile range. The magnitude of correlations were determined using Pearson's correlation coefficients where normality of distribution was confirmed and Spearman's rho for the non-parametric analyses. For an α (two-tailed) of 0.05, a β of 0.20 (80% power) and a r of 0.55 (expected correlation coefficient) a sample size of 24 was required. The SP's medical history, medication usage, ethnicity, PACES, and nutrition habits were recorded for descriptive purposes only and were not included in the correlational analysis.

Results

Table 7 presents the continuous variables and the consultation and assessment data of the 24 male SPs that were used for correlation analyses. As cornerstones of diabetes management include exercise, nutrition and medication (Jelleyman et al., 2015), Table 8 depicting the medical history, ethnicity, PA enjoyment and nutrition habits, and Table 9 displaying the

Table 7: Characteristics of the 24 male T2D study participants following the pre-intervention assessments

Participant Characteristics		Macrovascular Marker		Microvascular Marker	
Referral information		Blood pressure		Peripheral neuropathy	
Age (yrs)	52.3 ± 6.8	Resting SBP (mmHg)	135.8 ± 14.8	10g Monofilament (/20)	16.3 ± 4.1
T2D duration (yrs)	8.2 ± 5.1	Resting DBP (mmHg)	85.3 ± 6.7	Trace length: Firm (mm)	977 ± 395
HbA1c (mmol/mol)	64.1 ± 13.8	Resting MAP (mmHg)	102.0 ± 8.9	C90 area: Firm (mm^2)	959 ± 603
Current physical activity		SBP_{GXT} (mmHg/W)	0.86 ± 0.58	STD Velocity: Firm (mm/s)	17.1 ± 6.4
Total (MET min/wk)	1421 (866, 2220)	DBP_{GXT} (mmHg/W)	0.05 ± 0.32	Peak torque: 30°/s PF (Nm)	137.4 ± 26.6
Work (MET min/wk)	0 (0, 1215)	Lipid profile		Peak torque: 30°/s DF (Nm)	31.5 ± 8.9
Transportation (MET min/wk)	0 (0, 165)	Total cholesterol (mmol/L)	4.38 ± 1.17	Work - best rep: 30°/s PF (Nm)	75.9 ± 18.5
Domestic (MET min/wk)	250 (46, 735)	Triglycerides (mmol/L)	3.25 ± 5.92	Work – best rep: 30°/s DF (Nm)	17.7 ± 6.4
Leisure (MET min/wk)	198 (0, 608)	HDL (mmol/L)	1.06 ± 0.24	Autonomic neuropathy	
Vigorous (MET min/wk)	0 (0, 0)	TC:HDL ratio	4.53 ± 2.81	Decrease in SBP_{OTT} (mmHg)	8.2 ± 13.0
Moderate (MET min/wk)	540 (240, 983)	LDL (mmol/L)	2.20 ± 0.59	Decrease in DBP_{OTT} (mmHg)	1.7 ± 6.7
Walking (MET min/wk)	792 (206, 1267)	Adiposity		HRV deep breathing	1.13 ± 0.09
Sitting (hrs/wk)	93 (67, 97)	Weight (kg)	117.9 ± 26.3	Nephropathy	
Cardiovascular fitness		BMI (kg/m^2)	37.2 ± 8.0	uACR (mg/mmol)	1.0 (0.5, 2.1)
Peak wattage (W)	90.8 ± 24.8	Waist girth (cm)	124.8 ± 17.7		
SBPpeak (mmHg)	197.7 ± 25.2	Waist:height ratio	0.70 ± 0.10		
DBPpeak (mmHg)	85.3 ± 13.2	Sum of 7 skinfolds (mm)	260 ± 108		
eWLmax (W)	144.3 ± 41.8	Inflammation			
Predicted VO_2max (mL/kg/min)	21.1 ± 5.7	hs-CRP (mg/L)	2.70 (1.23, 4.50)		

Data are presented as mean ± SD or as median (interquartile range).

BMI, body mass index; C90, 90% confidence ellipse area; DBP, diastolic blood pressure; DF, dorsi-flexion; eWLmax, estimated maximum workload; HbA1c, glycated haemoglobin; GXT, graded exercise test; HDL, high-density lipoprotein cholesterol; HRV, heart rate variability; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein cholesterol; MAP, mean arterial pressure; MET, metabolic equivalents; OTT, orthostatic tolerance test; PF, plantar flexion; rep, repetition; SBP, systolic blood pressure; STD, standard deviation of the velocity; TC, total cholesterol; T2D, type 2 diabetes mellitus; uACR, urine albumin creatinine ratio; VO_2max, maximum aerobic capacity; (/20), possible maximum of 20.

Table 8: Medical history, ethnicity, exercise enjoyment and nutrition scores of the 24 study participants

Medical history	n (%)	Ethnicity	n (%)	Nutrition penalties	mean ± SD
Personal history of MI (≥ 2 yrs.)	4 (16.7%)	NZ European	19 (79.2%)	General Food Quality (/60)	28.5 ± 5.7
Atrial Fibrillation	1 (4.2%)	Māori	3 (12.5%)	Fast Foods (/30)	8.5 ± 3.5
Family history of MI	11 (45.8%)	Indian	2 (8.3%)	Refined CHO (/50)	9.1 ± 5.9
Ex-smokers (> 2 yrs.)	12 (50.0%)			Smoking (/30)	0.0 ± 0.0
Neuropathic Pain	0 (0.0%)			Alcohol Consumption (/30)	3.2 ± 4.2
Mild retinopathy	2 (8.3%)	Physical activity enjoyment	mean ± SD	Total (/200)	49.4 ± 11.8
Arthritis	2 (8.3%)	PACES (/80)	65.3 ± 11.0		
Gout	2 (8.3%)				
Total hip replacement	1 (4.2%)				

Data are presented as mean ± SD or as number of participants (sample %).

CHO, carbohydrates; MI, myocardial infarction; NZ, New Zealand; PACES, Physical Activity Enjoyment Scale; (/30), possible maximum of 30; (/50), possible maximum of 50; (/60), possible maximum of 60; (/80), possible maximum of 80; (/200), possible maximum of 200.

Table 9: Medication usage of the 24 qualifying study participants

Antihyperglycaemic medication	n (%)	Cardiovascular medications	n (%)	Other medications	n (%)
Biguanide (Metformin)	23 (95.8%)	Hypertension	20 (83.4%)	CPAP therapy for OSA	5 (20.8%)
Sulfonylureas	8 (33.3%)	ACE inhibitors	10 (41.6%)	Bronchodilators	3 (12.5%)
Exogenous insulin	9 (37.5%)	Non-ACE inhibitors	6 (25.0%)	Antihistamines	3 (12.5%)
No antihyperglycaemic	1 (4.2%)	(ACE and Non-ACE inhibitors)	4 (16.7%)	Reflux	1 (4.2%)
		Statins	16 (66.7%)	Anti-depressants	5 (20.8%)
		Anticoagulants	12 (50.0%)	Gout	2 (8.3%)
		Beta blockers	5 (20.8%)	Erectile dysfunction	1 (4.2%)
		Diuretic	1 (4.2%)	NSAID	1 (4.2%)
				Analgesics	1 (4.2%)

Data are presented as number of participants (sample %).

ACE, angiotensin-converting enzyme; CPAP, continuous positive airway pressure; NSAID, nonsteroidal anti-inflammatory drugs; OSA, obstructive sleep apnoea.

Table 10: The association between selected pre-exercise screening tests and macrovascular complication markers

	Referral note details			Habitual physical activity and nutrition					Resting physiological variables					Fitness
	Age	T2D duration	HbA1c	IPAQ TOTAL[a]	IPAQ MOD[a]	Sitting hours[a]	NZANS Total	Refined CHO	BMI	Waist girth	10g MFT	MAP	HRV (n=23)	Predicted VO_2max
Resting SBP	-0.25	0.15	0.24	-0.14	0.06	0.01	-0.04	-0.11	0.41*	0.38	-0.11	-	-0.33	-0.18
Resting DBP	-0.17	0.11	0.23	-0.14	0.04	0.09	-0.01	-0.10	0.22	0.20	-0.19	-	-0.39	-0.04
SBP_{GXT}	-0.38	0.16	0.48*	0.04	0.18	-0.14	-0.29	-0.05	0.46*	0.23	-0.06	0.22	0.04	-0.60**
DBP_{GXT}	-0.39	0.12	0.15	0.15	0.10	-0.12	-0.01	0.13	0.26	0.09	-0.13	0.10	0.08	-0.50*
HDL	0.40	0.29	-0.11	0.22	0.18	0.12	0.07	0.19	-0.31	-0.33	-0.16	-0.37	0.16	0.36
Weight	-0.03	0.02	0.19	-0.17	0.03	0.14	-0.08	-0.23	-	0.97**	-0.14	0.33	-0.46*	-0.71**
BMI	-0.17	0.16	0.37	-0.25	-0.02	0.11	-0.16	-0.23	-	0.93**	-0.08	0.33	-0.40	-0.77**
Waist girth	0.07	0.18	0.24	-0.19	0.01	0.12	-0.06	-0.18	0.93**	-	-0.24	0.31	-0.45*	-0.73**
∑7 skinfolds	0.03	0.12	0.06	-0.35	-0.08	0.19	-0.18	-0.04	0.85**	0.91**	-0.22	0.25	-0.43*	-0.71**
hs-CRP[a]	-0.15	0.32	0.20	-0.09	-0.05	0.15	0.28	0.04	0.48*	0.37	-0.03	0.27	-0.28	-0.11

n = 24 (unless reported otherwise). Data are r values. [a] Non-parametric analysis used.

Statistical significance is reported as follows: * $P \leq 0.05$, ** $P \leq 0.01$

BMI, body mass index; CHO, carbohydrates; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; GXT, graded exercise test; HDL, high-density lipoprotein cholesterol; HRV, heart rate variability; hs-CRP, high-sensitivity C-reactive protein; IPAQ, International Physical Activity Questionnaire; MAP, mean arterial pressure; MFT, monofilament test; MOD, moderate level activity MET min/wk; NZANS, New Zealand Adult Nutrition Survey; OTT, orthostatic tolerance test; SBP, systolic blood pressure; TOTAL, total MET min/wk; T2D, type 2 diabetes mellitus; VO_2max, maximum aerobic capacity; ∑7, sum of seven.

Table 11: The association between selected pre-exercise screening tests and microvascular complication markers

	Referral note details			Habitual physical activity and nutrition					Resting physiological variables					Fitness
	Age	T2D duration	HbA1c	IPAQ TOTAL[a]	IPAQ MOD[a]	Sitting hours[a]	NZANS Total	Refined CHO	BMI	Waist girth	10g MFT	MAP	HRV (n=23)	Predicted VO_2max
10g MFT	-0.48*	-0.53**	0.25	-0.08	-0.21	-0.06	-0.15	-0.35	-0.08	-0.24	-	-0.16	0.18	0.14
Trace length	0.13	0.18	-0.18	-0.06	-0.05	0.10	0.07	0.18	0.12	0.17	-0.52**	0.24	-0.16	-0.29
C90 area	0.03	-0.05	-0.10	-0.14	-0.11	0.22	-0.18	-0.06	0.13	0.14	-0.25	0.04	-0.01	-0.41*
STD Velocity	0.10	0.15	-0.17	-0.15	-0.13	0.19	-0.02	0.07	0.13	0.16	-0.43*	0.22	-0.16	-0.30
Peak Torque: PF	-0.03	-0.36	-0.05	-0.10	0.04	0.22	-0.17	-0.21	0.27	0.25	0.08	0.44*	-0.12	-0.17
Work - best rep: PF	0.15	-0.52**	-0.22	-0.04	0.04	0.06	-0.12	-0.08	-0.17	-0.23	0.28	0.12	0.12	0.10
Peak torque: DF	-0.26	-0.38	-0.09	-0.09	0.04	-0.00	-0.28	-0.18	0.12	0.07	0.11	0.37	-0.22	-0.03
Work - best rep: DF	-0.29	-0.47*	-0.12	-0.17	-0.14	0.01	-0.09	-0.20	-0.07	-0.23	0.39	0.16	-0.21	0.08
SBP_{OTT}	0.15	0.08	-0.20	-0.47*	-0.53**	0.35	0.56**	0.42*	-0.07	0.02	-0.16	0.14	-0.41*	0.09
DBP_{OTT}	0.46*	0.42*	-0.30	-0.24	-0.25	0.46*	0.23	0.06	-0.02	0.14	-0.41*	0.01	-0.24	-0.11
HRV (n = 23)	-0.22	-0.26	-0.25	0.54**	0.16	-0.18	-0.39	-0.17	-0.40	-0.45*	0.18	-0.38	-	0.19
uACR[a] (n = 22)	0.12	0.31	0.45*	-0.36	-0.20	-0.02	-0.28	-0.38	0.28	0.24	-0.16	0.42*	-0.50*	-0.40

n = 24 (unless reported otherwise). Data are r values. [a] Non-parametric analysis used.

Statistical significance is reported as follows: * $P \leq 0.05$, ** $P \leq 0.01$

BMI, body mass index; C90, 90% confidence ellipse area; CHO, carbohydrates; DBP, diastolic blood pressure; DF, dorsi-flexion (30°/s); HbA1c, glycated haemoglobin; HRV, heart rate variability; IPAQ, International Physical Activity Questionnaire; MAP, mean arterial pressure; MFT, monofilament test; MOD, moderate level activity MET min/wk; NZANS, New Zealand Adult Nutrition Survey; OTT, orthostatic tolerance test; PF, plantar flexion (30°/s); rep, repetition; SBP, systolic blood pressure; STD, standard deviation of the velocity; TOTAL, total MET min/wk; T2D, type 2 diabetes mellitus; uACR, urine albumin creatinine ratio; VO_2max, maximum aerobic capacity.

medication usage, are presented to further describe the SPs. The middle-aged men having moderate-duration T2D and while being under the care of their general practitioner (medication and lifestyle advice) presented as sedentary (elevated sitting hours and poor aerobic capacity) even though their PACES scores did not reveal any aversion to exercise.

Additionally, the SPs had normoalbuminuria and seemed to be following the Eating and Activity Guidelines of limiting alcohol consumption, refined carbohydrates and fast foods. However, while the SPs were taking medications as prescribed, they did present with elevated HbA1c, morbid obesity (central adiposity), and pre-hypertension. Although no SP presented with significant absolute contra-indications during the GXT it is noted that the SPs were cleared for exercise by their general practitioner and were assessed for eligibility prior to study entry (Figure 2). Tables 10 & 11 present the correlations between selected variables and macro- and microvascular complication markers, respectively. Due to this high statin usage rate only HDL was considered valid, as it is not greatly altered by statin therapy (Rodríguez-Vigil et al., 2016).

Discussion

The discussion of the association between variables in this study will be conducted in a sequence similar to that of a pre-exercise screening sequence (i.e., referral details, habitual PA and nutrition, resting physiological variables) so that CEPs can be aware of associations of initially-obtained variables with the variables being tested in the latter stages (i.e., the graded exercise test) of the screening.

Referral details

Within this cohort, neither SP age, T2D duration nor HbA1c (three typical referral note details) were associated with resting hypertension and hyperlipidaemia (Table 10). Of note, 96%, 83% and 67% of the SPs were receiving antihyperglycaemic, antihypertensive and statin medication, respectively, so it possible these high levels of medication usage confounded the results. Obesity and T2D are inextricably linked (Colberg et al., 2010; Jelleyman et al., 2015) and although the results for the men of my study indicated that for those who had lived with T2D for longer were not more obese (P = 0.47), for those who presented with a higher HbA1c at referral there was almost an association (P = 0.07). Furthermore, greater age and duration of T2D were both associated (P = 0.02) with poorer 10g

monofilament test and DBP_{OTT} scores, and greater duration of T2D was additionally associated with lower ankle function. However, the positive association of HbA1c with SBP_{GXT} (P = 0.02) can heed as a warning to CEPs that elevated HbA1c levels are associated with exaggerated rises in exercise SBP. To illustrate, the SP with an HbA1c of 101 mmol/mol had a SBP rise of 2.4 mmHg/W during the GXT, which was steeper than the study mean of 0.9 mmHg/W (Table 7). Essentially, assuming normal resting BP (120 /80 mmHg), such a SBP rise would require close monitoring with a peak wattage (W) of only 60 W, potentially, resulting in a peak SBP of 264 mmHg; a value exceeding current guidelines (American College of Sports Medicine [ACSM], 2014). In addition, there was an association between HbA1c and uACR (P = 0.03) (Table 11). Although the SPs of this study presented with normoalbuminuria, the presence of nephropathy is associated with mortality in people living with T2D (Russell & Cooper, 2015), so health professionals need to continue educating their patients on the importance of regularly monitoring and controlling both variables. Whereas relationships between glycaemia and systemic inflammation have been reported in people living with T2D (Goldberg, 2009; King, Mainous III, Buchanan & Pearson, 2003; Patil & Ganu, 2014), no such relationship was evident in this study (P = 0.34).

Habitual physical activity and nutrition

International scientific organisations recommend, for the management of T2D, the weekly accumulation of a minimum of 150 min of moderate-to-vigorous intensity aerobic activity spread over a minimum of three days a week coupled with RT at least two days a week (Mendes et al., 2016). Applied to the IPAQ scoring, these recommendations equate to a minimum 1200 MET min/ week of moderate-to-vigorous activity. While the current SPs accumulated a median total of 1421 MET min/week (the majority derived from walking), the volume of moderate activity was 540 MET min/ week, and with no SPs partaking in any vigorous activity, the SPs' accumulated weekly energy expenditure at baseline was only 45.0% of the minimum level required by the recommendations (Table 7).

In this study cohort neither habitual PA, nor habitual nutrition were associated with any of the macrovascular markers (Table 10). This is a noteworthy finding as PA and nutrition are cornerstones in T2D management (Colberg et al., 2016), but medication prescription targeting the macrovascular markers, potentially confound the findings. Nonetheless, there were strong associations of PA with markers of autonomic neuropathy (SBP_{OTT}, DBP_{OTT} and HRV) (Table 11). Similarly, the total nutrition

score was strongly associated to SBP_{OTT} (P = 0.005) and was only close to significance for HRV (P = 0.07).

Resting physiological variables

Notwithstanding that the resting physiological variables are themselves markers of diabetic complications, significant associations within this cohort emphasised the association of adiposity, in particular, with diabetic complications. For example, there were positive association of BMI with hs-CRP (P = 0.02), resting SBP (P = 0.048) and SBP_{GXT} (P = 0.02) (Table 10) and a negative association of waist girth with HRV (P = 0.03) (Table 11).

The significant negative association between the monofilament test and both TL (P = 0.009) and standard deviation of velocity (P = 0.04) (Table 11) demonstrated that poorer peripheral stimulation responses were related to larger balance deviations; characteristic of DPN (Colberg, 2013). However, there were no associations between the monofilament test and isokinetic ankle strength in this cohort; although the result for monofilament test and dorsi-flexion work was close to significant (P = 0.06). The negative association of the monofilament test with DBP_{OTT} (P = 0.05) highlights a relationship between these peripheral and autonomic complication markers. Interestingly, while MAP was positively associated with uACR (P = 0.05), the positive association of MAP with plantar flexion strength is counter-intuitive (P =0.03) (Table 11). The precise mechanism for this relationship is not obvious and further research may be warranted.

HRV was negatively associated with SBP_{OTT} (P = 0.05) and uACR (P = 0.02) (Table 11). Early-stage kidney disease is asymptomatic and is associated with both morbidity and mortality (Levey, Becker & Inker, 2015), so any means of assisting early detection, such as reduced HRV, becomes vital to nephropathy management in those with T2D.

The results of this study's resting physiological measures assist CEPs by demonstrating that obesity is associated with diabetic complication and should remain a focus in their lifestyle educational programmes. Monofilament and HRV testing also provide valuable information regarding the health status of men with T2D and should be included in pre-exercise screening where possible (e.g., electrocardiogram accessibility).

Aerobic fitness

The negative associations between VO_2max and both SBP_{GXT} (P = 0.002) and DBP_{GXT} (P = 0.02) (Table 10) demonstrated the relationship between poorer aerobic fitness and greater increases in exercise blood pressures. Moreover, while poorer aerobic fitness was associated with less favourable adiposity, and balance (C90 area) measures, it must be noted that the suboptimal aerobic fitness levels of this cohort were not associated with resting BP, HDL, ankle strength or HRV.

Summary

Data obtained during a pre-exercise screening provide key information to healthcare professionals and CEPs should be aware that a.) HbA1c, MAP and HRV are independently associated with renal function, b.) 10g monofilament test is associated with balance, c.) increased adiposity is associated with elevated resting SBP, hs-CRP and reduced HRV, and d.) higher HbA1c and BMI levels are independently associated with exaggerated rises in exercise SBP.

Limitations. Although all 24 males who met the entry criteria for an exercise intervention study were included for analysis, all of the participants were taking numerous medications, and until alternative research strategies around discontinuing prescribed medication obtain ethical approval, results, particularly for cardiometabolic markers will remain unclear. Furthermore, analyses were limited to pre-exercise screening variables with markers of diabetic complications, and not with clinical end points such as MI, stroke or amputations.

Strengths. This study presented a detailed profile of a homogenous group of middle-aged T2D males about to commence exercise interventions in a real-world commercial setting. Encompassed in the profile, a novel method to monitor nutrition habits was presented. The study also determined associations between select pre-exercise screening variables and macro- and microvascular complication markers that may assist CEPs in the management of similar patients.

Future research. While this study included those SPs who agreed and were able to be participants in an exercise intervention study, future research can build upon the current study by utilising a greater range of people with T2D including those presenting with complex comorbidities and/or not able to commit to the weekly requirements of an intervention study. Moreover, studies that analyse the efficacy of various intervention strategies on such a cohort (including exercise, pharmacological and,

in particular, nutrition interventions) that optimise the management of T2D, and its insidious complications, are warranted.

Conclusions

In men living with T2D, associations between diabetic complications are not glucocentric and other readily obtained variables, such as those obtained during a pre-exercise screening (specifically diabetes duration, BMI, the monofilament test and HRV) provide additional information to all healthcare professionals. Although associations do not determine causation, understanding of the relationships between selected variables and diabetic complications among my SPs will enable CEPs to provide enhanced lifestyle education and pre-exercise screening to middle-aged men with T2D.