Changing the time under tension: effects of different forms of concurrent training on inflammatory and cardiometabolic disease indicators

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Certificate of Original Authorship

I, Nicholas Allen, declare that this thesis is submitted in fulfilment of the requirements for the award of Doctor of Philosophy, in the Faculty of Health at the University of Technology Sydney. This thesis is wholly my own work unless otherwise referenced or acknowledged.

In addition, I certify that all information sources and literature used are indicated in the thesis. This document has not been submitted for qualifications at any other academic institution. This research is supported by the Australian Government Research Training Program.

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Abbreviations

ANOVA	Analysis of variance
AT	Aerobic training
BFR	Blood flow restriction
BMI	Body mass index
CAD	Coronary artery disease
CCL2	Chemokine (C-C motif) ligand 2
CET	Concurrent exercise training
CRL	Control group
CRP	C-reactive protein
CVD	Cardiovascular disease
DEXA	Dual-energy x-ray absorptiometry
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid
GIP	Gastric inhibitory polypeptide
GLP	Glucagon-like peptide
GLUT	Glucose transporter
HbA1c	Glycated haemoglobin
HDL	High-density lipoprotein
HIIT	High-intensity interval training
HOMA-IR	Homeostasis model for assessment of insulin resistance
HSD	Honestly significant difference
HR	Heart rate
HRR	Heart rate reserve
ICAM	Intercellular adhesion molecule
IL	Interleukin
IQR	Interquartile range
IRS	Insulin receptor substrate
LDL	Low-density lipoprotein
MCP-1	Monocyte chemoattractant protein 1
MI	Myocardial infarction
MMP	Matrix metalloproteinase
mRNA	Messenger ribonucleic acid
NAFLD	Non-alcoholic fatty liver disease
NFκB	Nuclear factor kappa-light-chain-enhancer of activated B cells
OGTT	Oral glucose tolerance test
PAD	Peripheral artery disease
PCI	Percutaneous coronary intervention
PPO	Peak power output
RA	Receptor antagonist
RM	Repetition maximum
RT	Resistance training
SAA	Serum amyloid A
SAT	Subcutaneous adipose tissue
SE	Stimulus exposure
TBFM	Total-body fat mass
TBLM	Total-body lean mass
TNFα	Tumour necrosis factor α
T2DM	Type 2 diabetes mellitus

TUT	Time-under-tension
VAT	Visceral adipose tissue
VCAM	Vascular cell adhesion molecule
VO2peak	Peak oxygen consumption
VL	Vastus lateralis
vWF	von Willebrand Factor

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Abstract

This thesis examines the effects of different forms of concurrent exercise training (CET) on physiological biomarkers related to cardiometabolic disease risk. Specifically, a modification of CET to emphasise muscle time-under-tension (TUT) during the resistance component is examined as a potential alternative for a population of sedentary older adults. The present thesis seeks to compare conventional CET methods to a modified version (i.e. TUT) on blood-based biomarkers related to systemic inflammation, glucose homeostasis, and cardiovascular disease (CVD) risk. Secondary outcomes include whole-body and regional tissue composition, ultrasound-derived muscular thickness, and physical fitness measures. Further, a greater understanding of the relationship between training stimuli and key functional outcomes is explored.

Data derived from the present investigation is presented within three distinct studies. Firstly, study 1 explored the effect of CET versus TUT on biomarkers related to T2DM, namely inflammatory cytokines (IL-6 and TNFα) and markers of glucose homeostasis, alongside body composition and physical capacity measures. Study 2 describes the effect of these training modalities on CVD-related parameters, including blood-based measures of platelet activity and endothelial function, as well as region-specific fat mass and physical fitness. Finally, study 3 examines the relationship between selected predictor variables (aerobic capacity, muscular strength, and whole-body lean and fat mass) and key prognostic disease indicators (IL-6, TNFα and insulin resistance). A secondary aim of study 3 is to assess the dose-specific response of CET and TUT by quantifying the relationship between overall training volumes and the associated changes in the abovementioned biomarkers.

Thirty-eight sedentary adults completed either 10 weeks of 3 sessions/week of traditional CET or TUT-based concurrent training. Based on baseline characteristics (age, sex, body mass index and fitness) participants were stratified and randomly assigned into CET (n=13), TUT (n=12), or a sedentary control (CRL; n=13). CET involved 30-40 min of resistance training using a 1.5-1.5s tempo, followed by 15-20 min of moderate-intensity endurance training. In contrast, TUT performed the same repetition-volume with a 3-3s tempo, entailing twice the time-under-tension with a reduced mechanical load (resistance lifted). The aerobic component was identical across both groups, comprising non-load-bearing modalities (cycling and rowing). During the intervention period, a control group (CRL) was instructed to maintain habitual lifestyle behaviours. Prior to and following the training intervention, participants underwent testing sessions comprising a venous blood sample for measurement of cardiometabolic disease indicators. Also, a dual-energy x-ray absorptiometry (DEXA) scan provided measures of total-body lean mass (TBLM), fat mass (TBFM) and visceral and subcutaneous adipose tissue mass (VAT and SAT). Other measures included muscle ultrasound of *m. vastus lateralis* thickness, and assessment of maximal strength and endurance capacity. Pre- to post-intervention changes in these health-related parameters were analysed using a mixed-design analysis of variance (ANOVA) for detection of main effects and group x time interactions. In the presence of significant effects, post hoc tests using Tukey's HSD correction located the source of significance at an α-level of 0.05. Moreover, Pearson's correlations were used to quantify relationships between primary outcome variables, and subsequently linear regressions were used to investigate the relationship of the changes in relevant predictors to the variance of individual changes in key disease biomarkers.

Overall, training loads showed the between-group difference in volume-load was not significantly different ($p=0.080$), although when incorporating total lifting time-under-tension, TUT showed a greater overall stimulus exposure (SE) ($p=0.003$). The key findings from this training intervention are that IL-6 showed a significant group x time interaction ($p=0.017$), whereby CET showed the greatest reduction of all groups ($p=0.021$). In contrast, only TUT significantly decreased TNFα ($p=0.016$), without any significant changes in any other inflammatory markers ($p>0.05$). Whilst all groups reduced plasma glucose ($p<0.05$), there were no significant changes in HOMA-IR or other glucose regulatory markers ($p>0.05$). Further, CVD-related markers of inflammatory and platelet activity showed no significant changes following training ($p>0.05$). CRP was unchanged ($p>0.05$), while MCP-1 increased in CRL ($p=0.015$), without significant change in CET and TUT ($p>0.05$). Exercise-induced reductions were only evident for p-selectin, which decreased in CET ($p=0.009$).

Whole-body lean and fat mass were improved most by CET, as it was the only group to show a decrease in TBFM ($p=0.027$) and an increase in TBLM ($p<0.001$). In contrast, regional measures showed TUT provided the greatest reduction in SAT ($p=0.030$) and CET preferentially decreased VAT ($p=0.049$). Further, thickness of *m. vastus lateralis* showed a significant group x time interaction ($p=0.002$), decreasing in CRL ($p=0.028$) and increasing in CET ($p=0.003$). Physical fitness parameters showed a mode-specific response whereby CET preferentially increased quadriceps strength ($p=0.001$) and TUT provided the greatest increase in VO_{2peak} ($p<0.001$). Both CET and TUT increased peak power output ($p<0.05$).

Linear regression analyses revealed that the change in IL-6 was explained by the change in strength and TBLM (y = 0.355 – (0.035 x strength) + (0.774 x TBLM)). In contrast, for HOMA-IR no predictors were significant in a linear regression model, and no significant correlations were present with any variable. The cumulative volume-load showed that the change in IL-6 was significantly and negatively correlated with total volume-load (r = -0.387, p=0.011). The change in TNFα was negatively correlated with total volume-load (r = -0.396, p = 0.018). However, when controlling for strength changes, these correlations were no longer significant. Moreover, in a linear regression equation volume-load was significantly associated with strength (y = 3.24 + (0.137 x volume-load); p = 0.023) and VO_{2peak} (y = 0.925 + (0.013 x volume-load); p = 0.022). Conversely, volume-load did not significantly explain TBLM (y = 0.431 + (0.002 x volume-load); p = 0.072) or TBFM changes (y = 0.002 – (0.004 x volume-load); p = 0.076).

The present findings suggest that modifying the resistance component through novel modalities such as TUT may have small, yet relevant consequences that can aid the tailoring of exercise stimuli to individual needs. Specifically, although CET was superior to reduce IL-6, TUT showed greater decreases in TNFα. By comparison, traditional CET was superior to increase TBLM and muscular strength and decrease TBFM, while TUT preferentially decreased VAT and increased VO_{2peak}. For individuals seeking to enhance body composition, physical capacity, and cardiometabolic disease indicators, conventional CET strategies may be most appropriate, although TUT does provide some distinct benefit. Importantly, increased muscular strength seems to be an important predictor of a decreased inflammatory milieu, and greater training volumes are associated with larger strength gains, recognising the standardisation of the aerobic component. Such

findings provide evidence for practitioners to tailor the exercise training stimuli from concurrent training to better suit the specific demands of sedentary, aged populations.

The present findings will assist exercise professionals and individuals in the prescription of CET for older adults. In particular, the safety and efficacy shown in the current studies reiterates the importance of CET modalities to offset age-related increases in cardiometabolic risk. More specifically, conventional CET strategies incorporating higher RT loads may provide superior strength adaptations, while prolonged TUT techniques may enhance endurance parameters. Mode-specific adaptations further show that traditional CET can confer enhancements in body composition, alongside an anti-inflammatory effect. Future research should investigate the role of these training strategies to manage existing cardiometabolic diseases, and elucidate the long-term effects of CET, particularly with regards to injury rates, training adherence, and sustainability

Chapter 1

Introduction

Background

A poor lifestyle-induced health status is characterised by physical inactivity, obesity, and an elevated presence of pro-inflammatory cytokines such as c-reactive protein (CRP), interleukin (IL)-6 and tumour necrosis factor-α (TNFα) (Pradhan, 2007). These inflammatory mediators contribute to the onset and progression of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) (Hotamisligil, 2006; Pearson et al., 2003). Specifically, these markers show a causative relationship with tissue-specific indicators of atherosclerosis (Pasceri et al., 2000), insulin resistance (Halse et al., 2001), and an exacerbated mortality risk (Soinio et al., 2006). Accordingly, the mechanistic importance of these cytokines has positioned them as key intervention targets for individuals seeking to reduce lifestyle-associated disease risk (Ridker et al., 2003). To achieve this, exercise training is understood to improve the systemic inflammatory profile and offset the risk of both CVD and T2DM (Gleeson et al., 2011). However, whilst the concept of "exercise as medicine" is well known (Pedersen & Saltin, 2015), the specific role of different training strategies, and the appropriateness for untrained individuals, remains generic and less well-defined (Burton et al., 2017b).

Aerobic- and resistance-based training are staples of exercise prescription and reside on opposite ends of the training stimulus spectrum, providing divergent physiological responses and adaptations (Coffey & Hawley, 2017). Specifically, aerobic exercise may improve cardio-pulmonary and metabolic adaptations, such as increased cardio-respiratory capacity, muscular endurance, enhanced substrate utilisation, and muscle capillarisation (Hackney, 2019; Hawley, 2002). These adaptations have shown to improve metabolic abnormalities related to impaired glucose homeostasis (Egan & Zierath, 2013) in conjunction with an ameliorated inflammatory profile (Petersen & Pedersen, 2005). By

comparison, resistance training results in increased muscle mass and strength (Braith & Stewart, 2006). Skeletal muscle is the predominant site of insulin-mediated glucose disposal (DeFronzo et al., 1981), and exercise acutely augments insulin-independent glucose uptake (Egan & Zierath, 2013). Accordingly, resistance-based training is associated with positive changes in glycaemic control and certain cardiovascular parameters such as lipid profiles and resting blood pressure (Braith & Stewart, 2006). These two respective exercise modes are the fundamental training methods prescribed to individuals seeking to enhance physical fitness and reduce the risk of chronic diseases (Ivy, 1997). However, the combined use of both respective modes, termed concurrent exercise training (CET) has shown promise as an effective method to provide the benefits of respective isolate modes (Donges et al., 2013) and may be applicable to older and sedentary populations who are in need of such generic adaptations (Nelson et al., 2007). Whilst performing CET in a cumulative fashion (i.e. full AT and RT loads) may inappropriately increase training loads for sedentary populations (Fyfe et al., 2014), half-dose CET combined within single sessions may still improve body composition and fitness adaptations significantly (Donges et al., 2013). A visual depiction of this phenomenon is shown in Figure 1.1.

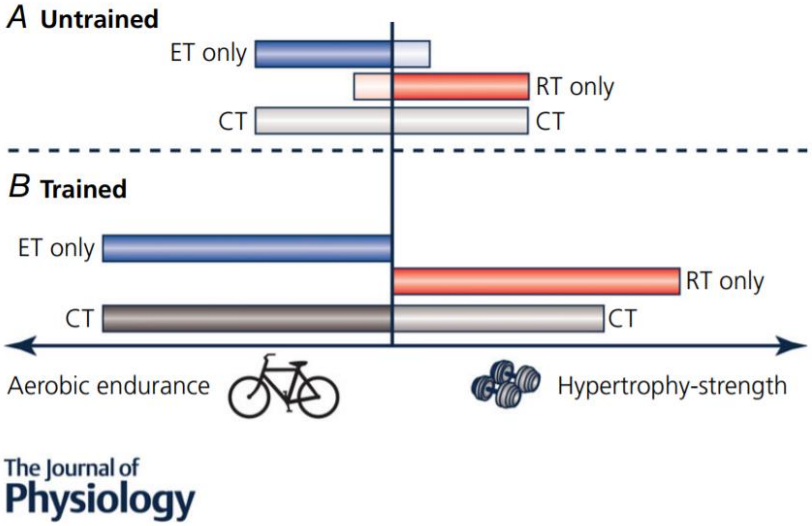

Figure 4. Adaptation to training in skeletal muscle of untrained compared with trained individuals
Schematic diagram showing, in *A*, the potential for endurance training (ET; light blue bar) to induce modest hypertrophy and resistance training (RT; pink bar) to promote oxidative capacity in the untrained state. The capacity for the different exercise modes to promote adaptive responses associated with the 'opposing' exercise also contributes to a lack of meaningful interference during concurrent training (CT; light gray) with short-term training in untrained or recreationally active individuals. *B*, specificity of adaptation with prolonged, intense training in well-trained athletes shows no significant 'cross-over' effects between exercise modes. Resistance training does not impair continued development of oxidative metabolism and endurance capacity but endurance training compromises gains in hypertrophy and strength with concurrent training (black/gray).

Figure 1.1: an illustration of the effect of training status on the interference effect of concurrent training, as featured in Coffey & Hawley (2017).

Previous research on CET in sedentary populations shows benefits for reducing chronic systemic inflammation. Specifically, CET interventions are shown to decrease CRP concentrations in overweight individuals (Lopes et al., 2016). Further, Ho et al. (2013) reported reduced TNFα after 12 weeks of CET in obese adults, which was greater than either AT or RT in isolation. Also, CET has shown efficacy in older adults to reduce IL-6 during prolonged training programs of 12 months (Nicklas et al., 2008).

As further evidence, research supports the use of CET to improve markers of glucose homeostasis. For example, decreased insulin resistance was observed following 12-week CET interventions in sedentary men and women respectively (Azarbayjani et al., 2014; Choi et al., 2007). Other key biomarkers related to glucose homeostasis have been shown to improve with CET, such as fasting leptin and glucose concentrations which decreased following 12 weeks of CET in obese individuals (Bharath et al., 2018). That said, when considering CVD biomarkers, a majority of data suggest CET can reduce adhesion molecules such as ICAM-1 (Saetre et al., 2011), although many of these studies relate to diseased populations (Tönjes et al., 2007). Similarly, vWF is reported to decrease with only 4 weeks of CET following a myocardial infarction (Vona et al., 2009), while Bjørnstad et al. (2008) observed significant decreases after 20 weeks of CET in heart failure patients. Accordingly, exercise training incorporating both aerobic and resistance components shows sufficient promise to improve markers associated with chronic disease in sedentary populations.

CET is typically undertaken in one of two ways – either AT and RT performed in separate sessions across a training program, or sequential AT and RT within a single session (Coffey & Hawley, 2017). Using the latter example, it is suggested that performing

endurance exercise immediately prior to resistance exercise may compromise the ability of the skeletal muscle to generate a sufficient stimulus to drive an adaptive response to RT (Leveritt & Abernethy, 1999). In particular, central and/or peripheral fatigue mechanisms following AT may impair subsequent strength performance (Jones & Howatson, 2019). In contrast, performing RT before AT within a session does not seem to cause the same level of interference, and seems to be the most practical option (Cadore et al., 2012). However, in sedentary populations, the effect of such interference holds less relevance given the untrained status and potential for generic adaptation (Fyfe et al., 2014). Thus, although exercise professionals should consider the order and structure of CET modalities, the role of any possible interference is beyond the scope of the present thesis, and indeed it seems that untrained persons can derive significant benefits from CET with a broad range of design strategies.

When used in untrained individuals, CET seems to confer a broad range of adaptations in a synergistic manner, whereby a generic adaptation profile is evident despite divergent exercise stimuli (Fyfe et al., 2014). More specifically, the health-related adaptations to AT and RT result from the activation of stress-induced cellular signals, producing positive changes in oxidative metabolism and mitochondrial respiration (i.e. AT) and muscle hypertrophy/strength (i.e. RT) (Coffey & Hawley, 2017; Fyfe et al., 2014). The simultaneous integration of these divergent exercise stimuli is shown to achieve positive changes in systemic inflammation (Balducci et al., 2010), abdominal adiposity (Ihalainen et al., 2018), and insulin sensitivity (Donges et al., 2013) in untrained populations. Thus, evidence suggests the anthropometrical and fitness improvements derived from CET can assist in reducing risk factors related to cardiometabolic diseases (Bartels et al., 2007). However, the increased mechanical loads associated with training both modes

concurrently may not be ideal for untrained individuals (Van Kan et al., 2009). Accordingly, further detailed exploration of the training stimulus is required, and for sedentary individuals, exploring the more granular aspects of training prescription through altered RT loads may provide significant benefits (Burton et al., 2017b). In explanation, increasing muscle strength and hypertrophy through higher-load resistance training is often prescribed (Marcotte et al., 2015), though this may be inappropriate for untrained individuals (Van Kan et al., 2009). Accordingly, recent research has shown that similar strength and hypertrophy gains can also be achieved using lower-load resistance training modalities, provided that working sets are performed to the point of muscular fatigue (Mitchell et al., 2012).

In accordance with Henneman's (1957) size principle, it is proposed that muscular adaptations are driven by maximal motor unit activation, and there are numerous ways in which individuals can achieve this response (Dankel et al., 2017). One such example, known as time-under-tension (TUT) training, represents a low-resistance strategy that may be applicable for older adults (Tanimoto et al., 2009). TUT involves lifting reduced RT loads at volitionally slow movement speeds, in order to deliver a prolonged contractile stimulus to the muscle (Burd et al., 2012). The resulting intramuscular metabolite accumulation (Dankel et al., 2017) and augmented motor unit activation may provide untrained persons with morphological and neuromuscular adaptations that parallel those of higher-load RT (Tanimoto et al., 2008). Importantly, the majority of current research seems to indicate that TUT is an effective low-load alternative to conventional RT to provide skeletal muscle hypertrophy and possibly fat loss, with preliminary evidence suggesting a potential benefit for reduced cardiometabolic disease markers (Okamoto et al., 2008; Tanimoto et al., 2009). The potential inclusion of TUT within CET provides a

theoretical vehicle to gain mutually beneficial responses from RT and AT, thus closing the gap in the training spectrum, whilst providing a training stimulus with reduced need for heavier resistance loads.

A number of studies have examined a time-under-tension strategy that involves lifting with a 3-3s tempo, and whether divergent outcomes are evident compared to repetition-matched and work-matched variants, although currently specific to RT (Rana et al., 2008; Tanimoto et al., 2008; Watanabe et al., 2013). Tanimoto and Ishii (2006) utilised such a method in untrained men, who performed unilateral knee extension exercise for 12 weeks at a low intensity (55-60% 1RM) with a slow cadence (3-3s), and on the opposite leg performed the same repetition-volume but at a higher intensity (80-90% 1RM) and a faster speed (1-1s). In this instance, both strategies produced equivalent muscle hypertrophy and strength gains. Importantly, a third protocol involving fast-speed lifting was matched for work with the slow-speed condition (entailing a non-fatiguing regimen) and was inferior with regards to strength and hypertrophy. This research provided a conceptual rationale for using TUT in a resistance training scenario, as the prolonged exposure to a reduced mechanical load was an effective alternative to higher-load RT. Later, the same group conducted a similar study involving whole-body resistance exercise, and again both high-load and TUT variants produced equal improvements in muscle cross-sectional area and maximal strength (Tanimoto et al., 2008). Therefore, by increasing the duration of loaded muscle contractions, TUT may deliver equivalent hypertrophic adaptations compared to conventional strategies. Within a CET design, modifying the RT component in this way may provide benefits for hypertrophy and/or strength in a more palatable and low-load strategy, although the effect on clinical disease-related parameters is unknown. Further, by incorporating TUT as a prolonged, low-load

RT modality, greater acute metabolic stress may provide a more consistent endurance-like stimulus (Scott, 2012) and accompany AT to improve cardiometabolic disease indicators. In particular, despite a reduced volume-load (Tanimoto & Ishii, 2006), the simultaneous delivery of AT and TUT is suggested to enhance endurance adaptations and confer anti-inflammatory and disease prevention benefits, though to date no evidence exists to support this more granular approach to training prescription.

In summary, substantial hypertrophy and cardiovascular fitness and body composition adaptations may be achieved with concurrent training (Schoenfeld et al., 2015a), that result in reduced chronic disease risk (Park et al., 2005; Visser et al., 2002; Ziccardi et al., 2002). However, the prescription of CET remains generic by both mode and stimulus-specificity of the exercise (Garber et al., 2011). Hence, by modifying the RT component of CET to emphasise TUT, older sedentary individuals may receive improved fitness, strength and body composition benefits, that in turn relate to reduced risk makers of chronic systemic inflammation, CVD and T2DM (Petersen & Pedersen, 2005; Van Gaal et al., 2006). Accordingly, the use of TUT within CET provides a theoretical vehicle to gain beneficial responses from RT and AT, without the need for heavier RT load. In turn, it is proposed that TUT will provide equivalent improvements in inflammatory and cardiometabolic disease markers compared to a conventional CET model.

Summary of Problem

Different exercise training modalities have distinct effects on fitness and health-related outcomes. Combining aerobic and resistance training strategies appears to be an effective way to achieve a broad range of physiological adaptations and improve disease risk factors (Cadore et al., 2014). For older adults, modification of specific exercise

prescription may be appropriate to reduce overall training loads while providing both AT- and RT-specific benefits. By altering the RT component of CET with slow-speed lifting (i.e. TUT), previously untrained individuals may increase muscle mass, reduce fat mass, and enhance physical fitness commensurate to conventional CET methods. In doing so, it is proposed that such individuals will reduce risk factors related to cardiometabolic disease including systemic inflammation, glucose homeostasis, and CVD markers.

Accordingly, the purpose of the present investigation is to examine the effect of CET and TUT within a CET program on markers of systemic inflammation, glucose homeostasis, and CVD risk, alongside body composition and fitness among sedentary older adults. Moreover, this thesis also aims to quantify the relationship between exercise-induced changes in strength, endurance, and body composition and the corresponding changes in levels of inflammatory cytokines as well as the relationship of training load with these parameters, to better understand exercise prescription.

Research Aims

This thesis comprises three studies aiming to determine the effect of 10 weeks of concurrent training with altered resistance training component (CET vs TUT) on:

1. The response of blood-based inflammatory and cardiometabolic disease indicators (chapters 3 & 4). It is hypothesised that CET and TUT will be equally beneficial to decrease systemic inflammation and ameliorate cardiometabolic risk.
2. Whole-body and region-specific lean and fat mass, as well as muscle thickness determined by B-mode ultrasound (chapters 3 & 4). It is hypothesised that both modalities will confer similar increases in skeletal muscle mass, alongside reductions in whole-body and regional adiposity.

3. Functional measurements of maximal strength and aerobic capacity (chapters 3 & 4). Mode-specific effects are expected to show increased strength via CET, and increased endurance parameters for TUT.
4. Determine the relationship between changes in key inflammatory and cardiometabolic prognostic indicators with training induced changes in body composition and fitness. In turn, to further explore the relationship between training volumes and changes in body composition and fitness markers (chapter 5). Based on previous studies, it is hypothesised that decreased adiposity, increased muscle mass, and an improved physical capacity will explain positive training-induced changes in disease biomarkers. Further, dose-dependent effects are expected to show a link between increased training volumes and the magnitude of improvement in these variables.

Limitations

- The present study involved participants who were classified as sedentary, aged 50-75y, and free from known diseases. As such, the findings cannot necessarily be extrapolated to younger populations, or individuals with existing medical conditions.
- Participants were instructed to refrain from any significant changes to lifestyle behaviours during the study period; however, compliance with this instruction was dependent on participants' willingness to do so, and was verified through self-reporting.
- Participant recruitment was conducted within the local geographical region, and as a result there was significant cultural and socioeconomic homogeneity within the participant cohort. Thus, the present methodology and/or findings may not be

applicable to persons from culturally diverse backgrounds, or those living in regional areas.

- Due to the small number of male participants, all data are pooled for statistical analyses. It is possible that men and women may respond differently to the respective intervention protocols, although no sex-based comparison is made.

Delimitations

- Participants were recruited based on inclusion criteria; specifically, a thorough screening questionnaire and interview were conducted with each individual to verify that all participants were sedentary, free from diseases, and not taking any medications that would influence blood markers or exercise performance.
- All testing measures were conducted by trained staff, using the same equipment, at the same time of day (± 1h) to minimise intertrial variability.
- For the 24h preceding baseline testing sessions, participants recorded all food consumed and physical activity completed. This document was returned before post-testing (with instructions to replicate these behaviours) to ensure identical preparation for physiological tests.
- Participants were stratified based on baseline VO_{2peak}, age and BMI so that, when randomised, similar physiological characteristics were present between groups.
- To maintain compliance the exercise protocol, participants were instructed to perform RT in time with an electronic metronome. This metronome was audible at all times and provided a 3-second count for concentric and eccentric phases in single-time (TUT) or double-time (CET).

Chapter 2

Literature Review

Overview

The use of exercise training to ameliorate age-related decrements in factors contributing to cardiometabolic disease has received significant attention (Abramson & Vaccarino, 2002). Particularly, chronic inflammatory, cardiovascular and diabetic disorders are a result of life-style related factors including sedentary behaviour and obesity (Pedersen et al., 2003; Van Gaal et al., 2006). As such, a need exists for tailored exercise-based strategies to provide health-related benefits in a manner that is physiologically and practically appropriate for individuals seeking to reduce disease risk (Burton et al., 2017a). Within the spectrum of exercise stimuli, combining aerobic- and resistance-based modalities through concurrent training may deliver a flexible and tailored approach to exercise prescription (Coffey & Hawley, 2017). Accordingly, this review of literature examines the mechanistic role of inflammatory, metabolic and cardiovascular biomarkers to development of disease, and the general role of exercise to offset this risk. Further, attention is given to the effects of training modalities and loads to improve these specific markers, and in particular the rationale for the use of CET. Moreover, specific effects on secondary outcome measures including body composition and physical fitness are investigated with consideration for the limitations of conventional CET models.

Literature Search Methods

This review constitutes a discussion of the role of CET to improve risk factors for cardiometabolic diseases, as well as an exploratory review of the potential application for TUT. To do this, scientific databases including PubMed and Google Scholar were searched using terms related to ‘exercise’, ‘resistance training’, ‘aerobic training’, ‘concurrent training’, ‘time under tension’, ‘inflammation’, ‘insulin resistance’, ‘cardiovascular disease’, ‘time under tension’, ‘hypertrophy’, ‘fat loss’, ‘cytokines’,

'TNFα', 'CRP', 'MCP-1', 'interleukins', 'insulin', 'glucagon', 'leptin', 'ICAM', 'VCAM', 'vWF', 'SAA', and 'p-selectin'. Abstracts were screened for relevance and highly relevant articles were included in a narrative review format. To be eligible for inclusion, articles were peer-reviewed, written in English, and available online in full-text format.

Due to the limited number of sources pertaining to older, sedentary individuals, studies across all population demographics were included. Broadly, the areas for which data were sought were:

- The mechanistic role of relevant biomarkers in the pathogenesis of chronic diseases.
- The prospective link between a poor lifestyle-induced health status and the risk of cardiometabolic diseases.
- The effects of aerobic exercise on cardiometabolic disease indicators.
- The effects of resistance exercise on cardiometabolic disease indicators.
- The effects of concurrent exercise on cardiometabolic disease indicators.
- The effect of TUT training on body composition, fitness, and biomarkers related to cardiometabolic and other diseases.

Background

The prevalence of lifestyle-related diseases represents a significant ongoing public health concern (Gleeson et al., 2011). The burden of conditions such as cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM) is considerable, particularly in developed countries (Bartels et al., 2007; Durstine et al., 2013). For example, data from the Australian Bureau of Statistics (2016) show that these conditions remain among the most

common causes of Australian deaths annually, with CVD featuring among the top three most common causes of death since 2000. These diseases are considerably burdensome and can impact upon social and economic prosperity (Durstine et al., 2013). Accordingly, strategies to prevent and/or lessen the impact of chronic health conditions continue to attract interest. In particular, given that increased disease-specific risk is related to inactive lifestyle factors (Van Gaal et al., 2006), altering exercise behaviours may be an avenue to offset the risk of CVD and T2DM.

Specifically, both CVD and T2DM are related to a poor lifestyle-induced health status characterised by sedentary behaviour, excessive energy consumption, and abdominal adiposity (Van Gaal et al., 2006). These lifestyle behaviours contribute to significant reductions in skeletal muscle function, impairment of mitochondrial and metabolic processes (Braith & Stewart, 2006), and the appearance of numerous subclinical disease risk factors such as insulin resistance, chronic inflammation, and vascular dysfunction (Berg & Scherer, 2005; Davignon & Ganz, 2004; Klein et al., 2004). Accordingly, a number of cardiovascular and metabolic pathologies are now understood to involve a complex relationship between humoral, hormonal and cellular changes (Niu & Kolattukudy, 2009). Specifically, the dysfunction of various autoimmune mechanisms shows a relationship with the onset and progression of numerous diseases (Libby et al., 2010). A chronic state of low-grade inflammation, characterised by elevated blood concentrations of pro-inflammatory cytokines, is identified as a key mechanism linking poor lifestyle habits and the eventual development of conditions such as T2DM and CVD (Libby et al., 2010).

Pursuant to obesity and physical inactivity, systemic chronic systemic inflammation causes alterations in metabolic and humoral characteristics (Trim et al., 2018). In CVD, pro-inflammatory cytokine activity promotes the initiation of adhesion molecules and coagulation processes (Pasceri et al., 2000), and contributes to plaque formation and eventual critical rupture (Davignon & Ganz, 2004; Kao et al., 2003). Separately, inflammatory mediators influence the tissue-specific changes leading to the onset of insulin resistance and T2DM (Pradhan et al., 2001). Namely, an elevated presence of inflammatory cytokines may interfere with insulin secretion (Khovidhunkit et al., 2000) and action (Pradhan, 2007). Hence, the balance of pro- and anti-inflammatory mediators is considered a useful biomarker of disease risk and, alongside disease- and tissue-specific markers, can provide insight into the progression of disease-related processes (Rocha & Libby, 2009).

Given the established causality between physical inactivity, obesity, and an elevated cardiometabolic risk status (Abramson & Vaccarino, 2002; Van Gaal et al., 2006), it is suggested that exercise-based strategies are an effective tool to decrease this risk by modifying the inflammatory milieu (Gleeson et al., 2011). Cross-sectional data indicate that increased aerobic capacity can decrease prognostic disease indicators (Aronson et al., 2004), whilst decreased fat mass and increase lean body mass may predicate a reduction in systemic inflammation and CVD risk (Pedersen et al., 2003; Van Gaal et al., 2006). As further support for exercise-induced benefit, experimental studies support the use of exercise training for reductions in systemic inflammation (Petersen & Pedersen, 2005), insulin resistance (Ivy, 1997), and atherosclerotic risk (Braith & Stewart, 2006). Consequently, the role of exercise to reduce physical inactivity, increase cardio-

respiratory fitness and reduce adiposity is important and represents an important intervention in the reduction of disease risk (Van Gaal et al., 2006).

The Role of Exercise

Exercise interventions are considered to be primary strategies in the context of reducing the risk and effect of chronic disease development (Durstine et al., 2013). Given that physical inactivity contributes a significant burden to global health (World Health Organisation, 2009), exercise training is a key focus of lifestyle-based health strategies. In particular, exercise interventions are increasingly important to offset the musculoskeletal and cardiometabolic decline associated with both ageing and lifestyle-related disease development (Burton et al., 2017b).

Importantly, different training modalities produce distinct adaptations (Coffey & Hawley, 2017), and thus mode specificity may have important implications for exercise prescription. Specifically, aerobic training (AT) enhances endurance via alterations in substrate utilisation (Hawley, 2002) and mitochondrial functioning (Egan & Zierath, 2013). As a key component of disease-prevention strategies, AT is effective to increase peak aerobic power and oxygen uptake, signifying an improved endurance capacity (Holloszy & Coyle, 1984). Importantly, AT is identified as a primary disease-prevention strategy due to its efficacy to reduce inflammatory cytokines (Petersen & Pedersen, 2005), enhance glucose regulation (Egan & Zierath, 2013), decrease adiposity (Pratley et al., 2000) and inhibit atherosclerotic processes (Farpour-Lambert et al., 2009).

At the opposite end of the training spectrum, resistance training (RT) is recommended for older adults to reduce the deleterious effects of sarcopenia (Van Kan et al., 2009), enhance

bone mineral density (Liu & Latham, 2009), and is shown to increase skeletal muscle mass and strength (Hurley et al., 2011). Importantly, the functional capacity gains derived from RT are key to maintaining quality of life with advancing age (Burton et al., 2017b). Further, some evidence suggests RT can improve cardiometabolic risk factors related to insulin resistance (Braith & Stewart, 2006) and systemic inflammation (Greiwe et al., 2001). As an isolate mode, RT may be suboptimal to improve cardiovascular risk factors (Braith & Stewart, 2006), although when incorporated with AT within a training regimen it may provide further benefits (Kadoglou et al., 2013).

For individuals seeking to maximise the health-related benefits of exercise, combining the different AT and RT training modes via concurrent training (CET) may be appropriate. Indeed, current evidence supports the inclusion of both aerobic- and resistance-based training modalities to offset disease risk factors (Ihalainen et al., 2018). For example, CET is shown to decrease inflammatory markers such as TNFα in obese individuals, above what is seen with either AT or RT alone (Ho et al., 2013), while sedentary populations have also shown decreased IL-6 and CRP after CET interventions compared to non-exercising controls (Lopes et al., 2016; Nicklas et al., 2008). Further, CET may be effective to improve glucose homeostasis parameters, as Azarbayjani et al. (2014) reported reduced insulin resistance with 12 weeks of CET in sedentary men (similar to single-mode training), while sedentary women also showed decreased insulin resistance over the same time period (Choi et al., 2007). By comparison, some data in diseased populations suggest CET to improve CVD-specific parameters such as adhesion molecules (Saetre et al., 2011), while short-term CET may decrease vWF following a myocardial infarction (Vona et al., 2009), and p-selectin within chronic heart failure patients (Bjørnstad et al., 2008). Thus, CET shows promise as a training method to

improve markers associated with systemic inflammation and, in turn, risk of T2DM and CVD in sedentary populations.

To explain the abovementioned reduction in disease risk markers, in sedentary individuals CET may provide enhancements in lean and fat mass (Van Gaal et al., 2006). As evidence, previously untrained men who performed 12 weeks of CET showed a decreased body fat percentage, alongside reduced central measures such as waist-to-hip ratio (Azarbayjani et al., 2014). Moreover, significant reductions in whole-body and visceral fat are observed alongside increased lean mass following CET over 1 year (Dâmaso et al., 2014), and this has been replicated over 16 weeks in overweight women (Duarte et al., 2015). Importantly, for untrained persons the simultaneous integration of AT and RT in a CET program may concomitantly improve multiple physical fitness parameters. For example, older adults who performed CET for 3 months showed both increased muscular strength and VO_{2peak}, (Villareal et al., 2011). Similarly, CET may provide increased endurance commensurate with AT, despite a 50% dose in a concurrent design (Kadoglou et al., 2013). Thus, there seems to be an additive effect for untrained individuals who undertake CET in a split-dose fashion, and improved body composition and fitness outcomes are evident following CET.

CET incorporates a variety of methods of prescription, and may require tailoring to individual needs and preferences. CET is conventionally designed as either split sessions (i.e. AT and RT on separate days) or as sequential completion of AT and RT within each session (Coffey & Hawley, 2017). The latter is common among non-athletic populations as may provide the respective benefits of AT and RT in a single session (Perez-Schindler et al., 2015). That said, adding AT and RT in a training program typically entails an

increase in training loads, and thus modifications may need to be made to mitigate the potential negative effects of this increase in volume (Baar, 2014). Several studies have explored the effects of split-mode sessions whereby individuals complete sequential CET using 50% of typical loads for each modality, resulting in a shorter session duration (Donges et al., 2013). Despite the evidence supporting use of CET to improve the abovementioned outcomes, it remains underutilised within older sedentary populations (Burton et al., 2017b). Further, although it is acknowledged that exercise strategies must be tailored to the needs of this population (Garber et al., 2011), the potential for modified CET strategies has not been thoroughly investigated. Given that a primary consideration of concurrent training is mitigating the potential load issues (Baar, 2014), altering the loading patterns of a CET regimen may warrant exploration.

Alternative Concurrent Training Modes: A Role for Time-Under-Tension?

There is an ongoing need for training modalities that provide more granular modification of exercise design to tailor the training stimulus and provide better responses for specific populations. In doing so, the manipulation of the RT or AT components of concurrent training allow for greater specificity of exercise prescription (Burton et al., 2017b). For example, reducing the resistance training load may still provide significant hypertrophy and strength adaptations (Mitchell et al., 2012), and such benefits may permit older, untrained individuals to enhance quality of life significantly (Van Kan et al., 2009). One such modification strategy is known as time under tension (TUT) training, involving resistance exercise at volitionally slow movement velocities in order to prolong the duration of resisted muscle contractions (Burd et al., 2012). Based on early work by Henneman (1957), motor unit recruitment occurs progressively from small to large units (i.e. the ‘size principle’). Accordingly, it was proposed that, in order to stimulate large

motor units, it is necessary to apply a high-magnitude mechanical load to the muscle, and thus drive adaptive responses within the contractile apparatus (Marcotte et al., 2015). Resistance training that involves applying large amounts of mechanical tension to the muscles is commonly prescribed for increasing strength and muscle mass, although recent research suggests these loading strategies may not be necessary (Mitchell et al., 2012) and modifying this aspect of resistance training design may provide substantial benefits that could be translated into concurrent training. Specifically, given that increased training loads may inhibit participation in CET for certain populations, achieving health-related benefits in a modified design may be particularly appealing.

Despite conventional recommendations that intensities >70% of 1-repetition maximum (1RM) are required to stimulate myofibrilar hypertrophy (American College of Sports Medicine, 2009), it is becoming increasingly apparent that equivalent hypertrophic adaptations can be achieved across a broad spectrum of intensities (Schoenfeld et al., 2015b). More specifically, since large motor units and the associated fast-twitch muscle fibres demonstrate a greater hypertrophic potential, it is important to fatigue the muscle to drive decreased force production and compensatory increases in motor unit activation (Sale, 1987). Thus, it is proposed that, by performing working sets at a slow movement speed, it is possible to progressively fatigue the muscle and ultimately provide a hypertrophic stimulus that would otherwise be diminished or absent (Burd et al., 2012). In turn, the addition of such contractile stimuli within concurrent training programs may provide additional benefits to enhance adaptations to energy expenditure and/or muscular endurance (Scott, 2012).

To further explore the above rationale, mechanical forces drive adaptive signalling and tissue remodelling across various cell types, and skeletal muscle typifies this phenomenon (Martineau & Gardiner, 2002). Specifically, the application of load across a muscle (such as from resistance exercise) initiates a local response characterised by increased muscle size and/or strength (Marcotte et al., 2015). In accordance with the notion that fibres are recruited based on the applied stimuli; to increase myofibrilar hypertrophy it is necessary to either a) administer high-magnitude mechanical stress to the muscle or b) provide a reduced load in conjunction with a fatiguing mechanism, such as TUT (Marcotte et al., 2015). Thus, it was recently postulated that various training techniques can be effective to increase hypertrophy provided that sufficient mechanical and/or metabolic stress is applied, and working sets are performed close to the point of concentric fatigue (Mitchell et al., 2012).

Subsequent research has focussed on alternative loading strategies, including TUT, whereby modified resistance exercise can deliver a sufficient metabolic stimulus to cause hypertrophy (Schoenfeld, 2013). Namely, during resistance exercise, localised hypoxia drives the accumulation of intramuscular metabolites, particularly Pi and H^+ (Schoenfeld, 2013). Although some authors have suggested a direct role for metabolic stress in muscle adaptations (Shinohara et al., 1997), current evidence indicates that this mechanism functions only to inhibit crossbridge formation and accelerate fatigue (Debold, 2012), resulting in the recruitment of higher-threshold motor units (Dankel et al., 2017). Thus, the metabolic strain placed on the muscle is generally considered a permissive mechanism for muscle activation rather than a direct cause of hypertrophy (Dankel et al., 2017). Within a CET design, modification of the RT component may assist in load mitigation and provide metabolic and functional benefits (Tanimoto et al., 2009). Thus, by

increasing the duration of loaded muscle contractions, the level of fibre activation is increased for a given workload (Burd et al., 2012), and may allow a sufficient mechanical and metabolic stimulus to drive an adaptive response (Mitchell et al., 2012). Hence, inclusion of TUT within CET may mitigate the potential issues stemming from increased training loads by enhancing the response to low-load exercise (Baar, 2014).

Given it is possible to deliver an efficacious training stimulus with a reduced load, several studies have identified a potential application for individuals for whom traditional techniques may be contraindicated and/or unappealing (Burton et al., 2017a). To provide conceptual evidence, several authors have compared slow-speed resistance training with work-matched fast-speed training. One group showed that among older adults, low-intensity training (50% 1RM) performed using a slow lifting cadence (3-3 sec concentric and eccentric phases) produced superior hypertrophy and strength gains compared to a work-matched protocol (1-1 sec tempo) on the contralateral leg (Watanabe et al., 2013). Later, the same group reproduced these findings using the same protocol with an even lower loading intensity (30% 1RM) in older adults (Watanabe et al., 2014). These findings concur with acute-response data (Burd et al., 2012), in that a slower movement tempo can offset the lack of mechanical stress (i.e. higher resistance) to the muscle and provide hypertrophy and strength adaptations that would not otherwise be present. Importantly, the efficacy of low-load modalities is predicated on working sets being performed close to the point of concentric fatigue, in order to drive the full culmination of the size principle (Schoenfeld et al., 2015a). That said, although this provides a conceptual basis for TUT training, how it could be used within CET training to amplify the physiological response is unknown. Acute exercise data suggest TUT may alter the post-exercise response to include signalling related to increased endurance (Burd et al.,

2012). Although little long-term data are available, one study shows increased aerobic power with TUT as an isolate mode, although the authors note the addition of AT may enhance this response (Keeler et al., 2001). Accordingly, alongside the hypertrophy effects, TUT may provide significant endurance adaptations when combined with AT.

At present, the majority of evidence suggests that volume-matched slow-speed training is generally as effective as traditional faster-speed training to drive muscle hypertrophy, although the latter may confer an advantage for improving strength. For example, Young and Bilby (1993) administered a 7-week training intervention in non-resistance-trained men with instructions to perform either an 'explosive' concentric phase (fast speed) or a 'controlled' lifting motion (slow speed). After training 3 times per week using barbell squats, the level of hypertrophy was equivalent across both groups, as measured by quadriceps thickness (ultrasound) and thigh circumference. In contrast, a cohort of older men training for 10 weeks with a 'power' training regimen (explosive concentric and 2-3 sec eccentric phase) demonstrated slightly greater hypertrophy of the biceps brachii and rectus femoris compared to a 'traditional' (2-3 sec concentric and eccentric phases) program, alongside greater improvements in muscle power (Nogueira et al., 2009). Previously, Shepstone et al. (2005) observed equal overall hypertrophy after 8 weeks of either 'fast' or 'slow' eccentric-only lifting, although the fast group showed greater hypertrophy of fast-twitch fibres and the eccentric-only protocol used may have contributed to the unexpected result. Gillies et al. (2006) observed greater muscle growth using a slow concentric/fast eccentric regimen versus the opposite. To consider the role of CET, individuals seeking to maximise strength gains may elect to use greater loads and/or faster-speed RT. However, to mitigate the overall training load, TUT may be used alongside AT as a reduced-load modality that will nevertheless provide significant

strength adaptations. Although TUT may be inferior for strength performance (Schoenfeld et al., 2015a), the adaptations derived are worthy of consideration, especially in a CET design whereby load management for both resistance and aerobic adaptations is of particular interest (Baar, 2014).

Separately, a novel protocol of resistance training at a cadence of 10-second concentric and 4-second eccentric phases showed inferior muscle growth versus a volume-matched conventional program (1-1 sec tempo) (Schuenke et al., 2012). Interestingly, this seems to indicate the existence of an upper threshold beyond which further reductions in lifting speed may be detrimental. Accordingly, a meta-analysis of the relevant literature revealed that repetition durations >10 seconds may be inferior with regards to muscle growth (Schoenfeld et al., 2015a), although it is unclear whether this is due to a reduction in overall volume-loads with 'super-slow' resistance exercise, or related to the lifting tempo directly. Conversely, a similar training regimen was used by Rana et al. (2008) in young, healthy women, involving either traditional strength (6-10 repetitions, 1-2 sec concentric and eccentric phases), muscular endurance (20-30 repetitions, 1-2 sec concentric and eccentric phases) or slow-speed training (10-4 sec tempo) and resulted in equal lean mass gains across all groups. In this instance, a short training period (6 weeks) may not have been sufficient to separate the respective training effects from the novelty of unaccustomed exercise. For sedentary individuals commencing training, TUT may accompany AT to produce significant hypertrophy and/or fat loss, while tailoring the training loads to allow untrained populations to receive the benefits of CET. That said, within the spectrum of TUT, different methods may have distinct effects, and the use of TUT in a CET design may vary.

Perhaps the most relevant research in this area has come from one group; initially, a 12-week program of unilateral knee extension training was conducted in untrained men – within this cohort, a slow-speed condition (3-3 sec tempo, 55-60% 1RM) showed equal increases in muscle cross-sectional area versus a higher-intensity protocol (1-1 sec tempo, 80-90% 1RM) when matched for repetition volume (Tanimoto & Ishii, 2006). Importantly, a 3rd condition was included in this study, involving a fast lifting cadence (1-1 sec tempo) and being matched for intensity and total work with the slow-speed group (i.e. sets not performed to fatigue). This group demonstrated inferior hypertrophy and strength gains compared with the other groups, to illustrate the role of TUT in providing metabolically-demanding muscle stimuli. Later, this group applied this concept to a whole-body resistance exercise regimen: 13 weeks of training using a similar slow-speed (3-3 sec tempo) versus fast-speed (1-1 sec tempo) training programs produced equal increases in strength and hypertrophy (Tanimoto et al., 2008).

Additional data from that Tanimoto et al. study (2008) published separately show equal improvements in health-related parameters; specifically, basal femoral blood flow improved equally across both training groups (Tanimoto et al., 2009), representing improved skeletal muscle vascularisation, possibly improved glucose tolerance and a reduced risk of metabolic syndrome (Lind & Lithell, 1993). However, specific cardiometabolic measures (fasting glucose, blood pressure, cholesterol, and triglycerides) did not change. That said, within a CET design, there may be a rationale for inclusion of TUT. Specifically, given that TUT has shown efficacy to enhance muscle mass and strength, it may provide an avenue to reduce inflammation alongside AT. Indeed, the age-related loss of muscle mass and function (i.e. sarcopenia) is associated with an augmented inflammatory profile (Visser et al., 2002). As such, activities that stimulate hypertrophy

or strength gains may assist in reducing the levels of cytokines such as IL-6, TNFα, and CRP (Schaap et al., 2006). Further, maintaining or increasing muscle mass in older adults is related to improved insulin sensitivity (Moon, 2014), and thus further benefits may be seen for glucose homeostasis. Accordingly, inclusion of TUT within a CET design may allow untrained individuals to reduce these biomarkers in a modified fashion.

Moreover, given the potential for CET to improve aerobic fitness (Azarbayjani et al., 2014), modifying the RT component to emphasise TUT may provide endurance adaptations, and subsequently drive improvements in cardiometabolic disease indicators. TUT methods are suggested to increase metabolic stress (Scott, 2012) and may increase muscular endurance (Keeler et al., 2001). In particular, cytokines such as CRP are inversely associated with aerobic fitness (Aronson et al., 2004), and during CET changes in VO_{2peak} correlate with reduced disease risk factors such as CRP levels, HbA1c, and blood lipids (Balducci et al., 2012). Thus, the endurance adaptations provided by concomitant use of TUT and AT within CET may provide less contrasting stimulus than traditional CET. In turn, maximising the aerobic adaptations, whilst providing RT stimulus via TUT may offer ensuing benefits in systemic inflammatory and glucose regulatory biomarkers.

In summary, for sedentary individuals seeking to maximise the benefits of CET while mitigating the potential training load limitations, incorporating TUT as the RT component may provide benefits of traditional CET. Particularly, TUT is shown to enhance muscle mass, strength, and aerobic power (Keeler et al., 2001; Rana et al., 2008; Tanimoto & Ishii, 2006), and thus represents a potential avenue to reduce cardiometabolic risk markers. Prescribing TUT within a CET regimen may provide the benefits of

conventional CET in a tailored approach to manage load demands in sedentary populations. Based on the evidence provided, CET seems to be the most effective strategy to provide benefits for multiple parameters. RT alone, with or without TUT, seems to be inferior to time-matched CET in this regard, and thus TUT may accompany AT in a CET design to deliver greater adaptations than TUT alone. Although TUT used in isolation may be suboptimal to decrease chronic disease risk (Tanimoto et al., 2009), inclusion of AT in a split-mode approach may provide a broad range of physiological adaptations.

Markers of Inflammation and the Effect of Exercise

A state of chronic systemic inflammation is characterised by an elevated presence of pro-inflammatory cytokines (Pearson et al., 2003) and is associated with an increased risk of developing CVD and T2DM (Ridker et al., 2003). More specifically, cytokines such as CRP, IL-6 and TNFα contribute to the physiological abnormalities that predicate these conditions, including insulin resistance (Hotamisligil, 2006) and atherosclerosis (Davignon & Ganz, 2004). A long-term inflammatory state is driven by lifestyle factors such as physical inactivity and excessive adiposity (Wedell-Neergaard et al., 2018), and thus preventative strategies to reduce disease risk may focus on modifying these targets. In particular, exercise training is suggested to decrease basal cytokine levels, although the exact mechanism remains to be elucidated (Gleeson et al., 2011). Some evidence suggests reducing visceral fat may contribute to an improved inflammatory profile, given macrophages residing in the adipose tissue are major producers of inflammatory cytokines (Ouchi et al., 2011). Separately, exercise may augment the release of anti-inflammatory cytokines (Petersen & Pedersen, 2005), alter macrophage characteristics (Kawanishi et al., 2010) or decrease expression of Toll-like receptors (Gleeson et al., 2011), resulting in an overall reduction in inflammation. Thus, the following sections will

outline these potential mechanisms, and explore the existing evidence for the role of exercise training modalities to decrease the inflammatory milieu.

C-Reactive Protein

Function & Relevance

C-reactive protein (CRP) is a pentameric protein that occupies a central role as a pattern recognition receptor in the immune response (Mantovani et al., 2008). Hepatic CRP production is largely under transcriptional control by interleukin (IL)-6, and is augmented during infections, tissue trauma, and vigorous exercise (Pepys & Hirschfield, 2003). Under such circumstances, CRP binds to phosphocholine residues and other ligands via calcium-dependent binding sites on the cell membranes of target organisms and promotes clearance through recruitment of complement proteins (Romero et al., 1998). It also exerts a non-specific protective function against infections via innate immunity (Pepys & Hirschfield, 2003). Recent studies have identified a potential contribution from CRP in the development of several inflammatory and lifestyle-related diseases. Inflammatory mediation via CRP may partially explain the association with poor disease prognoses (Pepys & Hirschfield, 2003). Epidemiological data support this relationship in that higher basal CRP concentrations were associated with a greater number of metabolic syndrome risk factors, as well as an increased likelihood of future coronary events (Ridker et al., 2003).

Although it has been suggested that CRP is an indicator of inflammation rather than a direct atherogenic mediator, mechanistic analyses have revealed modulatory functions of CRP in disease processes (Pasceri et al., 2000). For example, CRP is shown to bind selectively to oxidised low-density lipoprotein (LDL), subsequently activating

inflammatory cytokines (Pepys & Hirschfield, 2003). Further, it has shown pro-coagulant effects by facilitating endothelial induction of intercellular adhesion molecule (ICAM)-1, vascular cell adhesion molecule (VCAM)-1 and p-selectin, subsequently exerting a localised aggregating effect on platelets (Pasceri et al., 2000). The ensuing cascade of macrophage adhesion and foam cell formation is also influenced by CRP, whereby an influx of inflammatory cytokines is evident within the vessel intima (Libby et al., 2010). Contributing further to the disease process, CRP causes reductions in endothelial nitric oxide signalling and contributes to subsequent losses in smooth muscle dilation (Berg & Scherer, 2005). In summary, CRP represents a key prognostic outcome for disease risk in a variety of populations (Libby et al., 2010) and is now an established biomarker of disease progression.

Effect of Exercise Modalities

CRP has been identified as a target for therapeutic interventions such as medications, weight loss, and exercise training (Arikawa et al., 2011). Physical activity is a useful and cost-effective modulatory strategy, whereby regular training can reduce fasting concentrations of CRP and thus the risk of the associated conditions (Gleeson et al., 2011). This notion is supported by prospective data which indicate a clear negative association between aerobic fitness and plasma CRP concentrations (Aronson et al., 2004). Further, given the close relationship between CRP and obesity (Visser et al., 1999) and the strong prognostic capacity of CRP (Pearson et al., 2003), activity-based interventions have emerged as a tool for CRP reduction and disease prevention.

There is considerable experimental evidence to support a role for exercise interventions to decrease CRP. Endurance-based training has shown some effectiveness, as Arikawa et

al. (2011) observed a decrease in fasting CRP following 16 weeks of weight-bearing aerobic exercise in young women, while an 8-week cycling program reduced CRP in sedentary men (Mendham et al., 2014). Mostly consistent results have been found across exercise modalities, with mixed-mode aerobic training improving CRP in elderly individuals (Nicklas et al., 2008) and CVD patients (Goldhammer et al., 2005). In contrast, some authors have questioned the efficacy of endurance exercise alone, with studies showing no change in CRP with aerobic training after 16 weeks in insulin-resistant individuals (Marcell et al., 2005) and as long as 1 year in sedentary individuals (Campbell et al., 2008). As a result, some research has emerged comparing different training modalities. For example, in addition to the evidence pointing to the efficacy of CET compared to control (Lopes et al., 2016), three studies suggest that CET is as effective, or possibly better than duration-matched AT, although they are all specific to T2DM patients. (Balducci et al., 2010) showed similar reductions in CRP with 1 year of either CET or AT, alongside decreased IL-6 and leptin. Similarly, 12 weeks of either AT, RT or CET similarly decreased CRP in T2DM patients (Jorge et al., 2011), while a similar program over 6 months showed CET and AT both decreased CRP, without changes in RT (Kadoglou et al., 2013).

Given the findings reported above, there may be a rationale for using CET to reduce CRP. As evidence, sedentary men with no existing diseases completed 16 weeks of CET, and despite improving aerobic capacity, did not show any changes in CRP, IL-6 or TNFα (Libardi et al., 2012). Importantly, these individuals demonstrated baseline CRP levels < $2mg{\cdot}L^{-1}$, which may have minimised the potential for exercise-induced changes (Lakka et al., 2005). Similarly, obese adolescents undergoing CET for 5 months did not change fasting CRP levels, and despite very high levels of adiposity, were also below the

unhealthy cut-off threshold of 3mg·L^{-1} (Alberga et al., 2015). That said, other authors have observed significant improvements in basal CRP with CET interventions. For example, Ihalainen et al. (2018) delivered a 24-week CET protocol in recreationally active men, either with same-day (2-3 per week) or alternate-day (4-6 per week) volume-matched training splits. These authors showed that both conditions reduced CRP, although only the alternate-day group decreased TNFα and MCP-1. Interestingly, both groups reduced leptin and resistin levels, and these changes correlated significantly with the reduction in abdominal fat following training. Further, overweight girls training 3 times per week for 12 weeks decreased CRP, alongside significant reductions in TBFM, leptin, and insulin resistance (Lopes et al., 2016). Importantly, the overall group mean CRP for this cohort was classified as 'high-risk' (i.e. > 3mg·L^{-1}) (Pearson et al., 2003). Thus, although the relevance of certain training variables requires further research, there is a rationale for CET as a means to reduce CRP. In particular, given that aerobic training stimuli tend to drive reductions in adiposity and CRP, a shift towards a prolonged muscular endurance stimulus (through TUT) may provide benefit for those seeking to decrease these parameters. Accordingly, given CRP is a key prognostic biomarker for chronic disease, CET represents a positive strategy to offset age-related health decrements.

Monocyte Chemoattractant Protein 1

Function & Relevance

Also referred to as CCL2 (CC chemokine ligand 2), MCP-1 is a pro-inflammatory chemokine that is implicated in the progression of several cardiometabolic disease processes (Niu & Kolattukudy, 2009). Like other chemokines, MCP-1 elicits chemotaxis by binding to transmembrane G-protein-coupled receptors, activating cell signalling

processes and causing migration of neutrophils, monocytes and lymphocytes to specified locations (Deshmane et al., 2009). It is produced in numerous cell types (mainly macrophages) and is considered a primary regulator of leukocyte migration following oxidative, inflammatory, or growth stimuli (Deshmane et al., 2009). Some lines of evidence have implicated MCP-1 in the onset and development of CVD, specifically in vascular lipid accumulation (Dawson et al., 1999), foam cell formation, and plaque rupture (Niu & Kolattukudy, 2009). Recent research has also indicated a possible relationship with insulin resistance and T2DM (Kamei et al., 2006).

Specific to CVD, substantive evidence suggests a mechanistic role for MCP-1 in various stages of the disease process. Namely, MCP-1 is considered a major driver of the recruitment and retention of macrophages at atherosclerotic sites (Dawson et al., 1999). Moreover, a systemic inflammatory state is associated with increased release of MCP-1 from endothelial and smooth muscle cells (Niu & Kolattukudy, 2009). Under the influence of MCP-1, monocytes residing in the vascular lumen undergo diapedesis, infiltrate the sub-endothelial space and differentiate to macrophages, where they subsequently take up oxidised LDL and become foam cells (Niu & Kolattukudy, 2009). Meanwhile, MCP-1 mediates, in part, the adhesion of lipid debris to vessel walls (Jiang et al., 1992), and in advanced atherosclerosis stimulates activity of the ubiquitin-proteasome system, contributing to plaque instability (Niu & Kolattukudy, 2009). In humans, plasma MCP-1 concentrations > 238 $pg \cdot mL^{-1}$ independently predict mortality in the period following an acute coronary event (de Lemos et al., 2007). Overall, MCP-1 is proposed as a key mediator in development of CVD and a highly relevant prognostic indicator in the clinical setting. With regards to metabolic abnormalities, emerging evidence supports a mechanistic function of MCP-1. Data in mice show that acute

expression of anti-MCP-1 mutations protects the animals from diet-induced macrophage accumulation in adipose tissue and, subsequently, insulin resistance (Kanda et al., 2006). Similar results have been observed via pharmacological inhibition of MCP-1 receptors, purportedly through localised suppression of inflammation within the adipose tissue (Tamura et al., 2008). Studies in humans are fewer, although correlations have been shown between serum concentrations of MCP-1 and established risk factors including obesity, hyperinsulinemia and serum triglycerides (Simeoni et al., 2004).

In obesity, MCP-1 is considered a primary cause of macrophage proliferation in adipose tissue (Amano et al., 2014), and there is a positive relationship between the number of adipose-residing macrophages and the degree of whole-body insulin resistance (Wentworth et al., 2010). Similarly, a study in healthy adults showed that fasting levels of MCP-1 were positively correlated with obesity, waist circumference, and indices of insulin resistance (Kim et al., 2006). Considering the interrelatedness observed among cytokines, obesity and subsequent disease development, MCP-1 has frequently been the subject of intervention-based studies.

Effect of Exercise Modalities

It is suggested that MCP-1 may be a suitable target for behavioural (i.e. exercise, diet) and pharmacological disease-prevention strategies. Studies in mice demonstrate the positive effects of exercise, as Bradley et al. (2008) found a reversal of diet-induced inflammation and insulin resistance with 6 weeks of endurance training, characterised by reduced MCP-1 and tumour necrosis factor alpha (TNFα). Specifically to exercise training studies in humans, heart failure patients demonstrated substantial reductions in serum levels of MCP-1 after 12 weeks of moderate-intensity cycling training

(Adamopoulos et al., 2001). Conversely, in healthy women, there was no change in MCP-1 after 12 weeks of resistance training (Ogawa et al., 2010), although this outcome may be related to a low training volume (1h per week). Indeed, other literature emphasises the importance of training volume, with concurrent training showing differential outcomes between lower- and higher-volume conditions. For example, Bjørnstad et al. (2008) found no change in MCP-1 after a twice-per-week protocol involving resistance training and low-volume (6 min) endurance exercise, thus implying a possible role for the prolonged endurance-like stimulus provided by TUT (Burd et al., 2012). Meanwhile, a thrice-per-week intervention, incorporating high-volume resistance training (15-20 RM) and aerobic training for 45-60 min per session, was effective to reduce MCP-1 after 12 weeks in patients with metabolic syndrome (Trøseid et al., 2004). Hence, sufficient overall training loads may be necessary for improvements in MCP-1, though in the abovementioned studies demographic differences (heart failure versus metabolic syndrome) may confound comparisons. That said, an emphasis on larger durations and endurance stimuli, through both AT itself and possibly through TUT, may be necessary in healthy individuals.

As further evidence, (Bruun et al., 2006) administered a very high-volume exercise intervention to obese individuals (10-15 hours per week) in conjunction with a hypocaloric diet for 15 weeks, and observed reduced plasma levels of MCP-1, CRP, and IL-6. Interestingly, recent research has highlighted the importance of training intensity, with (Leggate et al., 2012) showing reduced MCP-1 after only 2 weeks of interval-based training in obese males. However, this was not reflected in functional changes (oral glucose tolerance) within this population. Overall, it is likely that exercise has a positive effect on fasting levels of MCP-1; however, the relevance of different exercise modalities, as well as the applicability to different populations, needs to be more thoroughly

investigated. It is suggested that, owing to positive effects on fat mass and other inflammatory cytokines, that CET may be an effective strategy to reduce MCP-1 (Balducci et al., 2010). Moreover, the increased metabolic stimulus provided by TUT resulting in increased energy expenditure and possibly enhanced muscular endurance (Burd et al., 2012; Scott, 2012) may provide additional benefits to the incorporation of AT may confer improved change in MCP-1 above that of traditional CET.

Tumour Necrosis Factor Alpha

Function & Relevance

Tumour necrosis factor alpha (TNFα) is a widely studied inflammatory cytokine that modulates several whole-body and tissue-specific processes (Hotamisligil, 2006). Under conditions of chronic low-grade inflammation, it is purported to play a central role in the onset and development of obesity-related pathologies (Hotamisligil, 2006). Specifically, there is a strong association with adipose tissue-based TNFα secretion and indices of insulin resistance (Kern et al., 2001). In humans, there is a strong and independent association between plasma TNFα concentrations and reduced whole-body glucose disposal (Paolisso et al., 1998). Considering these findings, it is noted that TNFα inhibits insulin signalling in skeletal muscle, contributing to hyperglycaemia and insulin resistance (Halse et al., 2001). Moreover, TNFα is involved in the inhibitory phosphorylation of serine residues on insulin receptor substrates, restricting tyrosine phosphorylation and impairing insulin signal transduction (Hotamisligil, 2006). Also, adipose tissues of obese individuals are shown to secrete greater amounts of TNFα compared to non-obese individuals, which may provide a link between obesity and insulin resistance, and perhaps explain the positive metabolic adaptations noted following interventions resulting in recued fat mass (Hotamisligil et al., 1995). Thus, TNFα is

considered a primary driver of insulin resistance and T2DM, and further associations are reported with various disease states.

TNFα mediates disease-related processes in various cell types, although its role in cardiovascular pathologies is of additional interest to the present investigation. The normal cytotoxic functions of TNFα are critical to protect the host organism from pathogens; however, when TNFα production is excessive (i.e. chronic inflammation), it is released into the circulation and thereafter demonstrates a causative role in CVD progression (Feldman et al., 2000). As an early sign of endothelial dysfunction, TNFα causes reduced nitric oxide synthase activity and an inhibited vasorelaxation mechanism (Goodwin et al., 2007; Zhang et al., 2006). Furthermore, increased endothelial cell apoptosis coincides with age-related increases in TNFα production, which can magnify vascular dysfunction in ageing (Csiszar et al., 2004). Libby and Ridker (1999) state that TNFα contributes to lipid accumulation in vasculopathy, noting that TNFα stimulates NFκB (nuclear factor kappa light chain enhancer of activated B cells) activity and subsequent expression of adhesion molecules in vascular endothelia, resulting in increased leukocyte migration and adhesion. The contribution of TNFα to CVD development may be related to its downstream effect on hepatic CRP production, whereby a systemic inflammatory state impacts negatively upon the vasculature (Berg & Scherer, 2005). Alternatively, it has been suggested that the main role of TNFα relates to the aforementioned effects on insulin signalling – specifically, that TNFα contributes to peripheral insulin resistance, the associated hyperglycaemia causes vascular dysfunction and, subsequently, CVD (Hotamisligil, 2006). Collectively, TNFα shows a mechanistic relationship with various clinical risk markers, and further epidemiological research has identified a strong relationship with poor disease prognoses.

Effect of Exercise Modalities

Considering the causality with TNFα and traditional subclinical risk factors (Park et al., 2005), it has emerged as a therapeutic target in the context of disease prevention. A clear association has been established between fasting TNFα and ostensibly 'unhealthy' characteristics, such as physical inactivity (Panagiotakos et al., 2005), low skeletal muscle mass (Visser et al., 2002) and abdominal obesity (Ziccardi et al., 2002), and thus there is an emphasis on activity-based interventions to reduce TNFα. Previous studies have shown mixed results, although aerobic exercise shows potential as an effective strategy. For example, Straczkowski et al. (2001) observed a significant reduction in fasting TNFα after a 12-week moderate-intensity cycling program in obese women. Conversely, in a study involving overweight, hypertensive women, there was no change in plasma TNFα following 6 months of cycling training (Arsenault et al., 2009). Notably, this discrepancy may be explained by differences in training intensity (70% vs 50% VO_{2peak}) or baseline TNFα values (6.6 vs 1.8 $pg \cdot mL^{-1}$). This is supported by Donges et al. (2013), who reported decreased TNFα in sedentary men after 12 weeks of aerobic cycling, with a baseline TNFα value of 4.4 $pg \cdot mL^{-1}$, and a training intensity of 75-80% HR_{max}. Accordingly, it is proposed that endurance-based training interventions may be effective in healthy participants provided there is sufficient intensity, although this effect could be related to elevated baseline concentrations in the abovementioned study populations.

Separately, growing evidence suggests a possible role for resistance training as an anti-TNFα strategy. For example, in older adults, there was a 34% decrease in TNFα mRNA in skeletal muscle after 3 months of resistance exercise (Greiwe et al., 2001) while another study showed a 27% reduction in plasma TNFα after a 12-week strength training program

in overweight individuals (Ho et al., 2013). Conversely, Ogawa et al. (2010) found no change in TNFα in older women performing 12 weeks' resistance training, although it should be noted that pre-intervention levels were low (0.91 $pg{\cdot}mL^{-1}$) in this population sample, which may have precluded any significant training effect. Accordingly, due to mixed results in single-mode training studies, some attention is paid to concurrent exercise training (CET) as a means to confer a greater breadth of training stimuli and effects. Specifically, equivalent improvements in plasma TNFα with a CET intervention are possible compared to duration-matched aerobic or resistance exercise in a sedentary population (Donges et al., 2013). However, this outcome is not replicated consistently in the literature, with some data showing no effect of CET in healthy men (Libardi et al., 2012) and others showing a superior outcome versus single-mode training (Ho et al., 2013). Nevertheless, the current evidence indicates that CET is likely beneficial for reducing TNFα, and as such its inclusion in the present study is justified as an indicator of the systemic inflammatory state. Moreover, given the diversity of findings in terms of training load and TNFα response, further consideration of the training modes and stimulus is required. Incorporating TUT within a CET design may also provide increased lean mass (Tanimoto et al., 2008) and endurance adaptations (Keeler et al., 2001). Given that TUT can impose greater demands on oxidative metabolism and possibly energy expenditure (Scott, 2012), it maybe that using TUT within CET contexts provides improved reductions in TNFα.

Interleukin-6

Function & Relevance

Interleukin (IL)-6 plays a central role as an inflammatory cytokine, and also regulates numerous other cellular processes (Scheller et al., 2011). It mediates early-phase innate

immunity via neutrophil recruitment (Scheller et al., 2011) and subsequently enhances monocyte-attracting mechanisms including chemokine induction (Romano et al., 1997) and increased production of cell adhesion molecules (Kaplanski et al., 2003). As an immune activator, IL-6 also upregulates the recruitment and activity of lymphocytes by triggering chemokine production, enhancing antibody responses (Kopf et al., 1994) and preventing apoptosis of T-cells (Curnow et al., 2004). However, evidence also reveal an additional role for IL-6 as an anti-inflammatory regulator in the post-exercise period (Covarrubias & Horng, 2014). Moreover, it is proposed that IL-6 exerts immunosuppressive effects via inhibition of myeloid cell lineages (Tilg et al., 1997). Due to the nuanced nature of IL-6 and its effects in different tissues, there are some conflicting findings regarding its role in the systemic inflammatory state and the associated cellular changes (Covarrubias & Horng, 2014). To reconcile this, Scheller et al. (2011) proposed differential regulatory effects of IL-6 depending on which signalling pathway is involved (i.e. classical or trans-signalling), ultimately leading to divergent outcomes.

Accordingly, IL-6 has attracted considerable attention in the clinical literature for its role in substrate metabolism, immunoregulation, and tissue chemistry. Cross-sectional associations are observed between plasma IL-6 levels and fat mass (Park et al., 2005), and the development of T2DM (Pradhan et al., 2001). In the context of glucose homeostasis, conflicting evidence has raised questions with regards to the effects of IL-6. There is some research showing a catabolic effect of IL-6, whereby it acts to enhance hepatic glucose output during exercise, via concomitant enhancement of glycogen phosphorylase and inhibition of glycogen synthase activity (Kanemaki et al., 1998). Similarly, Febbraio and Pedersen (2002) propose a role for IL-6 in hypertriglyceridaemia, owing to its localised lipolytic effects. Conversely, *in vitro* studies show increased whole-

body and adipocyte-based glucose disposal with administration of IL-6 (Stouthard et al., 1996), and there is evidence to suggest a role for IL-6 in supporting glucose transporter (GLUT)-4 translocation in skeletal muscle (Febbraio & Pedersen, 2002). Although some authors have reported IL-6-associated interference in hepatic insulin action (Senn et al., 2003), others have postulated that the elevated IL-6 levels observed in T2DM are indicative of an attempt to overcome impaired glucose uptake caused by other factors (Febbraio & Pedersen, 2002). The latter hypothesised that the relationship is putative rather than causal, and noted that in mice rendered insulin resistant, a hyperinsulinaemic/euglycaemic clamp caused increased IL-6 gene expression in muscle, reflecting a compensatory response to downregulated GLUT4 mechanisms (Febbraio & Pedersen, 2002). The precise mechanisms linking IL-6 with these metabolic perturbations is not entirely clear, and the functions of IL-6 may vary depending on its source and target tissue (Ouchi et al., 2011). However, irrespective of the degree of causality involved, reduced circulating levels of IL-6 are likely to reflect an improvement in insulin-dependent and -independent glucose uptake processes in liver and skeletal muscle.

Prospective data show an association between plasma IL-6 concentrations and negative anthropometrical characteristics including increased body mass index, waist-to-hip ratio, and visceral adiposity (Park et al., 2005). Further, IL-6 demonstrates a clear correlation with future cardiovascular pathologies, independent of traditional CVD risk factors (Koenig et al., 2006; Ridker et al., 2000). Generally, current evidence suggests that IL-6 mediates CVD-related mechanisms, via downstream effects on CRP as well as direct humoral and cellular regulation. Specifically, IL-6 shifts the vascular microenvironment from a haemodynamically stable to a procoagulant state by disrupting the balance of thrombotic and fibrinolytic mechanisms (Shebuski & Kilgore, 2002). Platelet formation

is under direct influence by IL-6, via its stimulatory effect on thrombopoietic progenitor cells in the liver and kidneys (Kaser et al., 2001). Further, IL-6 is involved in accelerating the endothelial release of adhesion molecules and fibrinogen, leading to platelet aggregation on vessel walls (Yudkin et al., 2000). This is further affected by the IL-6-induced accumulation of von Willebrand Factor (vWF) on endothelial cells (Bernardo et al., 2004). Ultimately, IL-6 triggers multiple pathways leading to a cascade of events that culminate with enhanced lipid uptake by macrophages and fibrin-mediated clot formation, representing the clinical characteristics of a localised cardiovascular risk (Berg & Scherer, 2005).

Effect of Exercise Modalities

Lifestyle-based strategies including physical activity, smoking cessation and dietary manipulation are suggested as potential tools to improve IL-6 as a representative marker of chronic systemic inflammation. Previous data show a clear association between IL-6 and obesity (Park et al., 2005), inactivity (Fischer et al., 2007) and low muscle mass (Visser et al., 2002), and therefore exercise interventions are widely suggested as methods to reduce IL-6 concentrations (Pedersen & Saltin, 2015). Conventional therapeutic exercise strategies such as cycling and walking have shown some effectiveness. Dekker et al. (2007) observed reductions in plasma IL-6 levels in sedentary participants after 12 weeks of moderate-intensity endurance training, and this outcome was consistent irrespective of somatotype and diabetic status. Similarly, Kohut et al. (2006) conducted a multimodal aerobic exercise regimen in older adults and found marked reductions in basal IL-6 after 10 months. Notably, this intervention was superior to a flexibility/balance program of the same duration. On the other hand, a study in overweight children showed no change in IL-6 levels after 8 weeks of cycling-based aerobic training (Kelly et al.,

2007), although the authors speculated that seasonal behaviour changes associated with the academic calendar may have contributed to this null finding. That said, a large study (n = 267) also revealed no change in IL-6 after 6 months of moderate-intensity exercise (walking and cycling), despite modest reductions in body mass and waist girth, in overweight older women (Arsenault et al., 2009).

Despite equivocal findings in 'apparently healthy' populations, there is some suggestion for the application of endurance-based training strategies in diseased individuals. Some studies in cardiac rehabilitation have shown promising results, and specifically 12 weeks of aerobic training reduced IL-6 concentrations in heart failure (Adamopoulos et al., 2002) and coronary artery disease patients (Goldhammer et al., 2005). Separately, no changes were reported following endurance training in heart failure patients over 3 months (Larsen et al., 2001) or 6 months (Gielen et al., 2003). Although an elevated baseline concentration of IL-6 predicts a significant finding in this population, in the abovementioned studies this was not the case. Significant reductions were shown with a baseline value of 2.50 ± 1.50 $pg{\cdot}mL^{-1}$ (Goldhammer et al., 2005), while separately a baseline concentration of 4.6 ± 3.9 $pg{\cdot}mL^{-1}$ did not change in 3 months of training (Larsen et al., 2001). That said, other studies have shown marked differences with ostensibly high (Adamopoulos et al., 2002) or low (Gielen et al., 2003) pre-training values, whereby there was a decrease and no change respectively. It is important to note also that among these studies in cardiac patients, those studies showing a benefit of exercise involved structured, monitored training programs, whereas those showing no change involved home-based exercise with no monitoring of compliance. Overall, current data relating to endurance-based training protocols is equivocal; accordingly, there has been some investigation into alternative exercise modalities.

Resistance training interventions have shown some promise in 'healthy' (i.e. non-diseased) individuals, and are particularly relevant given the association of IL-6 with reduced muscle mass and strength (Visser et al., 2002). For example, Prestes et al. (2009) administered a 16-week resistance exercise program in sedentary, older women and found reduced basal IL-6. Moreover, Forti et al. (2014) reported that older adults decreased serum IL-6 levels following 12 weeks' moderate-intensity resistance training using pin-loaded machines. In contrast, other research has shown a 1-year program in overweight, sedentary women did not alter fasting IL-6, despite improvements in CRP and adiponectin (Olson et al., 2007). As mentioned, Olson et al. (2007) prescribed a twice-per-week training program, which was largely unsupervised and thus stimulus exposure was unknown. In contrast, in the study by Prestes et al. (2009), participants undertook supervised training ensuring sets were performed to concentric muscle failure, and periodised to increase intensity via 4-week incremental blocks. More research may be needed to elucidate the effects of lifting intensity to reduce IL-6. In particular, in the abovementioned sedentary populations, TUT could be suggested to reduce IL-6, given its metabolic and strain result in hypertrophy and muscular endurance (Keeler et al., 2001). Hence, there is some efficacy shown for 'at-risk' individuals, although for non-diseased populations RT alone may be suboptimal in this regard. Therefore, incorporation of an aerobic training component or the inclusion of greater TUT to enhance the training response, and may allow a more tailored approach to exercise prescription.

As evidence, (Mendham et al., 2014) used small-sided games training in sedentary participants and found a superior reduction in IL-6 compared to an aerobic cycling protocol. Similarly, a combined intervention of aerobic exercise and a hypocaloric diet

was effective to decrease IL-6 in obese individuals after 1 year (Lira et al., 2011) and 6 months (You et al., 2004), with the latter showing a greater effect compared to a diet-only strategy. Even so, the concomitant use of multiple exercise modalities (i.e. concurrent training) is of interest to the present investigation. As evidence, a 1-year CET program in older adults caused a substantial reduction in IL-6, representing a multi-modal approach (Nicklas et al., 2008). Conversely, in overweight, sedentary individuals, 12 weeks' CET had no effect on basal IL-6 (Stewart et al., 2007), although reductions in CRP were observed. Evidently, there may be a rationale for use of CET to reduce IL-6 in healthy populations, although ensuring ongoing adaptation may raise practical issues regarding training loads. Thus, incorporating TUT via a tailored approach may provide body composition and fitness improvements, and subsequently reduce IL-6. Specifically, decreased IL-6 is associated with increased muscle mass (Visser et al., 2002) and endurance capacity (Hosick et al., 2013), and concomitant delivery of TUT and AT may be expected to improve IL-6 via these mechanisms.

Interleukin-10

Function & Relevance

Interleukin (IL)-10 is an anti-inflammatory cytokine characterised by a dimeric structure, presenting as a non-covalent homodimer of two polypeptide chains (Moore et al., 2001). It is produced by many cell types, and its primary role as an inflammatory mediator is to regulate the expression of cytokines by cells of myeloid lineage, thereby affecting their ability to activate and maintain immune responses and limiting the potentially harmful effects on host tissues (Moore et al., 2001). Moreover, IL-10 inhibits the expression of major histocompatibility complex (MHC) class II molecules by antigen-presenting cells, consequently reducing antigen presentation and T-lymphocyte activation (de Waal Malefyt et al., 1991). Further, it is suggested that IL-10 exerts anti-inflammatory effects

via both down-regulation of inflammatory mediators, as well as up-regulation of anti-inflammatory agents. For example, IL-10 stimulates IL-1ra production in granulocytes, corresponding with a reduction in the pro-inflammatory effects of the IL-1 cytokine family (Moore et al., 2001).

Circulating levels of IL-10 show a causative relationship with inflammatory conditions, as well as a protective effect against cardiometabolic diseases (de Waal Malefyt et al., 1991; Hickey et al., 1998). Specifically, elevated serum concentrations of IL-10 are associated with a reduced risk of future cardiac events, and correlate inversely with CRP, in a cohort of patients with acute coronary syndromes (Heeschen et al., 2003). Similarly, individuals with stable angina demonstrate increased levels of IL-10 compared to those with unstable angina, reflecting a reduced risk of plaque instability and the development of CVD (Smith et al., 2001). In addition, IL-10 acts to inhibit leukocyte adhesion to the vessel intima, and reduces endotoxin-induced microvascular dysfunction (Hickey et al., 1998). It also helps to maintain lipid homeostasis in blood vessels by mediating LDL efflux during foam cell formation, thus helping to reduce localised lipid loading (Han & Boisvert, 2015). Moreover, IL-10 inhibits the secretion of matrix metalloproteinases (MMP's) from activated macrophages, thereby maintaining collagen production and protecting against plaque rupture (Waehre et al., 2002). Ultimately, IL-10 acts to reverse several prothrombotic processes and is considered a key protective mechanism in this context. Accordingly, measurement of systemic IL-10 concentrations represents a means by which to assess the degree of disease progression and provides insight into the mechanistic factors involved.

Considering that metabolic dysfunction/disease is a key theme of the present investigation, it is important to highlight the role of IL-10 in the onset and progression of insulin resistance and T2DM. As evidence, a study of 599 older adults showed a clear association between low serum concentrations of IL-10 and increased metabolic syndrome symptoms (van Exel et al., 2002). This finding is corroborated by Straczkowski et al. (2005) who reported a positive relationship between plasma IL-10 levels and insulin sensitivity in response to a euglycaemic-hyperinsulinaemic clamp. These data are supported by mechanistic analyses, although there is still some controversy regarding the precise role of IL-10 in metabolic function. However, it has been proposed that IL-10 does not exert any direct effect on glucose transport machinery; rather, the insulin-sensitising effect of IL-10 is due simply to its inhibitory effect on inflammatory cytokines (Moore et al., 2001). More research is required to understand this phenomenon, although some lines of evidence have identified IL-10 as a mediator of the anti-inflammatory response to lifestyle interventions (e.g. exercise and nutrition).

Effect of Exercise Modalities

Some authors believe the health-promoting effects of these strategies are related to IL-10 and the inhibition of systemic inflammation. This is supported by a body of recent research that collectively shows long-term exercise training can cause increases in fasting IL-10, and that this effect may partially explain the anti-inflammatory effect of exercise (Petersen & Pedersen, 2005). For example, in a cohort of older adults, a 24-week moderate-intensity running program resulted in a modest increase in plasma IL-10, alongside decreases in IL-6 and TNFα (Santos et al., 2012). Also, Babbitt et al. (2013) showed non-significant increases in IL-10 after 24 weeks' aerobic exercise training in sedentary African-Americans using several modes of moderate-intensity exercise. Other

studies, in contrast, have shown no effect of exercise on IL-10; a 12-week swimming intervention had no effect on basal IL-10 in older adults (Nualnim et al., 2012).

Separately, Kadoglou et al. (2007) reported increased IL-10 with 6 months of endurance-based training in participants with T2DM. As further evidence, aerobic training has shown efficacy to improve IL-10 levels in metabolic syndrome (Farinha et al., 2015) and CVD patients (Goldhammer et al., 2005). Notably, the role of different training modalities has been questioned recently. The use of some novel exercise strategies has provided limited changes, with Mendham et al. (2014) reporting no change in IL-10 after 8 weeks of small-sided games training in sedentary men, and Leggate et al. (2012) showing no effect of high-intensity interval training in overweight men, although these participants completed only 6 sessions over 2 weeks.

Accordingly, some questions remain relating to the efficacy of such strategies that constitute a relatively mild mechanical and/or metabolic stimulus. Therefore, to maximise physiological adaptations, some authors have proposed the use of CET and/or dietary modification. For example, in obese adolescents, a 1-year program of aerobic exercise combined with a hypocaloric diet increased fasting IL-10, and the improvements in inflammatory profiles correlated with positive changes in body composition (Lira et al., 2011). Thus, there may be a rationale for the inclusion of multiple stimuli within a given intervention, and further, optimising training prescription through the use of TUT may allow a tailored approach for such populations.

In support, Balducci et al. (2010) delivered either aerobic, resistance, or duration-matched combined training programs in participants with T2DM and found that the combined

(CET) intervention conferred the greatest overall effect. Specifically, this condition showed superior adaptations in anti-inflammatory markers (IL-10, IL-4), pro-inflammatory markers (CRP, IL-6, resistin, TNFα, interferon-γ), and hormonal profiles (adiponectin, leptin). Also, CET provided reductions in abdominal adiposity and endurance capacity above RT alone – considering that TUT may be also an efficacious strategy to enhance physical capacity, incorporation into a CET design may permit commensurate changes in these inflammatory markers. Despite limited research, preliminary evidence has shown some promise for the use of CET to alter the inflammatory milieu. Regarding the relevance to the present study, IL-10 represents a prognostic biomarker that, in response to exercise training, may show an increased concentration in plasma and, alongside pro-inflammatory indicators, may reflect an improved inflammatory profile. Moreover, incorporation of TUT in the CET design may provide adaptations in the form of increased lean mass and strength (Young & Bilby, 1993), and possibly an augmented muscular endurance (Keeler et al., 2001). In turn, the metabolic and endurance-specific adaptation of TUT may provide potential for increased fitness capacity greater than that of CET, and provide reductions in IL-10 (Burd et al., 2012).

Interleukin-1 Beta

Function & Relevance

Interleukin-1 beta (IL-1β) is a pro-inflammatory cytokine produced mainly by activated macrophages, and represents the most thoroughly understood of the 11 members of the IL-1 cytokine family (Dinarello, 2011). Due to its haematopoietic properties, IL-1β was originally recognised as an exogenous therapy following bone marrow transplantation (Dinarello, 2011). In contrast to IL-1α, which mostly associates with the plasma

membranes of its producing cells, IL-1β firstly matures in the macrophage cytoplasm and subsequently enters systemic circulation (Dinarello, 2009). Thus, IL-1α is identified as a localised mediator of intracellular events, while IL-1β is hormone-like in its endocrine regulation of immune processes (Dinarello, 1996). Via its role in innate immunity, IL-1β acts concomitantly with IL-6 to stimulate hepatic CRP secretion (Kasapis & Thompson, 2005) and synthesis of myeloid progenitor cells in bone marrow (Dinarello, 1996). It is suggested that the latter effect is largely due to increased IL-6 production, as evidenced by studies in IL-1-deficient mice that show no impairment of haematopoiesis (Dinarello, 1996).

Regardless, IL-1β occupies a central role in the initiation and direction of immune responses via its effect on other pro-inflammatory mediators, and up-regulation of antibody production in lymphocytes (Dinarello, 2009). Further, the relevance of IL-1β in a chronic low-grade inflammatory state is a focal point in the literature and has precipitated numerous investigative studies. Previously, elevated concentrations of IL-1β have been prospectively associated with CVD (Hasdai et al., 1996), osteopenia (Dinarello, 2011), T2DM (Larsen et al., 2007), and neurodegenerative conditions such as Parkinson's disease (Schulte et al., 2002). Considering that the present study relates to cardiometabolic diseases, some examination of potential mechanisms is warranted.

With regards to T2DM, several studies show a role for IL-1β in either impaired pancreatic insulin secretion, reduced peripheral insulin sensitivity, or both. It has been suggested that diabetic β-cell destruction be viewed as an auto-inflammatory disease mediated by IL-1β (Tack et al., 2012), due to its cytotoxic effects in pancreatic islets (Mandrup-Poulsen et al., 1986). This notion is supported elsewhere in the literature; when exposed to glucose

in vitro, isolated islets of non-diabetics showed increased IL-1β production, resulting in DNA fragmentation and impaired secretory function of β-cells (Maedler et al., 2002). As further evidence, Larsen et al. (2007) demonstrated that long-term administration of recombinant IL-1ra improved markers of insulin secretion, alongside improvements in HbA1c in participants with T2DM. Thus, there is an inhibitory effect of IL-1β on insulin production mechanisms, although separately the effect on cellular glucose uptake has attracted some interest. It is shown that IL-1β inhibits insulin receptor substrate (IRS)-1 expression in vitro, resulting in reduced tyrosine phosphorylation (Jager et al., 2007), a result that has been replicated elsewhere and coincides with attenuated glucose uptake and lipogenesis in cultured adipocytes (Lagathu et al., 2006). In hepatocytes, IL-1β impairs glycogen synthase activity and concomitantly up-regulates glycogen phosphorylase activity, highlighting the role for IL-1β as a metabolic regulator in pathological conditions (Kanemaki et al., 1998). Regardless, the imbalance between IL-1β and IL-1ra is representative of a pathogenic inflammatory state, and therefore elevated levels of IL-1β indicate disease risk. Accordingly, achieving reductions in fasting IL-1β may be useful in establishing an improved lifestyle-related health status.

Effect of Exercise Modalities

Aside from pharmacological interventions, behaviour modification strategies have been investigated for anti-inflammatory purposes. For example, aerobic exercise-based regimens have shown efficacy across a diverse range of demographics. A 12-week program of moderate-intensity treadmill walking reduced serum levels of IL-1β in untrained women (Farinha et al., 2015). At present there are no other endurance-only training studies that measure IL-1β in healthy individuals; however there has been some investigation of the role of this modality for diseased populations. For example, in

coronary artery disease (CAD) patients, 12 weeks' multimodal AT was effective to reduce basal IL-1β (Goldhammer et al., 2005); however, another study in CAD patients showed no effect from 14 weeks of training, although in this case training was largely home-based and unsupervised (Kim et al., 2008b). Separately, Gielen et al. (2003) reported decreased IL-1β in heart failure patients after 6 months of aerobic exercise, although this program was performed on an in-patient basis whereby participants exercise 4-6 times per day for 10 minutes, in addition to group exercise classes and self-conducted activities. Thus, the marked differences in training methodology in the existing literature preclude any explicit inferences.

By comparison, there are even fewer resistance training studies on the effect on IL-1β . Phillips et al. (2010) reported reductions in fasting IL-1β concentrations after 10 weeks of RT in a cohort of older women training at their respective 8RM. Conversely, a 12-week program of either high- (80% 1RM) or low-intensity RT (20% 1RM) had no effect on IL-1β in a population of older men and women (Forti et al., 2016). In this instance, more studies are needed to fully elucidate the mode- or intensity-specific effects of exercise on IL-1β. Interestingly, the combination of intervention strategies (i.e. CET) has been the subject of recent studies. Although Stewart et al. (2007) showed no change in IL-1β after 12 weeks of CET in sedentary adults, Balducci et al. (2010) reported that, compared to an endurance-based program, CET caused superior improvements in IL-1β over 1 year in individuals with T2DM. Given that the protocol employed by Balducci et al. (2010) also provided benefits for body composition and fitness capacity, it is possible that other CET protocols that emphasise these adaptations may also assist in decreasing IL-1β. Further, given the low levels of CET participation among older adults (Burton et al., 2017b), modifying the training design by including TUT may provide an avenue for

untrained individuals to receive these benefits also. Moreover, TUT may accompany AT as the RT component to simultaneously provide hypertrophy and endurance adaptations that may in turn reduce IL-1β in sedentary populations (Keeler et al., 2001).

Interleukin-1 Receptor Antagonist

Function & Relevance

Interleukin-1 receptor antagonist (IL-1ra) is a secreted protein product of the IL-1 family whose function is to restrict the biological effects of the pro-inflammatory IL-1 cytokines (Dinarello, 2000). As an inflammatory mediator, IL-1ra does not exert any agonistic effects on host cells; rather, it acts by selectively binding to IL-1 attachment sites on target cells, thereby reducing binding of inflammatory agents and preventing downstream signalling via competitive inhibition (Herder et al., 2013). It is an acute phase reactant, presenting in varying levels in different biological systems corresponding to changes in IL-1 (Dewberry et al., 2000). Furthermore, it plays a key role in maintaining the balance of the IL-1 system, where it responds to acute increases in IL-1α/β that, if not sufficiently controlled, would result in severe systemic inflammation and possible cell damage (Ridker et al., 2011).

In accordance with its acute-phase functions, IL-1ra has been extensively investigated in the context of chronic disease. For example, it is suggested that IL-1ra confers an anti-inflammatory effect via two distinct yet related mechanisms: competitive binding to IL-1 type 1 receptors, and stimulation of type 2 'decoy' receptors which bind IL-1 but do not involve any signal transduction (Dinarello, 2000). These processes work in conjunction to restrict IL-1 binding to the preferred type 1 receptor, and thus obstruct its normal functioning (Symons et al., 1995). In terms of clinical utility, IL-1ra is paradoxically

associated with an augmented risk of CVD and T2DM. Although exogenous dosing often results in positive changes in disease-related parameters (Ikonomidis et al., 2008; Larsen et al., 2007), elevated circulating levels of IL-1ra are associated with an increased disease risk, although IL-1ra does not itself propagate disease development (Herder et al., 2013). It is proposed that this relationship reflects the inherent responsiveness of IL-1ra to increased IL-1, and is the result of an increased, but ultimately unsuccessful, attempt to reconcile systemic imbalances in the inflammatory microenvironment (Herder & Donath, 2015). Interestingly, earlier data suggest a bimodal response in pancreatic islets to IL-1 exposure; low levels of IL-1β actually improve insulin signalling, likely due to the balancing response of IL-1ra; however, high doses of IL-1β suppress insulin action, supposedly due to an 'overpowering' of IL-1ra defences (Donath et al., 2010; Spinas et al., 1988).

This reactive relationship with IL-1β is highlighted in several large cross-sectional studies that show an independent association between IL-1ra levels and future T2DM (Herder et al., 2009), and that these individuals demonstrate a sharp increase in IL-1ra in the 6-year period preceding diagnosis (Carstensen et al., 2010). This relationship is further emphasised by the finding that the spike in IL-1ra coincided with a decrease in peripheral insulin sensitivity, and preceded the marked hyperglycaemia observed in these individuals (Carstensen et al., 2010). Separately, Meier et al. (2002) reported a correlation between increased IL-1ra and elevated leptin concentrations in serum of obese participants and speculated that IL-1ra may interfere with the hypothalamic signalling activities of leptin, thereby contributing to obesity-related hyperleptinaemia. Accordingly, IL-1ra serves as a useful prognostic indicator for obesity-related conditions, and thus is recognised as a biomarker of the obesity-induced disease state.

Several data have identified increased plasma IL-1ra values in chronically inactive and/or overweight individuals. A study of over 1,000 adults aged > 65 y showed a significant inverse relationship between fasting IL-1ra levels and performance-based measures of aerobic fitness (Elosua et al., 2005). Accordingly, a reduction in plasma IL-1ra is a possible therapeutic target given that it may reflect a reduced demand for competitive IL-1 inhibition. However, the existing experimental research is highly equivocal. With regards to endurance-based interventions, Scheett et al. (2002) reported no change in basal IL-1ra after a 5-week aerobic exercise program in healthy children. Similarly, in sedentary men, 8 weeks of moderate-intensity cycling (approx. 20km in 40-50 min) had no effect on IL-1ra (Mendham et al., 2014). Conversely, Beavers et al. (2010) observed a reduction in fasting IL-1ra after 6 months of endurance training in older adults, although this trend did not continue for the following 6 months. Separately, there has been some investigation into the efficacy of resistance training in this context; however, there has been no evidence of decreased IL-1ra with this modality. Current resistance training literature shows no change after 16 weeks in older women, who performed 3 sets of 6-14 repetitions per session over 10 free-weight and machine exercises (Prestes et al., 2009), nor after 20 weeks in prostate cancer patients training twice weekly in a linear periodisation design (Galvão et al., 2008). Further, one study even showed an increase after 12 weeks of training in older adults, although this outcome may be related to the temporal proximity of post-intervention blood acquisition to the final training session (Forti et al., 2016). In summary, the use of conventional isolate-mode training designs may limit the potential for short-term adaptation, and thus modified and/or novel exercise strategies may be necessary.

Effect of Exercise Modalities

Following these findings, recent studies have explored the use of novel training modalities as potential treatment strategies. Specifically, an 8-week interval-training program in T2DM patients was effective to prevent the increase in systemic IL-1ra concentrations observed in a sedentary control group (Madsen et al., 2015). Perhaps a more significant finding is that a combined exercise and hypocaloric diet substantially reduced IL-1ra in overweight and obese children (Izadpanah et al., 2012). The possible application of a multimodal therapeutic approach gathered further credence when Mendelson et al. (2015) reported a decrease in IL-1ra after 12 weeks of concurrent strength and endurance training in obese adolescents. In contrast, a separate study showed no change after 12 weeks of CET, although in this instance the participants were sedentary but otherwise healthy (Donges et al., 2013). Despite heterogeneous participant demographics, combination-based methods such as diet/exercise and CET have shown some promise and may warrant further investigation. That said, there is a lack of data relating to concurrent exercise, and thus the present investigation seeks to explore the role of CET to alter IL-1ra in untrained populations. Further, examination of the role of TUT within a concurrent design will provide further clarity to the role of exercise prescription and loads. In summary, there are still insufficient data to formally describe IL-1ra in either a disease-causing or a disease-preventing context; however, the measurement of this cytokine alongside IL-1β in the present study will provide insight into both the mode-specific training response, and the interaction with IL-1ra and IL-1β.

Markers of Glucose Homeostasis and the Effect of Exercise

Reduced insulin sensitivity and action are the primary physiological disturbances that predicate the development of T2DM (Tripathy et al., 2000). A network of hormonal and

humoral factors contributes to a reduced insulin-stimulated glucose uptake (Hotamisligil, 2006), resulting in elevated levels of glucose and/or insulin in the fasting and postprandial states, representing primary risk factors for T2DM (Tripathy et al., 2000). Further, exercise training may be effective to ameliorate insulin resistance and glucose homeostasis, signifying a reduced risk of future complications (Ivy, 1997). Specifically, in addition to the association between activity levels and T2DM risk (Durstine et al., 2013), experimental data suggest short-term training interventions can reduce insulin resistance (Inoue et al., 2015), leptin resistance (Okazaki et al., 1999), and decrease the overall T2DM risk (Durstine et al., 2013). Accordingly, the following sections will explore the current evidence with regards to the mechanistic role of T2DM-specific biomarkers (leptin, insulin, glucose, glucagon, GLP-1), and the use of exercise to modify these markers, and subsequently improve glucose homeostasis.

Leptin

Function & Relevance

Leptin is produced mainly by adipocytes and acts as a regulator of energy homeostasis by influencing appetite perception and overall energy expenditure (Mantzoros, 1999). In doing so, it entails a negative feedback loop through which humans are able to respond to changes in adiposity and energy status (Huang & Cai, 2000). Leptin characterises the postprandial state, and regulates eating behaviours by altering the expression of numerous hypothalamic neuropeptides (Wolf, 1997) as well as several neuroendocrine mechanisms in various tissues (Mantzoros, 1999). Its receptors are expressed in many cell types including intestinal adipocytes, epithelial cells, vascular smooth muscle, hepatocytes and leukocytes, although the highly active long form receptor is particularly enriched in the hypothalamus (Huang & Cai, 2000). Thus, the role of leptin as a critical mediator of

energy signalling is well established, as is its importance to systemic afferent functioning. Accordingly, under conditions of leptin dysregulation (i.e. hyper- or hypoleptinaemia), the resulting metabolic abnormalities can have significant consequences on inflammation and glucose homeostasis (Iikuni et al., 2008; Ouchi et al., 2011).

Given that leptin is an adipocyte-derived hormone, it is feasible that a relationship exists between overall adiposity and systemic leptin activity. Indeed, obesity was originally associated with a relative leptin deficiency due to early studies in leptin-deficient rodents (Considine et al., 1996). However, it is now understood that obesity results in hypothalamic resistance to leptin, and consequently obese individuals frequently demonstrate elevated leptin levels (Mantzoros, 1999). Alongside central leptin resistance, obesity is associated with a low-grade inflammatory state, and evidence shows that these two obesity-related phenomena are closely linked, in that they demonstrate reciprocal activation (Fernández-Riejos et al., 2010). Leptin is a potent stimulator of leukocyte proliferation and survival via modulation of anti-apoptotic protein expression (Fernández-Riejos et al., 2010). Leptin receptors are expressed by both T- and B-lymphocytes (Busso et al., 2002), and leptin promotes the secretion of inflammatory cytokines such as IL-6 and TNFα (Fernández-Riejos et al., 2010). Equally, leptin production is up-regulated by IL-1β and TNFα (Sarraf et al., 1997) and leptin shows a particularly close relationship with the former, as evidenced in rodent studies in which central IL-1ra injection suppresses the regulatory activities of leptin (Luheshi et al., 1999). However, under conditions of energy abundance and increased adiposity, this relationship is a key driver of obesity-related comorbidities.

Obesity-induced leptin resistance is a key factor in the development of metabolic dysfunction (Ouchi et al., 2011). Specifically, obese individuals exhibit elevated circulating leptin levels without the concomitant anorexic response, indicating a possible deficiency in signalling mechanisms (Friedman & Halaas, 1998). Further, in a cohort of middle-aged Japanese-American men, increased leptin concentrations were associated with eventual T2DM diagnosis within 5 years (Mcneely et al., 1999). Likewise, among lean and obese women, the latter group showed a strong association with leptin and insulin resistance (measured by HOMA) (Silha et al., 2003). To understand this relationship further, cell culture studies have examined the effects of leptin on relevant intracellular processes. Namely, leptin is shown to inhibit β-cell function in the human pancreas (Huang & Cai, 2000), possibly via disruption of the IL-1β/IL-1ra balance within pancreatic islets, leading to functional impairments and β-cell apoptosis (Maedler et al., 2004). Thus, leptin may play a role in the dysfunctional insulin secretion associated with obesity. Collectively, there is ample evidence for leptin's role in the progression of metabolic dysfunction and eventual T2DM disease onset.

Further to the association with T2DM, leptin has shown a complex, multifaceted relationship with humoral and structural changes that predicate CVD. A study of 783 men revealed a capacity for leptin to predict coronary events over a 5-y follow-up period, independent of BMI, age, lipids, blood pressure, and plasma CRP (Wallace et al., 2001). Separately, Söderberg et al. (2004) identified basal leptin concentrations as an independent risk factor for stroke among adult males. Accordingly, current evidence suggests that several leptin-related processes contribute to the localised pathologies that constitute CVD. To concur, Singhal et al. (2002) identify leptin as a key link between adiposity and CVD, implicating a loss of arterial elasticity through stimulation of leptin

receptors in endothelial cells. More specifically, leptin enhances vascular smooth muscle cell proliferation (Oda et al., 2001) and augments tissue-specific oxidative stress (Bouloumié et al., 1999). To exacerbate the pro-atherogenic state, leptin also promotes intimal monocyte induction through increased MCP-1 activity (Yamagishi et al., 2001) and enhances foam cell formation via reduced hydrolysis of cholesterol esters in activated macrophages (O'Rourke et al., 2002). Ultimately, leptin increases the calcification of endothelial cells (Van Gaal et al., 2006) and negatively alters the coagulation-fibrinolysis balance via reduced fibrinolytic activity (Martin et al., 2008).

Effect of Exercise Modalities

Considering the existing evidence, leptin has featured in many research studies as a therapeutic target for disease treatment or prevention. There is evidence that endurance-based training is effective to decrease leptin in previously sedentary individuals: (Gutin et al., 1999) observed a marked reduction in leptin levels after 4 months of aerobic exercise in a cohort of obese children. Similarly, sedentary women showed decreased fasting leptin following 12 weeks' aerobic training, in conjunction with a lifestyle-counselling program (Okazaki et al., 1999). Moreover, Kohrt et al. (1996) reported reduced leptin concentrations among sedentary women following the completion of an 11-month endurance exercise intervention (walking/jogging), and noted that this occurred independently of concomitant hormone replacement therapy among these individuals. In contrast, other studies have questioned the efficacy of this single-mode strategy. Specifically, there was no change in leptin among sedentary adults after either 16 weeks (Arikawa et al., 2011) or 6 months of aerobic training (Lowndes et al., 2008) and separately, Kelly et al. (2007) reported no effect of 8 weeks' training in overweight children. Importantly, the latter group suggested that improvements in whole-body

adiposity are key determinants of changes in fasted leptin. This hypothesis is supported elsewhere by Kraemer et al. (1999) following a null finding with mixed-mode aerobic training in overweight women. In light of equivocal results from these studies, numerous authors have investigated the role of combination strategies involving physical exercise alongside other lifestyle-based modifications such as dietary manipulation.

Thus far, the results of investigations on combined exercise interventions have been overwhelmingly positive. Concurrent physical activity and hypocaloric diet programs have effectively reduced leptin over 4 months in sedentary women (Reed et al., 2010) and 12 months in obese men (Pasman et al., 1998). Short-term intensive strategies have also yielded positive outcomes in overweight children, whereby a 3-week diet/exercise 'bootcamp' reduced leptin levels in obese adolescents (Gallistl et al., 2001a) and a similar program in younger overweight children was effective after only 2 weeks (Izadpanah et al., 2012). Evidently, there is some promise in the use of multiple strategies to reduce leptin. Accordingly, several other studies have compared diet/exercise interventions to single-mode variants. For example, Galassetti et al. (2006) compared the effects of endurance-based training with or without a hypocaloric diet in healthy young men, and found that exercise combined with a hypocaloric diet decreased leptin after only 1 week, while there was no change in an exercise/normocaloric diet group. Clearly this outcome is not easily extrapolated to long-term interventions; however, programs of longer durations have shown similar results. Ben Ounis et al. (2009) implemented an 8-week program consisting of either a weight-loss diet (500kcal deficit), aerobic training (4 times per week) or a combination of both. These authors reported that, while exercise-only participants improved insulin sensitivity, and diet-only participants reduced BMI quite

effectively, the combined intervention (i.e. diet plus exercise) caused improvements in all areas, and also provided the greatest reduction in fasting leptin, IL-6 and TNFα.

The above findings have been replicated in overweight/obese individuals. For example, a 12-week regimen of physical activity, hypocaloric diet, or both was implemented in obese adults, and the authors report that the exercise-only condition had no effect on fasting leptin, while there were significant and similar improvements in the diet-only and combination groups (Christiansen et al., 2010). It is important to note, however, that the effects of these combined diet/exercise programs may simply be related to the addition of a greater therapeutic treatment, and thus it is necessary to examine split-dose interventions, whereby a 50% dosage of each is provided. To the authors' knowledge, no such study exists for dietary strategies, although the concept of combined/multimodal interventions has shown a broad application via the concomitant use of multiple and/or novel exercise modalities to deliver a larger spectrum of training stimuli. As evidence, Balducci et al. (2010) reported similar improvements in fasting blood chemistry (leptin, IL-6, HDL-C, HbA1c, insulin resistance) following a 12-month intervention of twice-weekly aerobic (60 min) or concurrent training (40 min aerobic and 20 min resistance training) matched for caloric expenditure. Other studies have shown improvements in fasting leptin using CET interventions compared to non-exercising controls (Hayase et al., 2002; Mendham et al., 2015); however, the comparison with single-treatment strategies is currently unclear. Regardless, the role of lifestyle-based therapies to reduce leptin levels is well established in the literature and these strategies represent a key component of intervention programs. Collectively, the available data show promise for the use of mixed-mode regimens such as diet/exercise, medication/exercise, and CET, although the importance of specific training variables remains unknown. Given that TUT

may provide similar hypertrophy and/or fat loss as the RT component (Keeler et al., 2001; Rana et al., 2008), it is possible that manipulating the RT component of CET may allow positive changes in leptin also, particularly considering leptin levels are augmented by increased adiposity (Kelly et al., 2007) and decreased by aerobic fitness (Jiménez-Pavón et al., 2012). Thus, the aim of the present investigation is to further ascertain the effects of CET and TUT on fasting leptin concentrations, and to identify the role of muscle time under tension in mitigating these outcomes.

Insulin & HOMA-IR

Function & Relevance

Insulin is an extensively studied and widely known biomarker relating to T2DM. It is a peptide hormone produced by β-cells on pancreatic islets and is considered a primary anabolic hormone of the endocrine system (Saltiel & Kahn, 2001). Specifically, it is a critical mediator of glucose homeostasis across quotidian cycles of feeding and fasting, via stimulation of cellular substrate storage and inhibition of catabolic processes in the liver, adipose tissue, and skeletal muscle (Saltiel & Kahn, 2001). In the muscle insulin binds to targeted surface receptors, stimulating tyrosine kinase activity and subsequent transphosphorylation in receptor β-subunits (Pessin & Saltiel, 2000). Subsequently, phosphorylated receptor proteins activate a series of intracellular reactions leading to increased GLUT4 exocytosis (Pessin et al., 1999). Translocation of GLUT4 from intracellular vesicles to the cell membrane facilitates glucose endocytosis, representing a primary regulatory mechanism in the postprandial state (Saltiel & Kahn, 2001).

Separately, insulin up-regulates glycogen synthase while concomitantly down-regulating glycogen phosphorylase to reduce the activity of gluconeogenic enzymes (Michael et al.,

2000). Given the pivotal role of insulin in the regulation of food substrates in the blood and peripheral tissues, it is considered a key prognostic measure within the context of metabolic dysfunction and disease. Defective insulin signalling and action predicate the development of T2DM (Tripathy et al., 2000). This is a complex, multifactorial process related to a number of potential causal factors including ectopic fat accumulation, endoplasmic reticulum stress, and chronic inflammation (Samuel & Shulman, 2012). The specific pathology of insulin resistance relates to several physiological changes resulting in resistance to the actions of insulin in the muscle and liver, and ultimately reduced glucose uptake leading to hyperglycaemia and/or hyperinsulinaemia (Pessin & Saltiel, 2000). Decreased concentrations of membrane receptors, intracellular enzyme activity, and phosphorylation of receptor substrates are all suggested as potential direct mechanisms leading to insulin resistance (Pessin & Saltiel, 2000). Moreover, circulating concentrations of insulin in the fasted state, as well as postprandial responses, can provide insight into underlying issues.

Elevated plasma insulin levels, representative of a pre-disease state, also correlate independently with visceral adiposity (Pouliot et al., 1992) and as such have been the focus of preventative treatments for many years. It is suggested that maintenance of healthy levels of adiposity, as well as frequent physical exercise, can help prevent age-related hyperinsulinaemia (Ryan, 2000). Moreover, in a large cross-sectional study, a positive correlation existed between fasting insulin levels and subsequent development of CVD (Folsom et al., 1997). Furthermore, the Paris Prospective Study measured a large population of men over 11 years, finding that baseline insulin concentrations in plasma were an independent predictor of CVD-related death at the 11-year follow-up (Fontbonne & Eschwège, 1991).

Effect of Exercise Modalities

There are many training-based intervention studies to identify the role of exercise in improving the basal metabolic state, measured via fasting insulin concentrations. Due to the quantity and heterogeneity of the existing literature, the present section will be limited to healthy (non-diseased) populations. Considering the relationship with obesity, Kim et al. (2009) reported a reduction in fasting insulin concentrations after 12 weeks of moderate-intensity (60-70% HRmax) running training in obese men. Similarly, aerobic exercise training has been shown to elicit improvements in obese children, who engaged in 5 days per week of active play over 4 months (Ferguson et al., 1999). Separately, a multimodal approach involving 3 weekly sessions of walking, sports games, and swimming was effective after 6 months in obese children (Meyer et al., 2006). Conversely, Despres et al. (1991) observed no change in plasma insulin concentrations after 14 months of mixed-mode endurance training in obese women, although these authors speculated that inconsistencies in fat loss outcomes, and a small sample size (n = 13), may have contributed to this null finding. In summary, strategies that alter body composition, as well as those incorporating load-bearing modalities, may provide superior benefits with regards to insulin levels.

With regards to non-obese individuals, research findings are rather more equivocal, as Okita et al. (2004) reported a substantial decrease in insulin after 2 months of aerobic training in a cohort of apparently healthy women, coinciding with a modest improvement in basal CRP. Likewise, endurance training modalities have resulted in improvements in fasting insulin among healthy men (Kahn et al., 1990) and older adults (Evans et al., 2005). Of note, aerobic exercise is as effective as surgical intervention (gastric bypass) to

improve metabolic profiles (insulin, glucose, and adiponectin) (Hulver et al., 2002). In contrast, some studies have shown no effect of aerobic interventions on insulin levels. For example, healthy adults showed unchanged insulin after 20 weeks of moderate-intensity cycling (Pérusse et al., 1997) while another cohort of sedentary individuals demonstrated no effect following a similar 17-week cycling program (Short et al., 2003). It is feasible that these outcomes result from the non-load-bearing nature of the exercise protocols used (i.e. stationary cycling), considering that hiking-based (Drexel et al., 2008) and mixed-mode endurance training (Kirwan et al., 1993) have shown effectiveness in this regard.

Furthermore, training intensity and volume may be important variables in this scenario as Pratley et al. (2000) reported no change in insulin with a 9-month aerobic training intervention comprising ~3 weekly sessions of low- to moderate-intensity exercise, of which the attendance rate was 80%. By comparison, a group of older adults (60-70y) training 4 times per week at 60-85% HR_{max} for 9 months showed marked reductions in basal insulin levels (Kirwan et al., 1993). Notably, two very similar exercise protocols (12 weeks' multimodal, moderate-intensity training) showed divergent results in that sedentary adults did not demonstrate changes in insulin levels (Pruchnic et al., 2004) while sedentary adolescents did show reductions with an almost identical training regimen (van der Heijden et al., 2010b). Collectively, the interpretation of the existing literature is somewhat hampered by low statistical power and differing experimental conditions, although at present it does seem that endurance training is an effective tool to reduce fasting insulin provided it is undertaken with sufficient volume and intensity. The importance of exercise modalities remains unclear, although based on the above, mechanical load-bearing of muscle may be a contributing factor. Accordingly, a number

of studies have investigated strength training as a possible treatment strategy, although at present the significance of overall loads (and thus the rationale for TUT) remains unclear.

Resistance training represents a potential means to elicit reductions in fasting insulin concentrations. As evidence, Craig et al. (1989) reported decreased basal insulin among both younger and older individuals following a 12-week whole-body resistance training intervention. Conversely, a cohort of older adults showed no change in fasting insulin levels, although this group did exhibit improvements in HbA1c, HOMA-IR, CRP and adiponectin (Brooks et al., 2007). Further literature relating to older adults is similarly equivocal. (Iglay et al., 2007) report no change in fasting insulin after 12 weeks' resistance training with either a low- or high-protein diet intervention, while Miller et al. (1994) found significant reductions after 16 weeks of RT alone.

Separately, resistance exercise has shown some effectiveness among overweight and obese individuals. For example, Rice et al. (1999) observed similar reductions in insulin concentrations using combined interventions of caloric restriction with either aerobic or resistance training in obese men. The same outcome is reported in obese women who undertook 1 year of multidisciplinary weight loss treatment (Weinstock et al., 1998), while Nybo et al. (2010) found no change with either aerobic, resistance, or interval-based running exercise in sedentary males after 12 weeks. By comparison, Ahmadizad et al. (2007) found equal reductions in fasting insulin with 12 weeks' endurance or strength training in healthy males.

In contrast to the above, studies in resistance exercise have inconsistent findings. Several studies show decreased plasma insulin with resistance training in untrained men over 10

weeks (Miller et al., 1984), while older men showed a decrease after 12 weeks, whereby the authors suggested muscle hypertrophy was a significant contributor to inflammatory and metabolic adaptation (Ogawa et al., 2010). Conversely, some studies show no changes in overweight adolescents after resistance training programs (Shaibi et al., 2006; van Der Heijden et al., 2010a), and after 1 year of training in overweight women, there was no change in insulin, alongside unchanged body composition and fasting glucose (Olson et al., 2007). These authors have provided several possible explanations for these inconsistencies, namely differences in training intensity (Nybo et al., 2010), and confounding factors such as changes in inflammatory and hormonal profiles (Olson et al., 2007). In some instances, functional measurements of metabolic function (e.g. OGTT) showed positive changes while fasting measurements did not (Shaibi et al., 2006), and as such the context in which these changes occur requires consideration.

Collectively, the present evidence is inconsistent; however, the concomitant application of synergistic intervention strategies has shown some promise. Further research is required to elucidate the role of training intensity and volume, but it seems that this approach may confer an additive effect whereby adaptations are superior to those seen with single-treatment regimens, when overall training loads are equated. In the absence of replication studies and clear trends in the data, it is proposed that the present intervention will elicit improvements in the metabolic risk profile indicated by a reduction in fasting insulin concentrations.

Mendelson et al. (2015) report a significant reduction in plasma insulin after 12 weeks of concurrent aerobic and resistance training in obese adolescents, while on the other hand a CET intervention did not alter insulin in obese adults after 6 months, while aerobic-only

and resistance-only regimens also had no effect (Davidson et al., 2009). Elsewhere, no change was reported following a 12-week CET treatment in healthy women (Choi et al., 2007), although a lack of a non-exercising control group complicates the interpretation. Glynn et al. (2015) administered a 6-month CET program in overweight individuals and observed a significant decrease in resting insulin levels compared to a sedentary control. Thus, there is a lack of consensus regarding CET, partly owing to a lack of data. By enhancing other subclinical risk markers such as inflammatory cytokines and abdominal adiposity, CET may provide positive changes in insulin and glucose homeostasis, although more studies are needed. Moreover, given that sedentary and/or diseased populations are in particular need of effective exercise strategies (Pedersen & Saltin, 2015), tailoring aspects of the CET design may warrant further investigation. In particular, altering the training load patterns to accommodate individual needs may provide an efficacious exercise prescription approach. For example, these benefits for glucose/insulin homeostasis seem to be independent of loading intensity (Forti et al., 2016), and incorporation of TUT may provide an endurance-like stimulus (Burd et al., 2012), such that it can be used alongside AT to enhance the abovementioned parameters.

HOMA-IR

Function & Relevance

Although fasting insulin is a useful prognostic measure in isolation, the pathogenic processes that predicate insulin resistance and T2DM relate to the inability of endogenous insulin to sufficiently regulate blood glucose concentrations. Accordingly, the most useful physiological data are provided when insulin is measured in conjunction with fasting glucose levels (Tripathy et al., 2000). Specifically, in the absence of functional measures, the homeostatic model of assessment (HOMA) represents a practical tool that delivers a

'snapshot' of insulin action (Wallace et al., 2004). Insulin sensitivity measured by HOMA is thus identified as a measure of metabolic function and, accordingly, an indicator of the effectiveness of intervention strategies (Wallace et al., 2004). Considering the positive cardiometabolic effects provided by exercise training, the HOMA index has been used extensively to assess changes in disease risk pursuant to activity-based interventions.

Effect of Concurrent Training

Throughout the existing literature, the HOMA model is frequently used longitudinally to identify changes over time (e.g. in response to an intervention). Generally, this measurement is considered particularly relevant in the treatment of obesity and/or T2DM, and thus the majority of research data pertains to these populations. Indeed, the results of CET-based interventions are largely positive in the clinical setting. Specifically, several authors have described CET programs in isolation (i.e. compared to no exercise), although the existing studies vary greatly in methodology. For example, a 12-week CET regimen conducted in adults with T2DM significantly decreased HOMA-IR alongside improvements in HbA1c (Bassi et al., 2016). Conversely, McGavock et al. (2004) reported that women with T2DM improved fitness with 10 weeks' CET and decreased insulin resistance by around 17%, although this was not significantly different to a control group. It is possible that this discrepancy is related to differences in study duration, program design (although the two are very similar), or that the latter involved a markedly smaller sample (n=21 vs n=11 in training groups) comprising women only. To explore further, after administering an 8-week CET program in adults with T2DM, Touvra et al. (2011) observed a significant decrease in HOMA-IR. Interestingly, these participants demonstrated concomitant reductions in CRP and HbA1c, but no changes in other key mediators such as IL-6 and TNFα. Compared to the abovementioned regimens, this

training program was very similar (30 min AT and 30 min RT per session, and similar session volume); however, these individuals exercised 4 times per week. Accordingly, it may be that training frequency influences training adaptations, although to the author's knowledge there are no data to verify this.

Of particular interest is the effect of CET compared to more commonly prescribed exercise modalities on HOMA-IR. Some studies suggest that a split-dose CET approach does not confer any additional benefit versus single-mode training; Thomson et al. (2008) showed that a rigorous 20-week regimen of a hypocaloric diet combined with either AT or CET 5 times per week showed reduced insulin resistance, but with no between-groups differences. Balducci et al. (2010) reported equal improvements in insulin resistance in adults with T2DM, with concomitant improvements in HbA1c, leptin, and inflammatory cytokines between AT and time-matched CET. Notably, these subjects trained twice weekly for 1 year and sessions involved only 20 minutes of RT (40 minutes' AT). Thus, it is possible that the training stimulus from CET was not sufficiently different from AT to produce any clear differences. Moreover, individuals who trained 3 times per week for 1 year in a 50-50 training split (i.e. 30 min AT and 30 min RT per session) demonstrated greater improvements in HOMA-IR compared to an AT-only condition (de Piano et al., 2012). These individuals showed greater increases in lean mass and adiponectin, which may have contributed to this outcome. However, differences in the disease state (these participants had NAFLD) may confound the comparison with other literature. Nevertheless, considering these two studies it is possible that sufficient RT volume is necessary to maximise the health-related benefits of CET. That said, a number of studies explore the effects of CET compared to either AT or RT, be it in a split-dose or additive fashion.

Thus far, due to a paucity of research data and a lack of replication studies, it is not entirely clear where the benefits of CET exist, and at what level of training they become apparent. It seems unlikely that short-term interventions in untrained participants will show modality-specific adaptations, as evidenced by Eskandary and Rahimi (2017) who reported equal improvements in insulin resistance with either thrice-weekly AT or duration-matched CET (i.e. 50% AT and RT) in T2DM subjects. Notably, these changes were superior to those observed in an RT-only group, despite equal improvements in HbA1c across all 3 groups. Longer-term studies in diseased populations show 6 months of training with either AT, RT or 50% of each improved fitness in 100 adults with T2DM, although reduced HOMA-IR was only observed within the AT and CET groups (Kadoglou et al., 2013). Here, CET caused greater cardiovascular improvements (blood pressure and lipid profiles), although it was comparable to AT with regards to inflammatory markers. An even longer training study, lasting 8 months, revealed a non-significant trend towards lower insulin resistance with CET compared to either AT or RT alone among overweight, dyslipidaemic adults (Slentz et al., 2011). Notably, participants in the AT group demonstrated larger reductions in subcutaneous and intrahepatic fat, although VAT decreased equally in AT versus CET. Collectively, the existing data within the clinical setting remains equivocal, although the benefits of CET in a diseased population may extend beyond the immediate modification of the metabolic state.

A potential application exists to attenuate disease-related risk factors in otherwise healthy participants, and as such a large portion of the literature relates to this population. In particular, CET is an effective prevention strategy in overweight but non-diseased individuals, given excessive adiposity is a major risk factor for many chronic conditions.

In the short-term (< 3 months), CET does seem to be effective to combat the metabolic decrements associated with obesity. For example, Kim et al. (2008a) reported significant reductions in HOMA-IR alongside fat loss in obese adolescents following 12 weeks of CET comprising 2 moderate-intensity walking sessions and 1 whole-body RT session per week. In contrast, a shorter training program (8 weeks) among overweight adults had no effect on insulin resistance, although fat loss and improved blood lipids were observed (Kraemer et al., 2007). These authors proposed that this null finding may be related to the short training period, or possibly an excessive washout period between the final training session and post-intervention testing, potentially masking the training response.

Nevertheless, it seems that 8 weeks of CET may not be sufficient to cause significant improvements in fasting glucose homeostasis despite fat loss. Indeed, two very similar studies show substantial physiological adaptations (including decreased HOMA-IR) after 12 weeks of CET in overweight/obese subjects (Bharath et al., 2018; Choi et al., 2007). Importantly, these individuals trained 5 times per week, with a larger emphasis on AT (40 min sessions), although the overall weekly training time was similar to that used by Kraemer et al. (2007). That said, other data seem to suggest that inflammatory markers must decrease in order to achieve significant changes in insulin resistance (which is feasible given the mechanistic relationship between the two). Villareal et al. (2011) reported no changes in HOMA-IR after 12 weeks of CET (30 min AT and RT, 3 times per week), coinciding with unchanged concentrations of CRP and TNFα. Conversely, Lopes et al. (2016) did find reduced HOMA-IR after 12 weeks' CET, alongside reduced CRP. However, these subjects did not show changes in TNFα, IL-6, IL-10 or adiponectin, and neither of these 2 studies included any description of the relationship between HOMA-IR and changes in inflammatory markers. Moreover, although Shabani et al.

(2018) found no change in insulin resistance after 12 weeks' CET (30 minutes' AT and RT), another study in a similar population (overweight adolescents) showed significant reductions in HOMA-IR (Mendelson et al., 2015). Despite very similar training interventions, the latter cohort demonstrated increased TBLM and small improvements in the inflammatory profile. Also, perhaps importantly, further analyses indicated that those who showed the largest decreases in VAT exhibited the greatest improvements in insulin resistance. Given that Shabani et al. (2018) did not include any rigorous measures of body composition, it is difficult to compare findings between the two, although a strong relationship has been shown with VAT and metabolic dysfunction (Fujioka et al., 1987).

In contrast, longer-term studies deliver rather more consistent results. For example, Davis et al. (2011) found pronounced reductions in HOMA-IR after 16 weeks of twice-weekly CET comprising circuit-style training in obese adolescents. This outcome coincided with improvements in SAT, VAT and physical fitness, and did not differ depending on whether participants received motivational counselling or not. Similarly, obese women training 3 times per week for 16 weeks demonstrated reduced insulin resistance alongside fat loss, both with and without the inclusion of anti-inflammatory laser therapy (Duarte et al., 2015). Interestingly, the group receiving the additional therapy showed greater decreases in ICAM-1 and leptin, although no between-group differences were observed for HOMA-IR. Thus, the duration of the exercise period seems to be of importance in this regard; however, there are few longer intervention studies in overweight individuals. For example, a 6-month CET regimen did not alter HOMA-IR in overweight postmenopausal women – these subjects exhibited increased lean mass but no change in adiposity (Glouzon et al., 2015). In contrast, a much longer intervention (1 year) in obese adolescents did improve insulin resistance, as well as positive changes in TBLM, TBFM,

VAT, SAT, adiponectin and blood lipid profiles (de Lima Sanches et al., 2011). Although these exercise programs were very similar (30 minutes' AT and RT, 3 times per week) the longer intervention (1 year vs 6 months) caused more pronounced changes in all physiological variables. Notably, in the latter study the change in HOMA-IR correlated negatively with the change in adiponectin, further emphasising the direct role of inflammatory mediators. Accordingly, the manner in which CET is prescribed seems to be a key mediator of the eventual change in insulin resistance and lends credence to exploring the alteration of the CET training stimulus.

Collectively, in overweight and obese individuals the literature seems to support CET as a strategy to reduce insulin resistance. Conversely, many non-obese individuals seek to incorporate CET into exercise regimens with the aim of reducing disease risk and enhancing functional capacity. Indeed, Glynn et al. (2015) reported marked improvements in HOMA-IR following 6 months of CET; interestingly, the training response did not differ between overweight and 'lean' subjects. Furthermore, a number of studies have explored the use of CET in individuals who are free from disease and at a healthy weight. Specifically, over 12 weeks of CET in older adults, Kodama et al. (2007) reported significant improvements in HOMA-IR, without concomitant improvement in cardiovascular parameters. Notably, these subjects trained 5 times per week (3 AT sessions and 2 RT sessions) although for only 30 minutes per session. In contrast, among untrained older adults there was no change in fasting metabolic biomarkers (HOMA-IR, HbA1c, CRP, IL-6) with 12 weeks of training (Tokudome et al., 2004). It is important to note that these individuals participated in only 1 supervised exercise session per week, which involved 1 set of 11 RT exercises. In lieu of supervised endurance training, participants were 'encouraged' to perform 2 RT sessions per week outside of the study

environment (using resistance bands) and increase daily step counts recorded by a pedometer. Hence this is not typical research methodology and highlights the pitfalls of drawing clinical inferences from unstructured training studies. Similarly, after 1 year of training involving 2 CET sessions, plus advice for an additional 30-minute home-based AT session per week, there was no difference in HOMA-IR among postmenopausal women (Van Gemert et al., 2015). It is possible that structured, supervised training is more appropriate in this regard, particularly given the low exercise literacy of the population.

Collectively, the current body of data suggests a positive effect of CET on HOMA-IR, although the role of different training variables remains unclear. Thus, a significant portion of the literature relates to the specific effects of CET compared to single-mode variants (i.e. RT or AT alone). For example, in the short term, CET appears to be similar to either RT or AT in terms of metabolic adaptations: on one hand, the addition of RT to an existing AT program for 4 months improves HOMA-IR more than simply continuing AT (Ferrara et al., 2004), although this is likely due to increased overall training volume. Perhaps more relevant is the possible additive effect of combining RT and AT in a split-dose fashion (i.e. 50% of each). As evidence, among obese women, Soori et al. (2017) observed significant reductions in HOMA-IR after 10 weeks of CET, although the improvements were equal to those provided by AT alone. By comparison, a 12-week training regimen of either AT (moderate-intensity walking), full-body RT, or a half-dose of each (CET) did not alter basal insulin resistance among obese individuals (Ho et al., 2012). Notably, the absence of between- or within-group changes occurred despite CET showing greater improvements in whole-body and regional adiposity. Interestingly, participants trained 5 times per week for 30 minutes, completing 3 sessions supervised

within a gymnasium setting and the remaining 2 sessions at home. Thus, variance in the actual exercise performed during unsupervised sessions could not be verified, and further, the RT component comprised mainly single-joint exercises, and thus it is possible that there was insufficient disruption of systemic metabolism to drive long-term adaptations.

Moreover, a separate study showed that among obese men, 8 weeks of thrice-weekly CET was more effective than either AT or RT alone to improve HOMA-IR, despite a 50% dosage of each modality (Tayebi et al., 2016). Within that study, the CET group demonstrated superior improvements in body fat percentage, and there are questions regarding the efficacy of the RT protocol, namely the low-intensity training prescribed, seemingly with no explanation from the authors. Thus, short-term studies (< 3 months) do not provide any clear conclusion with regards to the mode-specific effects of training in obese subjects; however, longer studies seem to suggest a slight advantage to CET within this population. Specifically, de Mello et al. (2011) reported that after 1 year of training, obese adolescents showed improved HOMA-IR after CET but not duration-matched AT. Notably, within this study there were no between-group differences in VAT and SAT (both groups decreased) although the CET group demonstrated greater increases in TBLM and adiponectin concentrations, which may have partially explained the difference in insulin resistance. This finding is not necessarily in agreement with other long-term studies. Both Campos et al. (2014) and Dâmaso et al. (2014) found improved HOMA-IR after year-long CET interventions, although in both cases CET did not confer any additional benefit compared to AT. Conversely, Inoue et al. (2015) reported that obese adolescents who undertook CET for 12 months showed greater reductions in HOMA-IR compared to those who performed duration-matched AT. Interestingly, within the CET group there were 2 subgroups who trained using either linear or undulating

periodisation strategies, and these did not differ in terms of physiological adaptations. Ultimately, for obese individuals there seems to be a possible benefit to CET; however, a separate application exists for individuals who are of a healthy weight and are seeking to improve health-related parameters.

Strategies that increase muscle mass and/or decrease fat mass are likely to coincide with improved metabolic profiles. Thus, CET may be appropriate to provide simultaneous integration of training stimuli. Also, insulin action is strongly influenced by inflammatory mediators and other chemical factors and thus, targeting other physiological markers such as TNFα or adiponectin may result in concomitant improvements in HOMA-IR. It is expected that in untrained and/or overweight individuals a short-term CET regimen will reduce basal insulin resistance, reflecting an overall improvement in glucose homeostasis. Moreover, these individuals demonstrate an increasing need for tailored strategies to enhance these disease indicators, and in particular may experience issues with the training loads involved in CET (Bishop et al., 2019). As such, modification of CET by incorporating TUT represents an option for these individuals to improve body composition (Keeler et al., 2001), strength performance (Young & Bilby, 1993), and drive positive changes in glucose homeostasis (Bartels et al., 2007).

Glucagon

Function & Relevance

Glucagon is a key mediator of glucose homeostasis in systemic circulation, serving as a biological antagonist to insulin (Unger, 1974). It is a peptide hormone produced in the α-cells of the pancreas that responds to hypoglycaemia by stimulating glycogenolysis and gluconeogenesis, thereby providing a key survival mechanism by ensuring adequate

substrate delivery to glucose-dependent tissues (Unger, 1974). Significant elevations in plasma glucagon concentrations are typically observed with glucose concentrations ≤ 4.5 $mmol \cdot L^{-1}$, and it is suggested that the primary driver of glucagon secretion is a decrease in insulin action (Sandoval & D'Alessio, 2015). Accordingly, fasting and postprandial measurements of glucagon represent valuable prognostic measures for T2DM, alongside insulin data. Specifically, elevated glucagon is associated with insulin resistance in that the inability of insulin to blunt glucagon production leads to hyperglucagonaemia and hyperglycaemia (Zhang & Moller, 2000). Moreover, it is likely that glucagon receptor density is reduced in T2DM and further, a localised resistance to insulin may play a role in the impaired insulin-stimulated suppression of glucagon secretion in the postprandial state (Ahren & Larsson, 2001). The association of fasting glucagon with T2DM is inconsistent as a standalone measure; however, the relative level of glucagon compared to insulin and/or glucose highlights the overall basal metabolic state, and high relative concentrations of glucagon may predispose T2DM (Dunning & Gerich, 2007).

A long-term inflammatory state may also contribute to hyperglucagonaemia, and a number of pro-inflammatory cytokines have been implicated in this process. Specifically, IL-6 is reported to increase glucagon secretion and stimulate the proliferation of glucagon-secreting α-cells in pancreatic islets (Ellingsgaard et al., 2008). Separately, the IL-1 cytokine family is linked with hyperglucagonaemia in rats (Dinarello, 1996), and TNFα is associated with increased serum glucagon levels, though this is generally not associated with increases in the hepatic activities of glucagon (Grunfeld & Feingold, 1991). As further evidence, activity in the pro-inflammatory NF-κB pathway promotes increased postprandial glucagon responses in obese mice, while inhibition of NF-κB in

hepatocytes may reduce glucagon secretion and the associated glycogenolysis (Sheng et al., 2012).

Effect of Exercise Modalities

In accordance with exercise-induced improvements in inflammatory mediators, a similar improvement in glucagon parameters is expected. Teixeira-Lemos et al. (2011) propose that glucagon suppression should be a frontline treatment for metabolic syndrome symptoms, and this may be achieved through increased glucagon-like peptide (GLP)-1. In turn, exercise training has been suggested as a possible intervention strategy. As evidence, several studies have shown improvements in hepatic glucagon signalling following exercise training. For example, the exercise-induced glucagon response is observed to be lower in trained vs untrained individuals (Bloom et al., 1976) and further, improved glucagon sensitivity is demonstrated after endurance training interventions in healthy males (Drouin et al., 1998) and younger adults (Gyntelberg et al., 1977). Considering the positive functional outcomes reported with exercise training, it is plausible that fasting blood GLP-1 or glucagon may also show improvements in this context. Indeed, a training-induced improvement in insulin signalling may indeed be reflected in a reduced basal glucagon concentration.

Several types of exercise have been successful in modifying glucagon and/or related processes. In the short term, Choi et al. (2013) reported decreased fasting glucagon, with no change in insulin or glucose, after 4 weeks of moderate-intensity AT in trained females. Importantly, those subjects trained for 1 hour, 5 times per week. Similarly, sedentary men undergoing a 3-week period of rigorous exercise (2h per day) decreased insulin and glucose with no change in glucagon, possibly indicating enhanced α-cell

sensitivity to insulin, although this was not measured (Poehlman et al., 1986). Considering intervention periods < 8 weeks in duration, it is feasible that greater weekly volumes are necessary to provide adaptations within this relatively short window. Further, Harmer et al. (2006) reported no change in glucagon or insulin concentrations after 7 weeks of high-intensity interval training 3 times per week. Moreover, this outcome did not differ between individuals with T1DM and those without. Thus, despite limited evidence, it may be that greater volume and/or frequency of training are necessary to elicit metabolic adaptations in short-term programs and greater specificity of the training prescription stimulus is required.

Non-weight-bearing modalities such as cycling have shown promise as an endurance training strategy to enhance glucose homeostasis. For example, after moderate-intensity cycling 5 times per week for 9 weeks, sedentary men showed decreased glucagon and insulin, alongside an improved body fat percentage (Bergman et al., 1999). An almost identical protocol by Friedlander et al. (2007) showed decreased insulin but unchanged glucagon, without any alteration in whole-body lean or fat mass. Again, the question of weekly volume is presented whereby in another study, older adults training 3 times per week for 8 weeks (moderate-intensity cycling) showed no change in glucagon, insulin, glucose or body composition (Poehlman et al., 1994). In contrast, men who trained for 12 weeks with 6 weekly sessions (4 moderate-intensity cycling sessions and 2 interval-training sessions) decreased insulin and blunted the exercise-induced glucagon spike, although there was no change in resting glucagon or glucose (Coggan et al., 1995). It is possible that for low-impact modalities such as these, longer and/or more vigorous interventions are required, such as the 5-month AT regimen conducted by Geyssant et al. (1981) which reduced basal glucagon in healthy men. Another possibility is that

incorporating muscle loading strategies will confer positive metabolic adaptations; indeed, combining running and cycling within a 9-week program decreased fasting glucagon in healthy subjects (Winder et al., 1979). Accordingly, exploration of tailoring specific loading strategies is warranted, whereby creation of a resistance training stimulus that provides AT-like metabolic strain may be of benefit.

More specific muscle loading via resistance training has produced unclear results thus far. Behall et al. (2003) administered 12 weeks of either AT (moderate-intensity walking) or whole-body RT 3 times per week in healthy women and report that both groups decreased insulin without modifying glucagon, as well as reducing the insulin and C-peptide responses to an oral glucose challenge. Conversely, older adults undergoing 12 weeks of RT, albeit with a markedly lower volume, showed no change in glucagon, insulin or glucose levels despite increased lean mass and decreased fat mass (Campbell et al., 1994). Interestingly, the results of that study did not differ between two sub-groups receiving either a low- or a high-protein dietary intervention. As such, there may be a rationale for combining AT and RT strategies via CET, and the role of the overall training load in this approach.

Subsequent to those data, there has been some investigation into strategies that combine moderate-volume endurance training with strength training, with the aim of providing a greater overall stimulus. However, to date only 2 studies have been conducted. In overweight adults, Glynn et al. (2015) conducted 6 months of concurrent endurance and resistance training, causing improved body composition and reduced insulin concentrations relative to glucagon. Importantly, those individuals also decreased HOMA-IR and leptin and further, the training prescription entailed significant weekly

loads (8 resistance exercises per session and 50,201 kJ per week of AT volume). In contrast, middle-aged women who underwent 2 weekly CET sessions for 12 weeks showed no change in glucose, insulin, glucagon, body composition or blood lipids (Volpe et al., 2001). Therefore, in the absence of clear consensus in the literature, it is hypothesised that the most effective methods to reduce glucagon levels relative to insulin involve training that is either greater in duration and/or weekly volume, and incorporates load-bearing modalities such as walking or RT. Based on the current data it is expected that 10 weeks of CET will decrease glucagon provided the intensity and duration of training sessions is sufficient. Thus, given that TUT is reported to provide a prolonged RT stimulus and in turn a greater metabolic cost (Burd et al., 2012), it is feasible that incorporating it into a CET design will enhance glucagon and other clinical parameters.

Glucagon-Like Peptide 1

Function & Relevance

Alongside the glucose-dependent insulinotropic polypeptide (GIP), GLP-1 is an incretin hormone which exerts a key function in the regulation of energy homeostasis and glucose metabolism (Sandoval & D'Alessio, 2015). It is produced by enteroendocrine L-cells in the gastrointestinal tract via posttranslational processing of proglucagon (Kreymann et al., 1987), and drives glucose uptake by stimulating insulin secretion, blunting glucagon secretion, and slowing the gastric emptying rate (Sandoval & D'Alessio, 2015). Furthermore, there is some inconsistent evidence that GLP-1 increases peripheral glucose uptake independent of its incretin effect on insulin (Ayala et al., 2008). Separately, GLP-1 is suggested to play a role in the regulation of hunger and satiety in a manner that is synergistic to, and to some extent interdependent with, that of leptin In humans, there is

a relationship with obesity and reduced basal and postprandial GLP-1 production, and fat loss partially reverses the satiating and anorectic effect on the brain (Verdich et al., 2001).

More specific experimental data suggest a possible role of GLP-1 to improve insulin sensitivity that is independent of its incretin effect. For example, under physiological conditions, GLP-1 stimulates glucose disposal in rat skeletal muscle (Villanueva-Peñacarrillo et al., 1994) while in humans endogenous GLP-1 production, stimulated by prior fat ingestion, improved glucose clearance during an intravenous glucose tolerance test (D'Alessio et al., 1995). In both studies, this effect occurred separately to the incretin effect. To separate the effects of GLP-1 as a direct mediator of glucose uptake versus as an incretin, Sandhu et al. (1999) investigated the response of insulin with or without GLP-1 during a hyperinsulinaemic-euglycaemic clamp in pancreatectomised dogs, and observed greater glucose clearance with the addition of GLP-1, suggesting a synergistic anabolic effect beyond that of insulin. Thus, in conjunction with fasting glucose and insulin measurements, GLP-1 may help to explain the metabolic responses to treatment interventions.

Effect of Exercise Modalities

GLP-1 has been used as an outcome variable across a number of exercise intervention studies, although the training-induced effects are unclear, owing to a small number of studies and inconsistent findings. For example, Morishima et al. (2014) reported increased GLP-1 after 4 weeks of moderate-intensity cycling in sedentary adults, and this effect was not augmented by hypoxic training conditions. Importantly, these individuals also decreased glucose, insulin, and leptin, without changes in body composition. Conversely, a similar protocol lasting 10 days in healthy men had no effect on fasting

GLP-1, nor on other hunger-related hormones, despite the participants cycling for 2 hours per day (Debevec et al., 2014). In the longer term, training intensity may prove to be a more important factor; over 12 weeks of thrice-weekly jogging at 60% HRmax, a cohort of healthy women showed no change in GLP-1, alongside decreased insulin and body fat percentage, but without alterations in fasting glucose (Ueda et al., 2013). Separately, HIIT was more effective to increase GLP-1 and reduce glucose, insulin, and HOMA-IR compared to continuous endurance training among diabetic adolescents when matched for within-session energy expenditure (Lee et al., 2015). Moreover, among adults with T2DM who trained for 4 months, aerobic interval training decreased basal insulin compared to moderate-intensity walking, despite no changes in GLP-1, glucose or glucagon (Karstoft et al., 2014). Thus, the evidence is largely equivocal with regards to single-mode strategies such as these.

Moreover, the present investigation is more concerned with non-diseased populations, and in these groups it is particularly important to consider GLP-1 alongside glucose homeostasis data to better understand the physiological responses to training. Indeed, in non-diabetic adults, 12 weeks of vigorous running training caused no change in GLP-1 levels; however, insulin sensitivity and body fat percentages improved significantly, and thus it may be deemed that for a given concentration of GLP-1, the glucose regulatory system was functioning more effectively (Martins et al., 2010). Considering this potential training effect, Mensberg et al. (2017) reported that 16 weeks of CET decreased whole-body and android fat mass, but the addition of a GLP-1 receptor agonist drug was needed to decrease HbA1c, glucose and HOMA-IR, and neither group changed GLP-1. In contrast, an extremely rigorous study by Bergouignan et al. (2010) demonstrated that women who underwent complete supine rest for 60 days increased GLP-1, provided they

performed structured CET throughout, while women who rested but didn't exercise showed no change. Interestingly, CET helped to offset the decrements in lean mass experienced by the rest-only group, although neither group changed leptin or ghrelin levels. Given that GLP-1 is a relatively under-studied biomarker in this context, the possible effects of CET are equivocal. Accordingly, a more thorough investigation of CET and the role of specific training variables is warranted; particularly, studies are needed that explore the prescription of CET in a real-world setting, and the appropriateness of existing recommendations. Given endurance-related adaptations seem to contribute to improved glucose homeostasis (Bartels et al., 2007), incorporation of TUT alongside AT may allow enhanced endurance capacity and muscle hypertrophy, in turn providing a decrease in T2DM risk profiles (Artero et al., 2012; Atashak et al., 2016; Young & Bilby, 1993).

Cardiovascular Disease Biomarkers and the Effect of Exercise

Under conditions of chronic inflammation, dysfunction in the vascular endothelium (Niu & Kolattukudy, 2009) and defective platelet responses (Pasceri et al., 2000) predispose the development of atherosclerosis (Davignon & Ganz, 2004). Accordingly, immunological mediators of these disease processes are targets for early intervention (Libby & Ridker, 1999), and modification of exercise behaviours is a primary strategy to reduce the overall CVD risk. Given that excessive adiposity and sedentary behaviour are among the greatest contributors (Van Gaal et al., 2006), exercise training may be important to decrease inflammatory and CVD risk (Durstine et al., 2013). Thus, the following sections will examine the evidence for the use of exercise to ameliorate biomarkers related to atherosclerotic risk. Particular attention is given to the role of exercise modalities, and the practical considerations for prescribing training.

Intercellular Adhesion Molecule 1

Function & Relevance

Expressed on the surfaces of leukocytes and endothelial cells, intercellular adhesion molecule 1 (ICAM-1) is a member of the immunoglobulin family and is directly involved in the progression of atherosclerotic lesions (Lawson & Wolf, 2009). A key step of the immune-mediated development of atherosclerosis is the localised recruitment and aggregation of leukocytes. Initially, under conditions of inflammation, trans-endothelial migration of leukocytes is largely driven by VCAM-1, while the subsequent adhesion to the cell surface is controlled by ICAM-1 (Nakashima et al., 1998).

As a prognostic biomarker, ICAM-1 has shown some promise in the context of obesity and the associated cardiometabolic abnormalities. For example, Pontiroli et al. (2004) reported a positive association between obesity and basal ICAM-1, and that among obese subjects those with T2DM showed higher ICAM-1. Other studies have shown that ICAM-1 is associated with an increased risk of future cardiac events (Willerson & Ridker, 2004) and is elevated in the plasma of individuals with existing CVD (Lawson & Wolf, 2009). Notably, Luc et al. (2003) observed a strong and independent relationship between ICAM-1 and coronary events within 5 years among a cohort of 9758 healthy men, adding that although ICAM-1 and CRP can independently predict CVD, concurrent measurement of the two may provide a more clinically useful risk assessment. Furthermore, clear evidence exists for a relationship between elevated fasting ICAM-1 and the presence of T2DM (Meigs et al., 2004), with the latter persisting after adjustment for established risk factors such as CRP and HbA1c.

Effect of Exercise Modalities

Strategies to reduce adiposity and improve cardiorespiratory fitness have shown some effectiveness to decrease ICAM-1 levels both in systemic circulation and on the luminal surface of endothelial cells. For example, among adults with T2DM, reductions in plasma ICAM-1 have been observed following endurance-based exercise training in isolation (Zoppini et al., 2006) or in combination with diet-induced weight loss (Roberts et al., 2006a). In contrast, subjects with impaired glucose tolerance showed no changes in ICAM-1 after 10 weeks of aerobic training (Østergård et al., 2006). Aerobic training interventions have been effective to reduce vascular dysfunction via reduced ICAM-1 across several disease states including heart failure (Adamopoulos et al., 2001), lung cancer (Jones et al., 2009) and stable angina (Jalaly et al., 2015). Yet, these outcomes are not consistent across all clinical populations, as Ranković et al. (2009) reported no changes in plasma ICAM-1 following 6 weeks of AT in CVD patients, while Saxton et al. (2008) found no differences from pre-training values among intermittent claudication patients performing 24 weeks of high-intensity interval training (HIIT). Thus, evidence for the role of AT in diseased populations is somewhat equivocal, and hampered by differences in methodology as well as the type and load of the training dose provided.

By comparison, CET studies show that across a cohort of healthy, pre-diabetic and diabetic individuals, a 4-week program of CET elicited marked reductions in basal ICAM-1; however, this effect was only evident among the diabetic and pre-diabetic groups (Tönjes et al., 2007). Further, no change in ICAM-1 was shown after 8 weeks of CET in breast cancer survivors (3 sessions per week) (Gómez et al., 2011) or heart failure patients (5 sessions per week) (Niebauer et al., 2005), whereas a cohort of peripheral artery disease (PAD) patients training for 8 weeks showed substantial decreases in ICAM-

1 using a CET protocol (Saetre et al., 2011). These studies demonstrate a possible application for CET, although the participant cohorts are markedly different.

Clearly, differences in population demographics and research design make comparisons difficult between these studies; however, it is of note that Saetre et al. (2011) incorporated intermittent bouts of exercise (walking until onset of claudication pain), while Gómez et al. (2011) and Niebauer et al. (2005) utilised continuous AT protocols. Also, the relative duration of aerobic exercise was greater in the study by Saetre et al. (2011) compared to a greater emphasis on RT in the other studies, thus representing another potential point of difference that may contribute to divergent outcomes. Nevertheless, the role of exercise is justified as a strategy to reduce ICAM-1 in clinical populations, although the effects of different modalities remains unclear. For the purpose of the present study, more attention is paid to the preventative effects of training in healthy individuals, and the possible application of altered CET stimulus.

Single-mode training interventions have been investigated across several studies, and thus far the results are promising, although not entirely clear. Walking-based training has shown effectiveness to reduce ICAM-1 among older subjects in as little as 6 weeks (Puglisi et al., 2008). Conversely, overweight women showed no change in ICAM-1 after 1 year of resistance training (Olson et al., 2007). While it is inappropriate to directly compare these 2 studies, it is noteworthy that Olson et al. (2007) utilised a largely home-based training program with little monitoring, whereas Puglisi et al. (2008) prescribed daily training in a manner that ensured progressive overload and ongoing engagement with the exercise protocol. Evidently, these 2 studies do not provide clear direction for future research; however, a number of other data have explored the role of novel training

modalities for the purpose of improving cardiometabolic risk profiles. Namely, a HIIT-based exercise program comprising 6 sessions over 2 weeks reduced ICAM-1 among overweight men (Leggate et al., 2012). Separately, a 12-week program of small-sided games in the form of modified hockey was also effective to decrease ICAM-1, and in this instance older women represented the study population (Nyberg et al., 2014). In that instance, eccentric load-bearing of the trained muscle is suggested to be a contributing factor. Moreover, a greater metabolic stimulus provided by AT volume may be an important consideration for training design. Ultimately, there are insufficient data to identify an optimal intervention modality for ICAM-1; however, according to Thompson et al. (2009), training interventions must be sufficiently robust in terms of intensity and/or volume to be effective in this regard.

An intensive lifestyle-based approach involving live-in weight loss programs may hold promise for at-risk individuals. As evidence, two very similar programs comprising 2 weeks of constant monitoring, daily exercise and nutrition assistance elicited significant reductions in ICAM-1 in both postmenopausal women (Wegge et al., 2004) and overweight children (Roberts et al., 2007). Furthermore, Roberts et al. (2006b) adopted a similar approach over 3 weeks, and reported concomitant improvements in ICAM-1 in a population of obese men. Clearly, this intensive approach may be an effective short-term strategy to improve ICAM-1 levels; however, this is not a feasible option for many individuals, and in addition some concerns have been raised regarding aggressive weight loss protocols, specifically in relation to weight regain and long-term metabolic adaptations (Fothergill et al., 2016). Collectively, there does seem to be a role for exercise to reduce circulating ICAM-1 concentrations; however, limited data prevent the identification of an optimal approach. Moreover, combining multiple intervention

strategies appears to be beneficial in this context. Currently, there are no studies investigating CET as a possible exercise mode, although considering the predominantly positive results of exercise trials, as well as the potentially synergistic effects of CET, it is proposed that this modality will confer positive cardiometabolic adaptations via reduced ICAM-1. Specifically, CET has shown efficacy to improve other disease-relevant parameters such as inflammatory cytokines (Balducci et al., 2010), abdominal adiposity (Davis et al., 2011), and insulin resistance (Azarbayjani et al., 2014). However, a lack of data on alterations to CET stimuli means that little is known regarding specific training prescription. Thus investigation is required to determine the role of intensity, volume, and frequency in this response. Considering the predominantly positive results of exercise, as well as the potentially synergistic effects of CET, it is proposed that this modality will confer positive cardiometabolic adaptations via reduced ICAM-1. In particular, the improvements in body composition and fitness capacity seen with CET may suggest a role for TUT, whereby its use in conjunction with AT may allow significant endurance adaptations (Azarbayjani et al., 2014; Keeler et al., 2001), in turn driving a metabolic response to decrease CVD biomarkers such as ICAM-1 (Thompson et al., 2009)

Vascular Cell Adhesion Molecule 1

Function & Relevance

Vascular cell adhesion molecule 1 (VCAM-1) is an immunoglobulin-like molecule that is expressed on activated endothelial cells (Osborn et al., 1989). The VCAM-1 receptor is expressed prominently on circulating T-lymphocytes (Yusuf-Makagiansar et al., 2002), and thus VCAM-1 occupies a main role in the localisation of both B- and T-cells, guiding the tethering and eventual transmigration of these cells across the endothelium (Leuker et al., 2001). Also, VCAM-1 acts to promote localised monocyte adhesion (Huo et al.,

2000), a mechanism that is largely driven by inflammation NF-KB signalling pathway (Kim et al., 2001). Evidence suggests that VCAM-1 plays a role in the development of atherosclerosis, alongside a possible causative relationship with autoimmune and cancerous diseases. Additionally, an increased presence of VCAM-1 is noted in advanced coronary lesions (O'Brien et al., 1993).

VCAM-1 levels show a positive correlation with BMI (Berg & Scherer, 2005) and under conditions of inflammation, CRP sharply increases VCAM-1 in cultured endothelial cells (Pasceri et al., 2000). As such, there may be some interaction with lifestyle-induced metabolic abnormalities. For example, endothelial cells exposed to intermittent fluctuations in glucose concentrations demonstrate an increased expression of VCAM-1 compared to those encountering more stable concentrations (Quagliaro et al., 2005). Thus, there may be a mechanistic relevance in the state of insulin resistance and/or hyperglycaemia. As further evidence, hyperinsulinaemia acutely potentiates the increased production of VCAM-1 (Montagnani et al., 2002). Similarly, in apparently healthy individuals, resting levels of VCAM-1 correlate with the degree of insulin resistance (Chen et al., 1999) and represent a significant predictor of future T2DM diagnoses (Meigs et al., 2004). On the basis of current evidence, the circulating level of VCAM-1 is identified as a clinically relevant indicator of ongoing cellular dysfunction, as well as a dynamic marker of intervention effects (Schmidt et al., 1996). Accordingly, reducing VCAM-1 concentrations through short-term treatment strategies is suggested to improve the CVD risk profile, and hence this has been the subject of numerous experimental studies (Adamopoulos et al., 2001; Ranković et al., 2009).

Effect of Exercise Modalities

Commonly, improving aerobic capacity is a primary aim in rehabilitating individuals with cardiometabolic diseases. For example, in heart failure patients, a 12-week aerobic cycling program (150 minutes per week at 70-80% HR_{max}) caused a significant decrease in serum VCAM-1 levels (Adamopoulos et al., 2001). Similarly, as little as 6 weeks of moderate-intensity endurance-based training was effective to reduce VCAM-1 in CAD patients, and notably this occurred in conjunction with reduced CRP (Ranković et al., 2009).

Endurance exercise has been used to treat the complications associated with T2DM, including vascular dysfunction as measured by VCAM-1. However, to date there are only 3 experiments relating to insulin resistance/T2DM, and all show no effect of exercise training. Specifically, 10 weeks of moderate-intensity cycling (Østergård et al., 2006), home-based rowing training (Scheede-Bergdahl et al., 2009), and multimodal AT (Hatunic et al., 2007) proved ineffective in modifying VCAM-1 levels in this population. Although, to contextualise these data, the one existing study in healthy individuals (older men) showed pronounced improvements in plasma levels of VCAM-1 after an 8-week endurance program (Gliemann et al., 2013). However, it is noted that the investigators utilised a rather aggressive training protocol incorporating cycling, walking and group fitness classes in relatively high volumes (~4h per week) and thus the results are interpreted with caution for aged and long-term sedentary populations.

In contrast, respective studies with different training modes showed no differences in VCAM-1 following RT. Olson et al. (2007) reported no improvement in VCAM-1 after a RT program spanning 12 months where overweight women trained twice per week at a relatively high intensity (~8RM). Secondly, Cook et al. (2013) found no changes in

VCAM-1 after a short-term program (6 weeks) in young, untrained men, in this case utilising a 2-way body-part training split. It is not clear why these discrepancies exist, although it is speculated that the larger per-week training volume in the previously mentioned study (Moraes et al., 2014) may have potentiated greater adaptations via increased acute overload, or indeed that the divergent outcomes may be attributed to the use of diseased vs healthy subjects. Ultimately, more studies are needed to establish the role of RT in this context, and whether TUT training stimulus within CET can provide the necessary adaptations. Given TUT may enhance muscular endurance (Keeler et al., 2001), and offers a contrasting metabolic response to conventional RT (Burd et al., 2012), it may be used alongside AT to enhance the cardiovascular adaptation.

Separately, some more novel strategies have been used with varying degrees of success across several populations. For example, HIIT, despite having attracted scientific interest and popularity, has shown equivocal effects on VCAM-1 thus far. Kargarfard et al. (2016) administered an 8-week program of HIIT versus continuous aerobic training in obese (n=30) and non-obese subjects (n=30), finding that only the HIIT protocol was effective to reduce plasma VCAM-1 levels. Importantly, the protocol used comprised 3 weekly 1-hour sessions with participants performing 4-minute running intervals at intensities of up to 90% heart rate reserve (HRR), interspersed with 2-minute recovery periods at 40-50% HRR, representing considerably less overall volume than the continuous training condition which consisted of 5 weekly 1-hour sessions at 60-95% HRR. Based on these findings, it may be speculated that HIIT would provide a highly effective training stimulus despite a markedly reduced volume load; however, two other studies call this hypothesis into question. After 4 months of twice-weekly HIIT (3 repetitions of 5-10-minute intervals (mixed-mode) at ~90% HR_{max}, interspersed with low-intensity

calisthenics and flexibility exercises) there was no change in serum VCAM-1 in heart failure patients (Byrkjeland et al., 2011). Furthermore, in a 6-month HIIT program (4 x 4-minute efforts at 80-90% HR_{max} with active recovery) conducted in the period following percutaneous coronary intervention, VCAM-1 actually increased – although it is not clear why this occurred (Munk et al., 2011). Thus, optimising the VCAM-1 may not be related to the modality itself, but rather to the overall duration of training and subsequently, the training dose received.

To further the idea of novel modalities, Saxton et al. (2008) treated intermittent claudication with either upper-body or lower-body endurance training for 24 weeks. This entailed an intermittent/discontinuous protocol, although it was not classified as HIIT because repeated efforts were terminated at the onset of claudication pain. The finding was that although both modalities decreased VCAM-1 levels, the data did not meet the designated significance level, and as such were interpreted as modest improvements. Separately, middle-aged women participated in a 12-week program of social small-sided games twice per week, and demonstrated pronounced improvements in resting VCAM-1 (Nyberg et al., 2014). Collectively, the use of such novel exercise modes as these remains questionable, although a role for either higher-intensity training (e.g. sprint interval training) and/or load-bearing modalities (e.g. running) is plausible. How this applies to adjustment of CET remains unknown, however TUT may provide the endurance and body composition adaptations that contribute to a reduced CVD risk (Rana et al., 2008; Van Gaal et al., 2006).

Traditionally, many researchers have emphasised fat loss as a key driver of improved CVD risk as an important component of cardiovascular prevention and rehabilitation

(Bartels et al., 2007). A cohort of overweight men with T2DM showed a reduced cellular VCAM-1 expression following a 3-week residential program of daily walking and dietary energy restriction (Roberts et al., 2006a), although blood concentrations were not measured. Separately, in individuals with T2DM, a 6-month home-based cycling program (30 minutes per day) combined with a 1500kcal·d^{-1} dietary regimen had no effect on serum VCAM-1 levels (Sixt et al., 2009), and similarly insulin-resistant subjects endurance training 3 times per week for 6 months, combined with an approximate 500kcal·d^{-1} energy deficit, did not demonstrate improved VCAM-1 (Hamdy et al., 2003). In contrast, the same program conducted over 2 weeks did not change VCAM-1 in postmenopausal women (Wegge et al., 2004), and thus there may be a dose-dependent adaptation to this type of intervention. Other studies have been longer in duration, but less intensive in the treatment approach. For example, Russo et al. (2010) provided a hypocaloric diet (1200-1800 kcal·d^{-1}) alongside exercise counselling for 6 months in obese adults and reported a significant decrease in serum VCAM-1. Conversely, overweight women undertaking thrice-weekly aerobic exercise (50-85% HRR) either alone or in conjunction with 'healthy eating' classes did not alter basal levels of VCAM-1 (Ryan et al., 2014). Thus, the current data do not provide clear evidence for the effectiveness of diet- and/or exercise-based strategies to improve vascular function as indicated by VCAM-1.

To further explore this topic, other authors have utilised multiple exercise-based strategies concurrently with the aim of improving VCAM-1-mediated endothelial dysfunction; however, the data are few in number and inconclusive overall. Specifically, concomitant aerobic and endurance training in T2DM patients did not alter serum VCAM-1 levels within 6 months (Gibbs et al., 2012) and heart failure patients training twice per week

with concurrent resistance training and HIIT showed no improvement after 20 weeks (Bjørnstad et al., 2008). However, across a sample of individuals with normal glucose tolerance, impaired glucose tolerance or T2DM, a 4-week program of CET decreased VCAM-1 concentrations, although this effect was only evident for the latter 2 groups (Tönjes et al., 2007). Evidently, there is insufficient homogeneity to appropriately compare these CET studies; however due to the strong, direct effect of inflammatory mediators such as CRP on VCAM-1 production *in vivo*, future studies may reveal a clearer training effect. At present, the exact role of different training variables in mediating the VCAM-1 response is not clear, although in many cases improvements are observed with load-bearing modalities provided they are performed at a sufficient intensity and volume to cause significant cardiovascular adaptations. That said, untrained individuals may experience issues with conventional training prescriptions such this, and modification of load and volume may be necessary (Van Kan et al., 2009). In turn there may be a role for adjusting the RT component of CET to maximise cardiovascular responses, without detriment to hypertrophic adaptations. Thus, although CET may confer these clinical benefits, increasing the endurance stimulus through low-load TUT may be applicable to accompany AT in a split-mode design.

Von Willebrand Factor

Function & Relevance

The large, multimeric glycoprotein von Willebrand Factor (vWF) occupies a key role in haemostasis and drives platelet aggregation during clotting responses (Sadler, 1998). It is synthesised primarily in endothelial cells and megakaryocytes, and acts as a key haemostatic agent by regulating the binding of platelets and clotting factors to subendothelial tissue (Bernardo et al., 2004). Under basal conditions, endothelium-

derived vWF is detectable in venous blood; conversely, under conditions of increased blood flow such as bleeding, activated platelets secrete vWF to optimise the haemostatic response (Ruggeri, 2003). A key stimulus for vWF release is the multidirectional shear stresses produced between adjacent fluid planes in the arterial lumen, leading to endothelial disruption and thrombus formation, particularly in the context of atheroma rupture (Ruggeri, 2003). Thus, vWF has emerged as a marker of endothelial dysfunction, and also a key mediator of the associated thrombogenesis. Importantly, platelet adhesion does not differentiate traumatic versus pathological vessel damage and thus, despite being a necessary healing mechanism, may contribute to disease progression (Ruggeri, 2003).

In the context of CVD, vWF is a sensitive indicator of the prothrombotic state within the systemic vasculature. Elevated basal concentrations are associated with established CVD risk factors such as obesity (Berg & Scherer, 2005) and cigarette smoking (Blann et al., 1997), and show a predictive capacity for future cardiovascular events such as recurrent myocardial infarctions (Jansson et al., 1991) and diabetic vasculopathy (Stehouwer et al., 1992). In accordance with the established relationship between chronic inflammation and CVD, a number of inflammatory cytokines including TNFα and IL-6 have shown a direct stimulatory effect on vWF (Vischer, 2006). Ultimately, plasma concentrations of vWF represent not only a marker of existing CVD risk, but also a key driver of thrombogenesis and the occurrence of critical CVD events (Spiel et al., 2008). Accordingly, aside from specific pharmacological interventions, it is suggested that targeting the modifiable risk factors for CVD (e.g. obesity, dyslipidaemia, inactivity) in treatment strategies may help to reduce vWF (Lip & Blann, 1997). Plasma vWF concentration is inversely correlated with physical activity levels in older men (Wannamethee et al., 2002), and separately Conlan et al. (1993) demonstrated a negative association of vWF with waist-to-hip ratio,

plasma triglycerides, and leisure time exercise behaviours. Considering this association, research has explored the effects of prescribed exercise training on resting vWF levels, with the aim of improving CVD risk.

Effect of Exercise Modalities

Several authors have examined endurance training as a therapeutic strategy, and in healthy individuals the results are equivocal. A 6-month training intervention showed limited effectiveness, with Stratton et al. (1991) reporting no significant change in plasma vWF in either older or younger men, while Hamdy et al. (2003) found no adaptation to endurance training in obese adults in the same timeframe. In these studies, however, an insufficient training intensity and/or volume may explain the null findings. Other studies support this finding, with Wang et al. (2005) observing marked reductions in plasma vWF with an 8-week training program performed 5 times per week versus 3 x 30-minute sessions in the aforementioned program (Hamdy et al., 2003). However, this was questioned later when Jahangard et al. (2009) found a significant decrease in vWF after only 10 sessions of moderate-intensity cycling in postmenopausal women. Evidently, in healthy populations there is no clear trend for a specific endurance-training effect, although some inferences can be drawn from clinical trials in diseased individuals.

Considering the role of training intensity as a possible mediator of the long-term response, a number of authors have investigated the adaptations to high-intensity continuous or intermittent training protocols, although more data may be required to fully understand the role of intensity and/or volume in this context. For example, 2 studies have explored endurance training programs of either a high or low intensity, and in both cases, there was no significant change with training. Specifically, in older women, training 3 times per

week for 10 weeks did not confer any change in vWF, irrespective of whether subjects exercised at 33% or 66% HRR (Cornelissen et al., 2011). Separately, Gram et al. (2015) reported no positive adaptations in plasma vWF after a highly demanding program of daily exercise for 3 months in overweight young men. These individuals trained to elicit an energy deficit of either 300 or 600 $kcal \cdot d^{-1}$; however, it is problematic to interpret the vWF data as the authors declare that post-intervention blood collection may have been performed too soon after the final training session, and thus the acute exercise-induced spike in vWF may have carried over to the following day.

Another line of evidence relates to high-intensity interval training (HIIT). Three studies have thus far utilised this modality to explore the effects on vWF, although the populations involved are highly heterogeneous. In subjects with stable angina, Munk et al. (2011) administered 6 months of HIIT (4-minute work intervals at 80-90% HR_{max}), and reported a significant decrease in plasma vWF compared to a sedentary control group. A similar protocol reduced vWF among a cohort of metabolic syndrome patients, in this case training for 16 weeks using 4-minute intervals at 90-95% HR_{max} (Bye et al., 2009). Interestingly, these HIIT programs both incorporated active recovery periods of 3 minutes at an intensity of 60-70% HRmax. By comparison, Nawaz et al. (2001) observed no changes in vWF after HIIT in patients showing intermittent claudication. In this study, only 12 sessions were performed over 6 weeks, and the training method comprised 2-minute work intervals interspersed with 2-minute passive rest intervals. The combination of passive recovery and a short program duration may have contributed to this outcome and provide some indication that training volume is an important consideration. Nonetheless, these methodological differences and the inclusion of vastly different subject populations necessitate further investigation to fully understand the role of HIIT.

The combination of multiple treatment strategies in synchrony has emerged as a promising strategy whereby different interventions can provide a more potent effect when used concurrently, compared to single strategies. Combined diet and exercise (i.e. weight loss) programs have shown some effectiveness to decrease vWF in obese individuals (Gallistl et al., 2001b). However it has been suggested that diet alone can be effective in this population (Fayh et al., 2013). With regards to the use of multiple exercise strategies (e.g. AT and RT), only 2 studies currently exist, both conducted in a cardiac rehabilitation setting. Vona et al. (2009) report reduced vWF after 4 weeks' CET following myocardial infarction, similar to single-mode interventions despite a 50% dose of each protocol. Conversely, Sabelis et al. (2004) found no improvement in plasma vWF after a 26-week CET program, although a lack of detail in reporting the exercise protocol impacts the interpretation of these results, and questions remain regarding the monitoring of training during home-based sessions. Again, it is unclear if combining interventions provides improved outcomes, and if so, what format is optimal.

Current evidence suggests that any intervention must be sufficient in volume and/or intensity, but the manner in which this training stimulus is delivered seems to be less important. As further evidence, Shimizu et al. (2016) compared resistance training interventions at 20% 1RM either with or without concomitant blood flow restriction (BFR). Interestingly, only BFR training elicited a reduction in serum vWF over 4 weeks. Given the short program duration and low session volume (15 minutes, 3 times per week), it is feasible that the BFR protocol utilised what was otherwise a suboptimal modality and modified it in a way that delivered an extra stimulus in the form of BFR, thus conferring a fatiguing mechanism that would not otherwise be present. Indeed, this seems to reflect

the permissive mechanism provided by TUT, whereby low-load RT can drive full motor unit activation (Burd et al., 2012). Therefore, in light of the existing evidence, and considering the gaps in the literature, the present study will provide valuable data to elucidate the effects of CET on resting vWF and build on existing research in the area of modified training strategies within the CET context.

P-Selectin

Function & Relevance

Occupying a key role in early inflammatory responses, platelet selectin (p-selectin) is synthesised in activated endothelial cells and platelets, and initiates the 'rolling' motion of leukocytes towards injury sites (Kaplanski et al., 2003). Under conditions of acute inflammation, pro-inflammatory cytokines drive leukocyte migration to sites of injury (Pasceri et al., 2000) and subsequently p-selectin binds loosely to cell-surface ligands, creating the characteristic rolling (McEver et al., 1995). This transient contact slows leukocyte movement, allowing exposure to locally-expressed chemokines and, eventually, integrin-driven adhesion (McEver et al., 1995). Moreover, p-selectin drives the localised clustering of platelets, and the level of endothelial p-selectin expression correlates strongly with platelet aggregate size (Merten & Thiagarajan, 2000). Ultimately, p-selectin acts in conjunction with ICAM-1 to mediate leukocyte migration and accumulation, and represents a key repair mechanism that, when dysregulated, is a major contributor to atherosclerotic diseases (Johnson-Tidey et al., 1994). Further, the majority of soluble p-selectin detected in the blood is that which has been cleaved from platelets, and an elevation in the circulating concentration denotes a procoagulant state (André et al., 2000). It is co-localised with vWF in the Weibel-Palade bodies, and thus its release is typically concomitant with that of vWF (Kappelmayer et al., 2004).

Thus, soluble p-selectin in plasma represents a useful *in vivo* marker of platelet behaviour and the degree of atherosclerosis progression (Ferroni et al., 2009). This measure is associated with increased BMI (Berg & Scherer, 2005) and an elevated risk of future cardiac events (Ridker et al., 2001) and hence it has emerged as a key therapeutic target in the context of disease development and monitoring (Burger & Wagner, 2003). Moreover, a positive relationship is noted between p-selectin levels and both visceral and subcutaneous fat mass (Pou et al., 2007b). Given that fewer than half of MI patients present with dyslipidaemia before the event, p-selectin is part of a group of blood markers that can identify at-risk individuals and predict CVD without traditional risk indicators (Blake & Ridker, 2001). As further evidence, current data indicate that p-selectin correlates positively with total cholesterol (Gallistl et al., 2000). Also, among a cohort of apparently healthy women, those in the highest quartile of soluble p-selectin concentrations were more than twice as likely than those in the lowest quartile to experience a cardiovascular event within 4 years (Ridker et al., 2001). Accordingly, by inducing reductions in platelet and endothelial expression of p-selectin, it is suggested that the circulating levels of this molecule will decrease and the prothrombotic effect will be attenuated. Aside from direct pharmacological inhibition, mass reduction through dietary modification has emerged alongside exercise training as the eminent intervention treatment strategy for p-selectin. Given the association between obesity and pathogenic platelet behaviour (Russo et al., 2010), a number of studies have focussed upon the role of specific fat loss interventions on p-selectin activity in overweight or obese populations.

Effect of Exercise Modalities

Aerobic endurance training is frequently used to improve biomarkers relating to cardiovascular risk, and thus far the evidence is promising in healthy individuals. For example, among sedentary males, 8 weeks of aerobic cycling (150 minutes per week) caused a significant decrease in plasma p-selectin compared to a sedentary control (Wang et al., 2005). Similarly, among a mixed cohort of men and women, twice-weekly cycling training (55 minutes per session) at 60-75% VO_{2max} also reduced resting p-selectin levels (Santilli et al., 2013). Conversely, studies conducted using aerobic exercise in clinical/diseased populations have been somewhat equivocal. Among subjects with T2DM, 12 weeks of moderate-intensity, multimodal endurance training did not alter plasma p-selectin (Hatunic et al., 2007) although a similar regimen did elicit a reduction over 6 months (Zoppini et al., 2006). Accordingly, some consideration may be made for the overall training volume; Keating et al. (2013) investigated this question by administering 2 contrasting 5-month walking-based programs, either with a high (5-7 hours per week) or low volume (1-2 hours per week) and reported that both conditions decreased p-selectin expression. Importantly, these authors did not report circulating p-selectin levels, and the subject demographic consisted of CAD patients. The only other study conducted in a clinical population is that of Schlager et al. (2012), who recruited PAD patients with intermittent claudication to receive normal treatment either with or without an intermittent walking program for 6 months. These authors reported no change in serum p-selectin in either group, again raising the question of overall volume considering that these participants exercised twice per week in an intermittent fashion.

Previous studies have suggested novel modalities may be effective, such as Munk et al. (2011) who conducted a HIIT program in the 6 months following PCI surgery, comprising 3 weekly sessions of 4-minute work intervals (~90% HR_{max}) interspersed with 3-minute

active recovery periods (~70% HR_{max}). Following training, the authors reported that exercising subjects did not change plasma p-selectin levels. Based on this evidence, it is reasonable to speculate that the overall training volume is an important consideration for those seeking to reduce p-selectin. Similarly, several other research studies have featured the use of multiple treatment strategies with the aim of achieving a synergistic effect, whereby the combination of different approaches confers an additive stimulus compared to single-treatment options. For example, combining multiple exercise modes (e.g. CET) or the concomitant prescription of exercise and nutrition appears to be a promising strategy. At present, there has been only one investigation into the effect of CET - Bjørnstad et al. (2008) observed a pronounced reduction in plasma p-selectin after 20 weeks of CET in heart failure patients. This training regimen consisted of 2 weekly sessions of resistance training and non-continuous endurance training (perceived exertion ~15/20) alongside 1 additional aerobic session performed at home.

Unfortunately, the relevant studies do not necessarily reflect feasible scenarios for large-scale studies in healthy individuals. Specifically, intensive live-in programs have been effective to reduce p-selectin levels in the obese over 3-week periods, either by specific energy restriction combined with daily exercise (Gallistl et al., 2001b) or targeted exercise training combined with *ad libitum* eating (Roberts et al., 2006b). Similarly, Ziccardi et al. (2002) found significant reductions in serum p-selectin concentrations in obese women receiving a hypocaloric diet program (~1300kcal·d^{-1}) in conjunction with exercise counselling. Importantly, the latter study also showed a strong relationship between improvements in p-selectin and concomitant improvements in IL-6 and TNFα. Therefore, alongside inflammatory biomarkers and adhesion molecules, p-selectin is a useful indicator of platelet behaviour and is likely to improve with CET. That said, for sedentary

populations, incorporation of TUT within CET may enhance the cardiovascular response, given its efficacy as endurance-like stimulus to improve body composition (Burd et al., 2012; Young & Bilby, 1993).

Serum Amyloid A

Function & Relevance

Serum Amyloid A (SAA) is the generic name for a family of apolipoproteins that are coded by different genes but highly homologous (Artl et al., 2000). Predominantly produced by the liver, SAA has the properties of a classic acute phase reactant in that it increases up to 1,000-fold in the period following a pro-inflammatory stimulus (Artl et al., 2000). SAA is identified as a mediator of the acute response to injury or infection (Yang et al., 2006) whereby it provides a tissue repair mechanism possibly via cytokine chemotaxis, release of degradative enzymes and/or altered lipid metabolism (Uhlar & Whitehead, 1999). Although the protective role of SAA is undoubtedly important for infection defence, under conditions of chronic inflammation the level of hepatic SAA catabolism is markedly reduced, and circulating SAA contributes to disease progression directly (Berg & Scherer, 2005). Specifically, SAA disrupts cholesterol homeostasis and drives lipid uptake in macrophages (Khovidhunkit et al., 2000). It binds to HDL, altering its protective functions, ultimately contributing to systemic oxidative stress and the inappropriate deposition of lipids at atherogenic sites (Artl et al., 2000; Berg & Scherer, 2005).

Accordingly, SAA is identified as a clinical biomarker of disease risk, and of the severity of existing conditions (Berg & Scherer, 2005). Yang et al. (2006) suggest that SAA occupies the role of an inflammatory cytokine, and further, among a cohort of 686

women, circulating SAA concentrations were strong predictors of future critical events (Johnson et al., 2004) and this result has been replicated in middle-aged men (Danesh et al., 2000). Similar to other pro-inflammatory mediators, SAA demonstrates an inverse relationship with exercise behaviours. Namely, individuals classified as having 'high' activity levels (upper tertile) exhibit SAA levels 22% lower compared to individuals classified as having 'low' activity levels (lowest tertile) (Panagiotakos et al., 2005). Moreover, SAA concentrations are elevated in obesity (Berg & Scherer, 2005) and thus SAA may be a clinically relevant therapeutic target. Indeed, a number of authors have investigated the effects of long-term intervention strategies, such as physical exercise and dietary energy restriction, on plasma SAA and the associated cardiovascular abnormalities.

Previous investigations have identified obesity treatment as a key focal point, and as such many studies explore changes in SAA within this context, whereby improvements in body composition can be effective to reduce resting SAA levels. For example, Campbell et al. (2009) reported a non-significant reduction in serum SAA after a 1-year intervention comprising moderate-intensity, multimodal aerobic exercise in obese, postmenopausal women.

Effect of Exercise Modalities

Currently, there are 3 studies measuring changes SAA following an exercise-based intervention period. A home-based aerobic exercise plus banded resistance exercise did not affect serum SAA levels after 8 months in patients with stable angina, despite a relatively high training load for this population (Astengo et al., 2010). Unfortunately, within that study the training protocol is poorly reported, confounding its interpretation.

In contrast, two studies show a positive effect with more aggressive exercise strategies; Tisi et al. (1997) administered a 6-month program of daily walking in intermittent claudication patients, and found a significant decrease in serum SAA. Moreover, among subjects deemed 'at risk' for CVD, a rigorous residential program of daily exercise and diet guidance provided a significant reduction in serum SAA (Wegge et al., 2004). Thus, various exercise strategies may hold promise, although more investigation is needed to establish a mode-specific effect.

Another line of evidence relates to the role of exercise, nutrition, or a combination of the two as a preventative strategy in apparently healthy individuals. Given that this field of investigation is relatively new, there are few studies on the topic. Namely, Okita et al. (2004) observed a sharp reduction in serum SAA following 2 months of moderate-intensity endurance training in healthy women. Notably, this intervention was performed for over 2 h, 3 times per week and comprised both load-bearing (walking, dancing) and non-load-bearing (cycling) exercise. In contrast, sedentary females training 5 times per week for 16 weeks (moderate-intensity, load-bearing exercise) showed no improvement in plasma concentrations of SAA (Arikawa et al., 2011). The only other existing study in healthy subjects was conducted by Ogawa et al. (2010), and showed a marked decrease in plasma SAA after a somewhat less aggressive program comprising resistance training of only 4-6 working sets per week. Collectively, the effect of exercise and/or fat loss strategies on resting SAA is unclear; however, the preponderance of the evidence suggests a possible positive effect, particularly with more aggressive strategies. Clearly, more evidence is needed to elucidate the role of resistance training, as some level of promise is shown. Moreover, given the cardiovascular benefits typically associated with endurance training (Braith & Stewart, 2006), using RT and AT simultaneously may allow untrained

individuals to receive a broader range of adaptations (Donges et al., 2013). Moreover, TUT may provide an efficacious strategy within CET to enhance the endurance response (Keeler et al., 2001), and particularly for CVD biomarkers whereby the aerobic component seems to confer the greatest overall benefit. For the sedentary populations who are in need of such adaptations, more investigation is warranted regarding tailored training prescription, and the role for altered modalities such as TUT in the context of CET.

State of the Literature

Low physical activity levels and increased adiposity are associated with an elevated risk of cardiometabolic diseases including CVD and T2DM (Van Gaal et al., 2006). This poor lifestyle-induced health status is further characterised by an underlying state of chronic systemic inflammation (Pedersen et al., 2003; Van Gaal et al., 2006). Elevated biomarkers such as CRP, IL-6, and TNFα contribute directly to the development of cardiometabolic conditions such as T2DM and CVD (Berg & Scherer, 2005; Hotamisligil, 2006). As such, blood-based biomarkers such as these are identified as targets for therapeutic intervention (Gustafson, 2010). In particular, exercise training is suggested to provide a decreased disease risk by modifying these parameters (Gleeson et al., 2011).

Training modalities such as AT and RT are staples of exercise prescription and are recommended to decrease the disease risk (Garber et al., 2011). Specifically, AT demonstrates efficacy to increase endurance capacity via improved circulatory function, substrate utilisation, and muscular endurance (Hackney, 2019; Hawley, 2002). These adaptations are suggested to ameliorate the inflammatory profile (Petersen & Pedersen, 2005), and in turn reduce the risk of cardiometabolic diseases (Egan & Zierath, 2013). By

comparison, RT demonstrates efficacy to enhance skeletal muscle mass and strength (Braith & Stewart, 2006) and enhance functional performs in activities of daily living (Van Kan et al., 2009). RT is also associated with improved glycaemic control and decreased CVD parameters such as blood pressure and lipid profiles (Braith & Stewart, 2006).

Combining RT and AT modes through CET may confer the greatest benefit in untrained populations (Donges et al., 2013). CET may incorporate numerous exercise prescription techniques, and is commonly prescribed in a dual-mode format whereby AT and RT are performed sequentially within a given exercise session (Coffey & Hawley, 2017). In untrained individuals, this form of CET may confer a broader range of health-specific benefits (Perez-Schindler et al., 2015). For example, CET is shown to improve biomarkers related to inflammation such as IL-6 and CRP (Balducci et al., 2010). Moreover, evidence shows a benefit for sedentary populations to improve insulin resistance and subsequent glucose homeostasis (Azarbayjani et al., 2014). Also, biomarkers related to atherosclerotic risk may be improved by this type of training, including adhesion molecules and markers of platelet activity such as vWF (Tönjes et al., 2007; Vona et al., 2009).

However, some practical aspects relating to the prescription of CET may require modification for untrained individuals (Burton et al., 2017b), and hence investigation into tailored training strategies is warranted. Specifically, by altering the RT component of CET to incorporate TUT, sedentary individuals may receive significant benefits for body composition and fitness capacity (Young & Bilby, 1993), although currently there are no data to establish a role for this approach to decrease disease-specific biomarkers. Given

that an augmented disease risk is characterised by excessive adiposity and physical inactivity (Bartels et al., 2007), this strategy is proposed to decrease disease biomarkers related to systemic inflammation, T2DM, and CVD. In addition, older adults seeking to participate in some form of CET may benefit from a tailored design that is modified to suit their needs.

Moreover, elements of the training design such as intensity and volume require investigation as potential contributors to the training response of CET. Indeed, increased overall training volume is suggested to provide superior adaptations for body composition (Schoenfeld et al., 2017) and fitness capacity (Slentz et al., 2011), with some evidence suggesting longer or more intense training programs may enhance inflammatory and glucose homeostasis responses (Duarte et al., 2015). Although, in sedentary populations increased training volume is not necessarily appropriate (Van Kan et al., 2009), and my not even provide the desired adaptations (Van Gemert et al., 2015). Thus, examination of the load-response relationship is required, to elucidate which aspects of CET contribute to the proposed improvements in cardiometabolic risk.

Chapter 3

Study 1

As based on the manuscript:

"Changing the time under tension: different concurrent training strategies to improve fitness, body composition, and cardiovascular disease markers"

N.G. Allen, A.E. Mendham, J.T. Kalkhoven, C.F. Wilke, S.M. Higham, D. Lu, G.C. Smith & R. Duffield.

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Abstract

Purpose: To examine the effects of concurrent training (CET) with the resistance component modified as time-under-tension (TUT) on body composition, fitness, and inflammatory and cardiovascular disease (CVD) biomarkers. **Methods**: Thirty-eight adults performed either 10 weeks' CET (n=13) TUT (n=12) or control (CRL; n=13). Pre- and post-intervention testing included dual-energy x-ray absorptiometry to measure total-body lean mass (TBLM), fat mass (TBFM), abdominal subcutaneous (SAT) and visceral fat (VAT), alongside muscle ultrasound of *m. vastus lateralis* thickness. Collected plasma was analysed for C-reactive protein (CRP), von Willebrand factor (vWF), serum amyloid A (SAA), intercellular and vascular adhesion molecules (ICAM-1; VCAM-1), monocyte chemoattractant protein (MCP)-1, and p-selectin. Peak oxygen consumption (VO_{2peak}) and power output (PPO) from a maximal cycle test and maximal quadriceps force were also measured. **Results**: TBLM increased and TBFM decreased ($p<0.05$) within CET only, while body fat percentage decreased in CET and TUT ($p<0.05$). Moreover, regional measures showed only CET decreased VAT ($p=0.049$) and TUT decreased SAT ($p=0.030$). Ultrasound muscle thickness showed greater *m. vastus lateralis* hypertrophy in CET ($p=0.001$). CET provided superior strength gains ($p=0.001$), while TUT improved VO_{2peak} ($p<0.001$) and both groups increased PPO ($p<0.005$). For inflammatory markers, CRP was unchanged and MCP-1 showed an increase in CRL ($p=0.015$), with no changes in either exercise group ($p>0.05$). Neither exercise mode significantly affected any CVD markers, although p-selectin was reduced in CET ($p=0.009$). **Conclusions**: Conventional CET provided positive body composition and fitness outcomes, irrespective of changes in CVD-related biomarkers. A mode-specific response indicates higher loads via CET increased isometric strength, whilst a longer time exposure (TUT) increased aerobic capacity.

Introduction

Chronic systemic inflammation represents a key risk factor for cardiovascular disease (CVD) and associated comorbidities (Durstine et al., 2013). Specifically, pro-inflammatory mediators such as c-reactive protein (CRP) and monocyte chemoattractant protein (MCP)-1 are associated with vascular dysfunction and contribute directly to the development of CVD (Niu & Kolattukudy, 2009; Ridker et al., 2003). Consequently, inflammatory markers are key outcomes representing potential intervention targets for disease prevention (Libby & Ridker, 1999). Further, these markers show a prospective and causative relationship with cell-specific indicators of atherogenesis, including serum amyloid A (SAA), p-selectin, von Willebrand Factor (vWF) and intercellular and vascular adhesion molecules (ICAM-1; VCAM-1) (Pasceri et al., 2000). Accordingly, there is a need for strategies to reduce CVD-related risk by targeting modifiable risk factors. In particular, excessive adiposity and sedentary behaviour are among the most important contributors (Van Gaal et al., 2006), and lifestyle intervention via exercise training are important to reduce inflammation and CVD risk (Durstine et al., 2013).

Respectively, resistance (RT) and aerobic training (AT) are important strategies to reduce the risk of CVD, predominantly via normalising vascular function, platelet activity, and systemic inflammation (Braith & Stewart, 2006; Gleeson et al., 2011; Hurley et al., 2011). Combining these respective modes through concurrent training (CET) is a time-efficient method to improve several CVD-related parameters. Particularly, CET can reduce fat mass and increase skeletal muscle mass, predicating a reduction in systemic inflammatory markers (Gleeson et al., 2011) and the overall risk of CVD (Braith & Stewart, 2006). However, for some individuals, a full CET program may be impractical and/or unappealing due to the large training loads and time required (Fyfe et al., 2014).

Consequently, undertaking RT and AT in a split-mode approach (50% of each modality) may be more time-effective and physiologically appropriate (Donges et al., 2013). Compared to single-mode training, this approach has shown to confer similar improvements in inflammatory markers (CRP, interleukin-6), glucose tolerance, and fat mass (Donges et al., 2013; Nicklas et al., 2008). In particular, the possibly dual benefit from split-dose CET may appeal to individuals who are time-poor or unable to tolerate increased single-mode training (Coffey & Hawley, 2017). Whilst split-mode training may be pragmatic to decrease inflammation and CVD-related biomarkers, uncertainty still exists as to the appropriateness of stimuli within this training design. Given the typical physiological adaptations to CET result from the concomitant delivery of stress-induced cellular signals (Fyfe et al., 2014), altering the type of RT alongside the endurance stimulus may provide improvements in muscular strength and/or hypertrophy, concomitant to improved endurance capacity (Coffey & Hawley, 2017).

When manipulating the RT stimulus, the load-mediated signals that produce these muscle and/or fitness changes may require muscle contractions being performed to the point of fatigue (Mitchell et al., 2012). Therefore, various RT strategies may involve either high or low mechanical loads taken to muscular failure that produce these improvements (Marcotte et al., 2015). A reduced-load modality known as time under tension training (TUT) involves RT at volitionally slow movement speeds, designed to prolong working sets and apply a greater temporal stimulus (Burd et al., 2012). Implementing TUT within working sets may fatigue the contractile apparatus sufficiently to permit recruitment of more muscle fibres and confer the benefits of conventional training with a reduced external resistance load (Burd et al., 2012; Marcotte et al., 2015). As evidence, TUT has demonstrated efficacy across several studies (albeit in younger, healthy individuals)

whereby low mechanical loads (30-50% 1RM) are equally effective to stimulate hypertrophy compared to higher mechanical loads (>70% 1RM) when lifted slowly (Rana et al., 2008; Tanimoto et al., 2008; Young & Bilby, 1993). Importantly, slow-speed RT may be more effective for hypertrophy than work-matched fast-speed RT, suggesting that TUT can drive acute metabolic disruptions and long-term adaptations that would be diminished or absent with low-volume training (Watanabe et al., 2014). Whilst such perspectives may seem granular in the exercise prescription for sedentary individuals, current guidelines for CET remain generic in nature for populations that require tailored training strategies (Burton et al., 2017b). Indeed, simple modifications such as this may allow practitioners to customise exercise prescription with greater specificity for desirable health outcomes. However, the effect of TUT on disease-related outcomes (systemic inflammatory cytokines, body composition, and aerobic capacity) in older sedentary populations remains unknown.

This study seeks to elucidate the effect of varying the RT component of CET with volume-matched TUT or conventional CET. By lifting at slow speeds (3 s phases) with reduced mechanical loads in TUT, the training adaptations may be similar to conventional CET (1.5 s phases), despite CET typically involving higher levels of resistance-load. Accordingly, the present study assessed the effects of altering lifting speed and training exposure in the RT component of CET on body composition, and systemic inflammatory and CVD-related biomarkers within an untrained population.

Methods

Participants

Participants were recruited within the local geographical area. Inclusion criteria ensured participants were aged 50-75 y, inactive (exercise < twice per week), non-smoking for at least 6 months, and free from medical conditions or medications that may alter inflammatory and cardiovascular markers. Fifty-three subjects were recruited and 38 completed the intervention (Figure 3.1). Approval was granted by the institutional ethics committee (ETH16-0742) in accordance with the Declaration of Helsinki (World Medical Association, 2013). Prior to data collection participants provided written informed consent and completed the Exercise and Sports Science Australia Pre-Exercise Screening System to determine safety and suitability for participation.

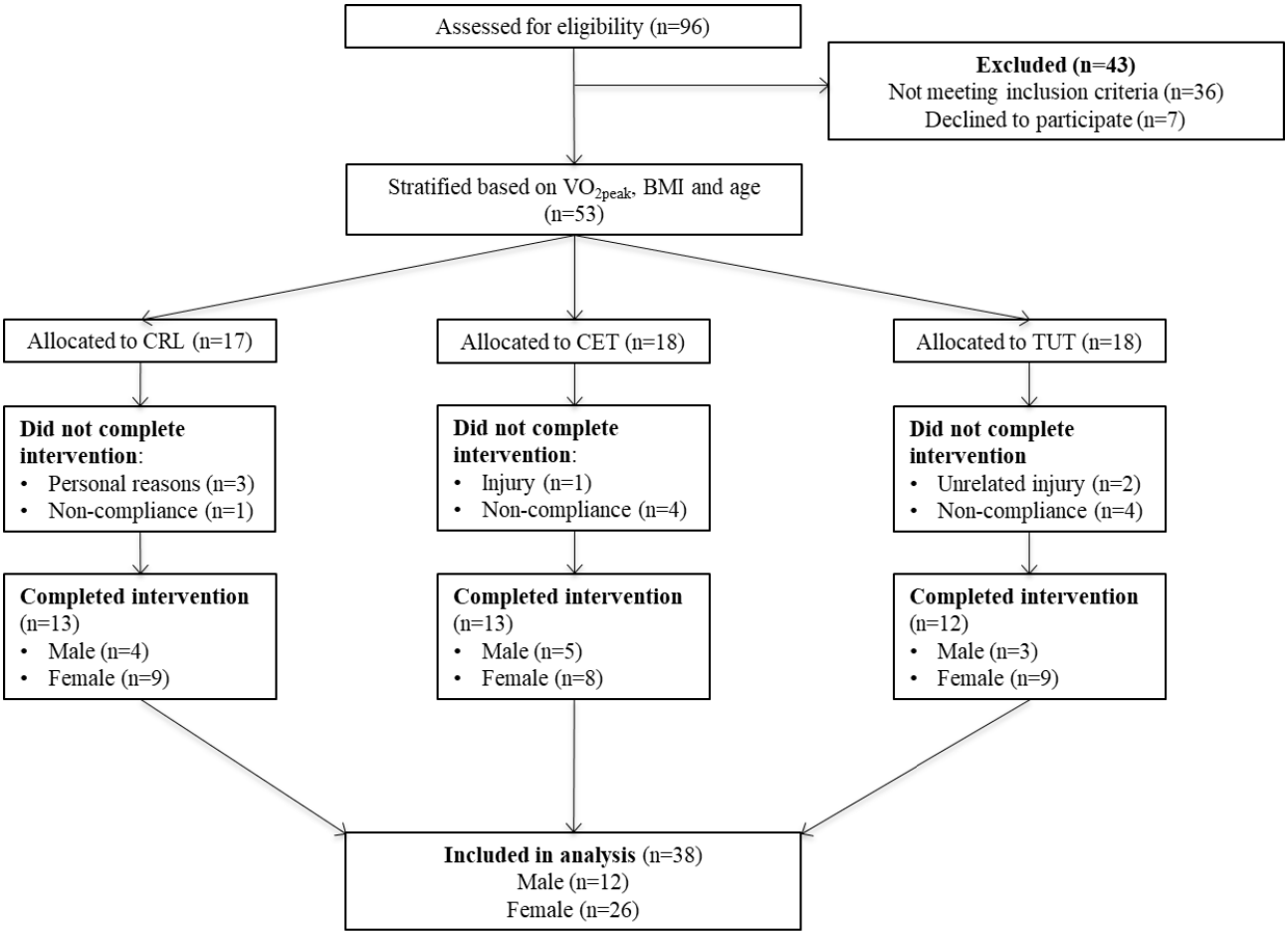

Figure 3.1: CONSORT diagram of recruitment process and participant dropouts.

VO_2 peak, peak oxygen consumption; BMI, body mass index; CRL, control group; CET, concurrent training group; TUT, time-under-tension training group. Non-compliance defined as having completed < 80% of prescribed sessions, or a significant change in lifestyle behaviours in CRL.

Overview

Participants attended pre- and post-intervention testing sessions at standardised times (06:00-09:00 h) having fasted overnight (10-12 h) and abstained from planned exercise for 72 h. Testing comprised a dual-energy x-ray absorptiometry (DEXA) scan, venous blood sample, vastus lateralis ultrasound, isometric strength assessment and maximal graded exercise test. All participants recorded their physical activity and diet for 24 h before testing, and this document was returned for post-testing with instructions to replicate lifestyle behaviours beforehand. Further, participants adhered to the baseline testing procedure following training by allowing >72 h between the last training session and post-testing. Participants were stratified by age, peak oxygen consumption (VO_{2peak}) and body mass index. Subsequently, an independent party randomly allocated subjects using de-identified codes into CRL (n=17), CET (n=18), or TUT (n=18).

Venous Blood Sample

Blood was drawn from the median cubital vein into ethylenediaminetetraacetic acid tubes. Samples were immediately centrifuged at 3500 rpm for 10 min at 4^{o}C, and aliquots stored in low protein-binding tubes at -80^{o}C. Plasma concentrations of CRP, vWF, ICAM-1, VCAM-1, p-selectin and SAA were measured using a chemiluminescent immunoassay (Magpix, Luminex Corporation, Austin, USA) and quantified using the associated software (Analyst, Merck-Millipore, Burlington, USA). For all analytes, multiplex assays were used with intra-assay coefficients of variation < 15%. Negligible cross-reactivity was present.

Body Composition

Participants underwent full-body DEXA scans to determine body composition (Lunar Prodigy, GE Medical, Milwaukee, USA). Measures included total-body lean (TBLM) and fat mass (TBFM), regional measurements of android, gynoid, abdominal subcutaneous (SAT) and visceral (VAT) fat mass, using standardised body landmarks for reference. Specifically, the android region was set between the iliac crest and 20% of the distance to the base of the skull (Kaul et al., 2012). Accordingly, SAT and VAT were estimated within the android region by manufacturer software using a constant conversion factor for adipose tissue (Encore 16, GE Medical, Milwaukee, USA). Scanning mode was set to manufacturer defaults based on participant size, at a resolution of 4.8 x 13 mm.

Muscle Ultrasound

A brightness-mode ultrasound (LOGIQ e; GE Medical, Milwaukee, USA) was used to determine *m. vastus lateralis* (VL) thickness. The site was determined at 50% distance from the greater trochanter to the lateral epicondyle of the femur. The technician collected three measurements and recorded the mean. A standardised distance between the scanning location and the mid-way point from the central patella to the medial aspect of the anterior superior iliac spine was used for inter-trial reliability (Blazevich et al., 2007). A linear-array probe was used at a frequency of ~10 MHz. Participants were positioned with the hip and knee extended, and the leg suspended to prevent thigh muscle compression. Measurement of ultrasonic images in the present study demonstrated inter-trial reliability of r=0.88–0.97 and typical error of 0.74–0.97 mm.

Strength Assessment

A maximal isometric knee extension was used to assess quadriceps strength. Participants completed a cycling-based warm-up (2 min at 50 W) and were seated on an isokinetic dynamometer (Biodex Medical Systems, Shirley, USA). The device was adjusted to standardised positions for each participant such that the axis of the rotating arm aligned with the tibiofemoral joint and the ankle support aligned with the lateral malleolus. Warm-up comprised five isokinetic knee extensions against light resistance and a submaximal isometric contraction at 50% effort. Following a 15 s rest, participants performed a 4s maximal effort, from which peak force was recorded.

Graded Exercise Test

Participants completed a graded exercise test on a mechanically braked cycle ergometer (Wattbike, Nottingham, UK). The test started at 25 W and increased 25 W each minute until volitional exhaustion, representing a modified Bruce protocol (Bruce et al., 1973). Throughout, VO_2 was determined via O_2 and CO_2 concentrations from an electronic gas analyser (Medgraphics Ultima, Saint Paul, USA). The device was calibrated using a pneumotachometer and a gravimetric air mixture with pre-determined gas concentrations (CO_2 4.1 (0.1) %; O_2 15.7 (0.2) %). At volitional exhaustion, VO_{2peak} and power output (PPO) were recorded based on the highest 30-second average values during the test.

Training Protocol

Participants trained for ~1 h, 3 times weekly for 10 weeks. Sessions comprised ~30-40 min RT followed by 15-20 min of AT. The AT component was identical across training groups, performed at a continuous intensity of 65-80% maximum heart rate (HR_{max}) using non-load-bearing modalities (cycling/rowing). The RT portion comprised 8 exercises

targeting the lower (leg press, split squat, and knee extension) and upper body (chest press, latissimus pulldown, shoulder press, biceps curl, and triceps extension). The CET group completed RT in the 1-4 sets of 10-15 repetition range with a 1.5-1.5 s lifting tempo (Kraemer et al., 2002). In contrast, the TUT group completed the same repetition-volume with a 3-3 s tempo, providing twice the time-under-tension per set but entailing reduced mechanical intensities, measured by a percentage of 1RM (Tanimoto & Ishii, 2006). During the training period, the CRL group was instructed to maintain normal lifestyle behaviours. Adherence within CRL was verified through regular conversations and use of a behavioural questionnaire (Godin & Shephard, 1985). Likewise, all training sessions were guided using an audible metronome, in conjunction with verbal guidance by research staff. Specifically, an amplified metronome was played at 0.5s intervals, with CET subjects performing 3 counts for concentric and eccentric lifting phases, and TUT subjects performing 6 counts. Verbal instructions ensured compliance and understanding. Training loads were recorded as overall volume-load [repetitions x load] and total stimulus exposure (SE) as [volume-load x time-under-tension].

Statistical Analysis

Data not meeting parametric assumptions were logarithmically transformed based on skewness, and a 3x2 mixed-design analysis of variance (ANOVA) was used to assess main effects and group x time interactions. In the presence of significant effects, post hoc tests using Tukey's HSD correction located the source of significance at an α-level of 0.05. All analyses were performed using the Statistical Package for Social Sciences (v.24, IBM, Armonk, USA). Normal data are described as mean ± SD, and non-normal data as median (interquartile range (IQR)).

Results

Adherence

As per Figure 3.1, 38 of the 53 participants completed the intervention and were included in statistical analyses (CRL n=13, CET n=13, TUT n=12). Adherence to training was not significantly different between the two groups (CET 99 ± 2.9%; TUT 98 ± 5.2%, p=0.572). Training loads generally followed an expected pattern; although the between-group differences in overall volume-load did not reach statistical significance (170 (138-239) vs 137 (116-191) AU, p=0.080), when multiplied by time-under-tension there were significant differences between CET and TUT (510 (414-716) vs 823 (696-1145) AU, p=0.003) whereby TUT conferred a larger overall time exposure.

Body Composition

As shown in Table 3.1, both TBLM and TBFM showed a significant effect of time ($p<0.05$), and a within-group time effect was only evident for CET, which increased TBLM ($p<0.001$) and decreased TBFM (p=0.041). No other significant within-group changes or interactions were present. That said, the overall body fat percentage was reduced in both CET (p=0.004) and TUT (p=0.019), though there was no significant group x time interaction (p=0.058). For VAT, there was a significant effect of time (p=0.012) with no interaction effect (p=0.800), and within-group changes were only evident for CET (p=0.049). In contrast, SAT showed a significant group x time interaction (p=0.011), with an increase in CRL (p=0.030) and a decrease in TUT (p=0.030). Separately, VL thickness showed a significant group x time interaction (p=0.002) whereby CRL decreased and CET increased (p=0.001 post hoc).

Table 3.1: Changes in anthropometry and body composition in response to the 10-week intervention.

	Control Group		Concurrent Training		Time-Under-Tension	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
Age (y)	56 ± 5.6		58 ± 5.3		56.4 ± 5.5	
TBLM (kg)	46.3 (40.0, 60.4)	47.5 (39.7, 60.7)	48.9 (37.1, 61.4)	49.2 (38.3, 62.7)*	40.8 (38.3, 45.4)	41.3 (38.7, 46.0)
TBFM (kg)	26.91 ± 9.86	26.95 ± 8.84	24.04 ± 7.75	23.24 ± 7.48*	27.42 ± 7.48	26.60 ± 7.74
TBFM (%)	35.93 ± 10.16	36.00 ± 9.79	31.67 ± 6.04	30.57 ± 6.51*	37.15 ± 8.86	36.20 ± 9.18*
VAT	0.63 ± 0.29	0.60 ± 0.25	0.62 ± 0.48	0.56 ± 0.50*	0.87 ± 0.45	0.81 ± 0.46
SAT	1.23 ± 0.54	1.34 ± 0.67*	1.25 ± 0.49	1.23 ± 0.51	1.42 ± 0.55	1.30 ± 0.55*#

Normally distributed and skewed data are reported as mean ± SD and median (interquartile range), respectively. Significant change from baseline $p<0.05$*. TBLM, total-body lean mass; TBFM, total-body fat mass; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.

Inflammatory and CVD Markers

Inflammatory cytokines showed no within- or between-group differences for CRP ($p>0.05$; Table 3.2). MCP-1 showed a significant effect of time ($p=0.004$), with an increase in CRL ($p=0.015$), but no interaction ($p=0.628$). P-selectin showed as significant decrease in CET and CRL ($p<0.05$). No other training effects were present for CVD biomarkers ($p>0.05$).

Physical Capacity

A significant group x time interaction was evident for VO_{2peak} ($p=0.027$; Table 3.3) and TUT increased significantly compared to CRL ($p=0.021$). By comparison, PPO showed a significant time effect ($p=0.033$), increasing in CET ($p=0.036$) and TUT ($p=0.032$) although the group x time interaction did not reach statistical significance ($p=0.100$). Separately, CET was superior to increase muscular strength; peak knee strength showed a significant interaction ($p=0.020$) and CET was increased versus CRL ($p=0.015$).

Table 3.2: Changes in CVD-related biomarkers in response to the 10-week intervention.

	Control Group		**Concurrent Training**		**Time-Under-Tension**	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
CRP ($mg \cdot L^{-1}$)	4.2 (2.4, 10.8)	3.6 (2.4, 8.1)	1.6 (0.8, 2.8)	2.4 (1.5, 6.3)	2.4 (1.5, 10.8)	11.6 (1.7, 20.0)
vWF ($mg \cdot L^{-1}$)	13.8 (10.5, 43.2)	15.9 (10.7, 30.5)	11.3 (7.7, 19.9)	31.5 (19.1, 172.7)*	16.8 (7.3, 26.1)	31.3 (13.7, 103.2)
SAA ($ng \cdot mL^{-1}$)	3081 (2064, 7815)	3658 (2191, 7606)	1877 (1371, 3471)	2398 (1507, 7308)	2153 (1509, 2761)	1908 (1152, 5657)
ICAM-1 ($ng \cdot mL^{-1}$)	108 (80, 120)	71 (58, 94)*	93 (82, 116)	92 (63, 124)	88 (66, 101)	84 (56, 97)
VCAM-1 ($ng \cdot mL^{-1}$)	468 (377, 647)	264 (238, 424)*	446 (357, 525)	485 (277, 624)	463 (431, 502)	349 (301, 532)
P-selectin ($ng \cdot mL^{-1}$)	437 (379, 592)	214 (163, 269)*	377 (323, 460)	246 (182, 398)*	371 (360, 455)	246 (167, 560)
MCP-1 ($pg \cdot mL^{-1}$)	269.4 ± 118.5	360.0 ± 136.5*	282.5 ± 297.1	341.2 ± 104.5	257.3 ± 58.3	299.3 ± 100.3

Normally distributed and skewed data are reported as mean ± SD and median (interquartile range), respectively. Significant change from baseline $p<0.05$*. CRP, C-reactive protein; vWF, von Willebrand Factor; MCP, monocyte chemoattractant protein; ICAM, intercellular adhesion molecule; VCAM, vascular cell adhesion molecule; SAA, serum amyloid A.

Table 3.3: Changes in endurance and strength parameters in response to the 10-week intervention.

	Control Group		**Concurrent Training**		**Time-Under-Tension**	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
VO_{2peak} ($mL \cdot kg \cdot min^{-1}$)	22.02 ± 4.30	23.01 ± 5.01	24.98 ± 3.93	27.44 ± 3.97*	21.58 ± 4.80	26.15 ± 4.10*#
PPO (W)	153 (127, 203)	154 (137, 201)	176 (142, 235)	198 (150, 238)*	173 (144, 220)	177 (155, 249)*
Peak Torque (Nm)	150.2 (132.9, 163.9)	143.7 (120.6, 187.9)	169.4 (131.8, 208.6)	201.5 (165.2, 252.0)*#	162.0 (148.6, 204.9)	190.6 (161.4, 237.2)*

Normally distributed and skewed data are reported as mean ± SD and median (interquartile range), respectively. Significant change from baseline $p<0.05$*. Significant change vs control $p<0.05^{\#}$. VO_{2peak}, peak oxygen consumption; PPO, peak power output.

Discussion

This study investigated the effect of time-under tension as part of a CET program on CVD biomarkers, body composition and aerobic capacity. The CET group increased TBLM and decreased TBFM and VAT, though TUT was superior in reducing abdominal SAT. CET provided the greatest increase in VL thickness and quadriceps strength, while conversely, the largest increases in aerobic capacity were observed in TUT. Consequently, mode-specific adaptations are evident with CET (TBLM, TBFM, VAT, peak strength) and TUT (VO_{2peak}, SAT), compared to CRL. However, limited changes in CVD-related biomarkers existed, with no training-induced changes in MCP-1, CRP, SAA, or ICAM-1. Regardless, these results suggest that altering the resistance component of CET may have subtle, yet relevant, mode-specific consequences that can aid the tailoring of the stimulus to individual needs.

It was expected that improvements in CVD-related biomarkers would result from exercise training, indicated by reduced markers of platelet aggregation and atherosclerotic risk (Lip & Blann, 1997), though this was only true for p-selectin, which decreased in the CET cohort. Different exercise strategies have been shown to reduce markers of platelet activation across various populations (Campbell et al., 2009; Tisi et al., 1997), though these observations were made in participants with existing cardiometabolic conditions not evident in the current population (Vona et al., 2009). Furthermore, adhesion molecules unexpectedly decreased in CRL, with comparable studies only conducted in CVD patients, where 4-8 weeks' CET resulted in decreased VCAM-1 (Saetre et al., 2011; Tönjes et al., 2007). These findings contrast with the present study, and indeed the between-group variation may be related to quotidian variation in these markers rather than a clear exercise effect (Troisi et al., 2000) as the differences between groups did not

produce a significant interaction effect. Though difficult to compare with the present study, it is possible that within the spectrum of CET, a greater emphasis on the aerobic component would produce greater changes in adhesion molecules (Duarte et al., 2015). Moreover, despite the apparent effectiveness of CET within CVD patients, non-diseased subjects may not possess the same predisposition for training-induced adaptations, particularly if other CVD-related parameters are ostensibly healthy.

Although CET is previously shown to improve CVD-related markers such as ICAM-1 and fasting lipids in sedentary adults (Atashak et al., 2016), no training-induced changes were observed in the present study for the key CVD biomarkers of CRP and MCP-1. Previous research reports pronounced reductions in TBFM and/or VAT to precipitate greater changes in systemic inflammatory markers (Alberga et al., 2015; Fayh et al., 2013). Hence, the small reductions observed in fat mass reported here may limit the adiposity-driven influence on reduced chronic systemic inflammatory markers. However, decreased inflammation is not always associated with fat loss or muscle hypertrophy (Meyer et al., 2006) and other mechanisms unrelated to body composition may influence the inflammatory milieu (Kasapis & Thompson, 2005). Previously, short-term CET performed 3 times per week was effective to improve inflammatory markers, including CRP (Balducci et al., 2010; Stewart et al., 2007). Both training groups in the present study demonstrated mean CRP values within the "normal" range ($<3 mg \cdot L^{-1}$), and thus there may have been minimal potential for change. Indeed, this seems to lend credibility to the notion of 'regression towards the mean', whereby CRP values further from the overall mean demonstrate a greater propensity for change (Lakka et al., 2005).

Adiposity represents a confounding factor when interpreting the chronic inflammatory state, particularly given VAT is an important contributor to pro-inflammatory cytokines (Park et al., 2005). Thus, training-induced effects on TBLM, TBFM and abdominal VAT were evident within CET, and TUT showed the greatest reduction in abdominal SAT. This is the first study to compare these training modes in this context, and whilst speculative, it is possible that the greater duration in TUT contributed to a different metabolic stimulus during training. Indeed, Scott (2012) observed greater within- and post-session energy expenditures with greater TUT, although the long-term effects on substrate metabolism and tissue morphology are unknown. Importantly, TUT showed a larger time exposure during training, and this be a novel strategy to enhance the efficacy of a low-load training regimen.

By comparison, the higher-load CET produced the largest increase in quadriceps strength. While increased isometric strength was expected due to the high mechanical loads during CET, the between-groups difference in hypertrophy is inconsistent with previous literature (Tanimoto et al., 2008; Young & Bilby, 1993). Again, a lack of previous data makes comparison difficult, but for this population there may be an advantage to more conventional strategies. That said, TUT showed the largest gains in aerobic capacity, and it is possible the prolonged contractile stimulus may have placed a greater stress upon oxidative metabolic pathways and conferred greater localised muscular endurance, although there are no explicit data to support this (Keeler et al., 2001). Given that the differences in short-term energy metabolism produce a greater energy expenditure during TUT (Scott, 2012), there may be an application for those seeking training methods to increase aerobic fitness alongside RT exposure. In this instance, load- and duration-

specific stimuli produce distinct performance adaptations, although the CVD biomarkers appeared to change independently of these outcomes.

Despite the novel findings, some limitations are acknowledged. Specifically, the use of a sedentary but ostensibly healthy participant cohort (as opposed to CVD patients) may have limited the potential for significant changes in disease-associated markers. Although there is evidence for the efficacy of exercise training to offset CVD risk, such positive changes may not manifest in a short-term training study. Furthermore, although TUT represents a low-load resistance training alternative, it is not clear whether the associated changes are intrinsic to TUT, or if prolonged contractions are simply a permissive mechanism for muscle activation, per the size principle (Henneman, 1957). Indeed, it is possible that similar outcomes could be achieved by performing fast-speed contractions to the point of muscular fatigue (Mitchell et al., 2012).

Conclusions

Overall, 10 weeks of concurrent training using conventional methods preferentially improved whole-body composition, while reductions in VAT and SAT were present in CET and TUT respectively. However, these changes manifested minimal improvements in markers of CVD-related biomarkers, with modest changes evident for CET. Further, higher mechanical loading of muscle (i.e. CET) produced greater improvements in isometric strength, whereas a longer time exposure (i.e. TUT) resulted in more pronounced improvements in aerobic capacity. Thus, there may be subtle mode-specific effects that can help to customise exercise regimens according to individual needs. Further research is required to explore these specific responses and refine the use of concurrent training in exercise prescription.

Chapter 4

Study 2

As based on the manuscript:

"Inflammatory and metabolic responses to concurrent training: modifying temporal and mechanical loading for sedentary populations".

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*Under review Journal of Science and Medicine in Sport***.**

Abstract

Purpose: To assess the effect of conventional concurrent training (CET) versus greater time-under-tension (TUT) training within a CET program on biomarkers associated with type 2 diabetes, body composition and physical capacity in sedentary adults.

Methods: Thirty-eight sedentary adults underwent 10 weeks of CET (n=13), TUT (n=12), or control (CRL; n=13). Testing conducted before and after training included dual-energy x-ray absorptiometry for total-body lean (TBLM) and fat-mass (TBFM), peak oxygen consumption (VO_{2peak}), peak power output (PPO) and peak isometric quadriceps strength. Plasma concentrations of interleukin (IL)-6, IL-1β, tumour necrosis factor-alpha (TNFα), leptin, glucose, insulin, glucagon, glucagon-like peptide 1 (GLP-1), and insulin resistance (HOMA-IR) were also assessed in the fasting state.

Results: TBLM increased and TBFM decreased ($p<0.05$) within CET only, while body fat percentage decreased in both CET and TUT ($p< 0.05$). All groups decreased fasting glucose ($p<0.05$), and CET decreased IL-6 ($p=0.021$). Conversely, only TUT reduced TNFα ($p=0.016$). Both CET and TUT increased PPO ($p<0.005$) and TUT provided the greatest gains in VO_{2peak} ($p<0.001$), while CET showed superior increases in muscular strength ($p=0.001$).

Conclusions: Concurrent training can improve body composition and physical fitness. Further, incorporation of TUT may preferentially improve endurance adaptations, and shows mode-specific responses within concurrent training. Group-specific effects show CET and TUT may preferentially improve IL-6 and TNFα, respectively.

Introduction

Physical inactivity is associated with elevated systemic inflammation and an increased risk of cardiometabolic diseases (Pradhan et al., 2001). Specifically, the increased presence of pro-inflammatory cytokines such as interleukin (IL)-6, IL-1β, and tumour necrosis factor-α (TNFα) is inversely related to physical activity levels and predisposes the development of metabolic conditions such as type-2 diabetes mellitus (T2DM) (Pradhan, 2007). In turn, attenuation of systemic inflammation may accompany improved metabolic functioning, including insulin sensitivity, HbA1c, and leptin sensitivity (Fernández-Riejos et al., 2010). Accordingly, strategies targeting improved systemic inflammation and glucose homeostasis are of importance in the long-term prevention of T2DM. Considering the contribution of inactivity, exercise-based interventions may offset the metabolic abnormalities that precede T2DM. By ameliorating the inflammatory milieu, exercise training may reduce the risk of insulin resistance and T2DM (Gleeson et al., 2011). Indeed, the specificity of exercise modalities may also have important ramifications on the resulting physiological adaptations and reduced disease development (Coffey & Hawley, 2017).

Aerobic training (AT) is suggested to improve mitochondrial respiration and oxidative metabolism, and is identified as a primary disease-prevention strategy (Coffey & Hawley, 2017). Separately, resistance training (RT) increases skeletal muscle mass and bone mineral density (Hurley et al., 2011). The simultaneous integration of the two modes, termed concurrent training (CET) is suggested to confer the respective benefits of AT and RT in untrained individuals, even when administered in a split-dose approach, i.e. 50% of respective single mode doses (Donges et al., 2013). For individuals seeking to reduce inflammation and biomarkers related to T2DM, CET represents a feasible strategy and

may be the most efficient way to achieve a broad range of disease-prevention outcomes. Thus, there is increasing interest in tailored exercise strategies to achieve mode-specific cardiometabolic benefits in a way that is safe, effective, and sustainable.

One method to tailor the effects of CT involves customising the RT component to achieve physiological adaptions more relevant for individual disease risk amelioration (Forti et al., 2016). For example, although evidence suggests hypertrophy and strength adaptations pursuant to RT are achieved using high mechanical loads (Marcotte et al., 2015), these loads may not be ideal for sedentary populations (Van Kan et al., 2009). However, similar hypertrophic effects exist with lower-load contractions performed to the point of muscular fatigue via longer time under tension (TUT) stimuli (Mitchell et al., 2012). Within the spectrum of CET, modifying the RT component via novel modalities such TUT training may increase skeletal muscle mass and/or fitness, and may be more applicable for sedentary individuals.

TUT involves deliberately reducing lifting speeds to increase the time a targeted muscle is under load (Burd et al., 2012). In doing so, greater temporal exposure to mechanical tension may stimulate the contractile apparatus to a similar level as traditional RT techniques, and drive improvements in strength, hypertrophy, and/or fat loss (Burd et al., 2012; Dankel et al., 2017). Several studies have demonstrated that TUT can provide hypertrophy and/or strength adaptations that parallel those of conventional (faster-speed) RT, despite a reduced load (Tanimoto et al., 2008). Specifically, low-intensity RT protocols involving slow-speed lifting have shown significant muscle and strength increases with loads as low as 30-50% of 1-Repetition Maximum (RM) (Tanimoto et al., 2008) and importantly, these adaptations may be inferior with work-matched, fast-speed

protocols (Watanabe et al., 2014). Although the majority of current evidence pertains to younger, healthy populations, it is suggested that a potential application exists for older individuals seeking to improve health outcomes. In particular, improvements in body composition and/or fitness may help to reduce risk factors related to T2DM (Bartels et al., 2007), and thus tailored strategies for sedentary individuals may help to offset lifestyle-related risk.

Given that both RT and AT are widely recommended to enhance various health- and disease-related parameters, tailoring a CET design by using TUT may provide an opportunity for sedentary individuals to obtain preferential improvements in fitness and/or body composition whilst still undertaking split-mode concurrent training. Accordingly, such positive changes may assist in improving clinical parameters related to T2DM. Therefore, the primary aim of this study is to elucidate the effects of traditional and modified CET modalities on body composition, physical capacity, and inflammatory and metabolic biomarkers related to T2DM. Within CET, it is proposed that TUT will confer similar improvements in body composition, inflammatory biomarkers and glucose homeostasis compared to traditional CET.

Methods

Participants

Fifty-three sedentary adults volunteered to take part in the present study following recruitment within the local area, and 38 completed the study (descriptive data in Table 4.1). Inclusion required that participants be aged 50-75 years, sedentary (exercise less than twice per week), non-smoking for >6 months, taking no medications, and free from cardiovascular, autoimmune, and metabolic conditions. Approval was granted by the

institutional ethics committee (ETH16-0742) in accordance with the Declaration of Helsinki (World Medical Association, 2013). Participants received written and verbal information regarding the nature of the study and provided informed consent before participating.

Methodology Overview

Following familiarisation, participants attended testing sessions at standardised times (06:00–09:00 h) before and after the 10-week intervention. All participants arrived having fasted overnight (8-12 h) and abstained from vigorous activity for >24 h. Testing sessions comprised anthropometrical measurements (height and mass), a dual-energy x-ray absorptiometry (DEXA) scan, venous blood sample, strength assessment, and maximal graded exercise test (GXT). Based on baseline characteristics, 53 participants were stratified and randomly allocated to CRL (n=17), CET (n=18), or TUT (n=18) and 38 completed the intervention. Training was performed 3 days per week for 10 weeks, while control participants were instructed to continue normal lifestyle behaviours. Participants documented food intake and physical activity for the 24 h preceding baseline testing, and again before post-testing to ensure diet and exercise patterns were standardised before each.

Table 4.1: Changes in anthropometry and body composition in response to a 10-week intervention.

	Control Group		Concurrent Training		Time-Under-Tension	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
Age (y)	56 ± 5.6		58 ± 5.3		56.4 ± 5.5	
TBLM (kg)	46.33 (39.97, 60.36)	47.45 (39.65, 60.67)	48.85 (37.12, 61.41)	49.23 (38.32, 62.65)*	40.82 (38.30, 45.41)	41.27 (38.68, 46.02)
TBFM (kg)	26.91 ± 9.86	26.95 ± 8.84	24.04 ± 7.75	23.24 ± 7.48*	27.42 ± 7.48	26.60 ± 7.74
TBFM (%)	35.93 ± 10.16	36.00 ± 9.79	31.67 ± 6.04	30.57 ± 6.51*	37.15 ± 8.86	36.20 ± 9.18*

Normally distributed and skewed data are reported as mean ± SD and median (interquartile range), respectively. Significant change from baseline $p<0.05$*. TBLM, total-body lean mass; TBFM, total-body fat mass.

Anthropometry and DEXA

Provided no medical contraindications were presented, participants underwent whole-body DEXA scans (Lunar Prodigy, GE Medical, Milwaukee, USA) in a supine position with no metal-based clothing or piercings. A whole-body scan was performed with settings automatically selected based on anatomical characteristics, at a constant resolution of 4.8 x 13 mm. Analyses were performed using manufacturer software (Encore 16, GE Medical, Milwaukee, USA) and provided measures of total-body lean (TBLM) and fat mass (TBFM).

Venous Blood Sampling and Analysis

Approximately 5-7 mL of blood was collected from the medial antecubital vein via venepuncture. Targeted protease inhibitors were added to whole blood to preserve sensitive analytes. Samples were collected in EDTA tubes and immediately centrifuged at 3500 rpm for 10 min at 4^{o}C, and plasma stored at -80^{o}C for later analysis. Plasma was analysed using a chemiluminescent immunoassay (Magpix, Luminex Corporation, Texas, USA) for quantification of IL-6, Il-1β, TNFα, C-peptide, GLP-1, glucagon, insulin, and leptin. Additionally, glucose was measured using an oxidase/peroxidase reagent kit (Fisher Diagnostics, Middletown, USA) at a concentration of 1:150 (sample:solution). Insulin resistance (IR) was assessed via the Homeostatic Model Assessment (HOMA)-2 computer model (Wallace et al., 2004). For quality assurance, each sample was analysed in duplicate with the derived mean used as the index value. The assays used demonstrate intra-assay variability of <13% for IL-6 and TNFα, and <10% for the other analytes.

Strength Assessment

Using an isokinetic dynamometer (Biodex Medical Systems, Shirley, USA) isometric strength of the right knee extensors was measured. Following a cycling-based warm-up (2 min at 50 W), participants were positioned such that the axis of rotation of the dynamometer aligned with the tibiofemoral joint, with the ankle brace affixed at the lateral malleolus. Once secured in this position, participants performed a task-specific warm-up comprising 5 unilateral knee extensions against a small inbuilt resistance. After a 30 s rest, participants performed a 4 s submaximal isometric knee extension at 80^{o} flexion and then, after a 15 s passive rest, a second 4 s isometric contraction at maximal effort to determine peak knee extension strength.

Graded Exercise Test

Finally, after ~10 minutes of rest, participants underwent a maximal GXT on a mechanically-braked cycle ergometer (Wattbike, Nottingham, United Kingdom) to determine peak oxygen consumption (VO_{2peak}) and power output (PPO). Participants began the test at 25 W and increased power output by 25 W each minute until volitional exhaustion. Heart rate was recorded at each increment (FT7, Polar Electro, Kempele, Finland) and oxygen consumption was determined via O_2 and CO_2 concentrations in a metabolic gas analyser (Medgraphics Ultima System, Saint Paul, USA). The cart was calibrated according to manufacturer's instructions, involving pneumotachometer calibration, analysis of ambient air, and gas calibration with a gravimetric mixture of known concentrations (CO_2 4.1(0.1)%; O_2 15.7(0.2)%).

Training Procedures

The training period lasted 10 weeks, during which time participants trained 3 times per week for ~1 h. Each session comprised 20-30 min of RT followed by 15-20 min of AT (rowing/cycling). The AT was matched across the training groups, performed at an intensity of 65-80% of age-predicted maximal heart rate (208 – (0.7 x age)) as per Mahon et al. (2010). Separately, RT entailed 5 exercises targeting the upper body (chest press, shoulder press, lateral pulldown, biceps curl, and triceps extension) and 3 for the lower body (leg press, leg extension, and split squat) increasing in volume and/or intensity each week. Both CET and TUT completed the same repetition-volume (1-4 sets, 10-15 repetitions per set), although CET lifted at a 1.5-1.5 s cadence (i.e. 1.5 s concentric and eccentric phases) while TUT lifted using a 3-3 s cadence, producing two-fold longer set durations and a reduced volume-load (Tanimoto and Ishii 2006). A 1.5-1.5 s tempo is representative of a controlled lifting style, and previous studies of this nature utilise 1-2 s tempos to represent conventional strategies (Rana et al., 2008; Schuenke et al., 2012; Tanimoto et al., 2008; Young & Bilby, 1993). Training order placed RT first in the session, in order to minimise fatigue-related interference (Fyfe et al., 2014). Participants were supervised by research staff at all times and guided during RT by an audible and visible metronome, and the initial training days were used as familiarisation sessions. Volume-loads during training were recorded as [repetitions x weight used]. Outside of the study, participants were instructed to maintain habitual activity and dietary behaviours, and this was verified using multiple measurements of leisure-time physical activity (Godin & Shephard, 1985) and frequent verbal feedback.

Statistical Analysis

Data were checked to confirm normal distribution (Shapiro-Wilk test), homogeneity of variance (Levene's test) and the absence of outliers (Tukey's fences). Data not meeting these assumptions were logarithmically transformed for parametric analyses. A group-by-time mixed-design analysis of variance (ANOVA) was used to assess between-subject differences, and when analyses indicated significant main effects or interactions, post hoc comparisons using Tukey's adjustment located the source of significance. Further, a one-way ANOVA was performed to compare differences between groups for overall training loads, and the pre-to-post changes in primary outcomes. Analyses were performed using the Statistical Package for Social Sciences (v.25, IBM, Chicago, USA), using an α-level of 0.05. Normally distributed data are presented as mean ± standard deviation, and non-normal data are presented as median (interquartile range).

Results

Training Responses

Thirty-eight participants completed the intervention (CRL n=13, CET n=13, TUT n=12). For overall volume-load, the differences between CET and TUT did not reach statistical significance (170 (138-239) vs 137 (116-191) AU, p=0.080), although when overall volume was multiplied by time-under-tension, the TUT group showed a significantly higher exposure (510 (414-716) vs 823 (696-1145) AU, p=0.003). Training adherence did not differ significantly between CET and TUT (99 ± 2.9% vs 98 ± 5.2%, p=0.572).

Glucose and Inflammatory Blood Markers

As presented in Table 4.2, no significant changes were evident for glucagon (time: p=0.920, condition x time: p=0.840, C-peptide (time: p=0.453, condition x time: p=0.726)

or GLP-1 (time: p=0.415, condition x time: p=0.549). Glucose showed an overall effect of time (p<0.001) with small reductions within all three groups (p<0.05) and no differences between the groups (p=0.825). No other T2DM marker was altered by training (p>0.05). For inflammatory biomarkers, IL-6 showed a significant group x time interaction (p=0.017), whereby only CET decreased (p=0.021). There was no interaction for TNFα (p=0.633), although there was a significant overall time effect (p=0.008) and a within-group time effect only for a decrease in TUT (p=0.016).

Body Composition

For TBLM, an overall time effect was shown (p<0.001) with an increase only present in CET (p<0.001). Similarly, TBFM showed an effect of time (p=0.027) for a within-group change for CET (p=0.041). That said, the body fat percentage was significantly reduced in both CET (p=0.004) and TUT (p=0.019).

Physical Capacity

As reported in Table 4.3, for VO_{2peak} there was a significant group x time interaction (p=0.027) and an increase within both training groups (CET p=0.007; TUT p<0.001). Notably, one-way ANOVA revealed a significant difference in change values between TUT and CRL (p=0.021). In comparison, PPO data showed a significant effect of time (p=0.033) with increased observed within CET (p=0.036) and TUT (p=0.032). A significant interaction was present for peak isometric quadriceps strength (p=0.020), with a significant increase in CET compared to CRL (p=0.015).

Table 4.2: Changes in biomarkers related to inflammation and glucose homeostasis in response to the 10-week intervention.

	Control Group		Concurrent Training		Time-Under-Tension	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
IL-6	0.81	1.92	1.32	0.46	3.15	2.35
(pg·mL^{-1})	(0.52, 1.16)	(0.41, 5.91)	(0.40, 3.47)	(0.23, 0.64)*#	(1.52, 4.62)	(0.86, 2.98)#
TNFα	0.62	0.41	0.99	0.63	1.26	0.59
(pg·mL^{-1})	(0.60, 1.26)	(0.38, 1.35)	(0.87, 1.39)	(0.45, 1.73)	(0.89, 1.68)	(0.43, 1.26)*
C-peptide	1254	1280	1241	1430	1104	1086
(nmol·L^{-1})	(955, 2203)	(1070, 2380)	(1115, 1635)	(1135, 1716)	(958, 1281)	(867, 1283)
GLP-1	39.3	20.1	23.4	18.8	31.9	27.6
(ng·mL^{-1})	(18.3, 47.1)	(14.7, 34.5)	(12.2, 40.4)	(7.1, 40.6)	(25.5, 48.8)	(18.6, 63.9)
Glucagon (ng·mL^{-1})	128.7 ± 31.0	126.1 ± 38.3	101.2 ± 36.8	106.3 ± 37.1	99.1 ± 52.2	98.3 ± 29.8
Insulin	76.5	57.4	52.2	54.9	49.9	41.0
(pmol·L^{-1})	(43.2, 97.9)	(37.8, 105.5)	(45.4, 60.6)	(35.0, 59.2)	(40.1, 73.0)	(30.3, 50.7)
Leptin	7624	5948	4286	5028	5547	4395
(pg·mL^{-1})	(3009,11012)	(3523, 8707)	(3096, 13393)	(2517, 12768)	(3167, 11441)	(2198, 10891)
Glucose	5.2	4.7	4.8	4.7	4.9	4.6
(mmol·L^{-1})	(4.8, 5.8)	(4.37, 5.4)*	(4.6, 5.4)	(4.0, 4.9)*	(4.6, 6.3)	(4.0, 5.2)*
HOMA-IR	1.47	1.09	0.96	0.98	0.99	0.72
(AU)	(0.82, 1.82)	(0.71, 1.93)	(0.87, 1.12)	(0.63, 1.07)	(0.84, 1.33)	(0.59, 0.92)

Normally distributed and skewed data are reported as mean ± SD and median (interquartile range), respectively. * $p<0.05$ vs. baseline; # $p<0.05$ vs. CRL. IL, interleukin; TNF, tumour necrosis factor; GLP, glucagon-like peptide; HOMA-IR, homeostatic model of assessment for insulin resistance.

Table 4.3: Changes in endurance and strength parameters in response to a 10-week intervention.

	Control Group		Concurrent Training		Time-Under-Tension	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
VO_{2peak} ($mL \cdot kg \cdot min^{-1}$)	22.02 ± 4.30	23.01 ± 5.01	24.98 ± 3.93	27.44 ± 3.97*	21.58 ± 4.80	26.15 ± 4.10*#
PPO (W)	153 (127, 203)	154 (137, 201)	176 (142, 235)	198 (150, 238)*	173 (144, 220)	177 (155, 249)*
Peak Torque (Nm)	150.2 (132.9, 163.9)	143.7 (120.6, 187.9)	169.4 (131.8, 208.6)	201.5 (165.2, 252.0)*#	162.0 (148.6, 204.9)	190.6 (161.4, 237.2)*

Normally distributed and skewed data are reported as mean ± SD and median (interquartile range), respectively. Significant change from baseline $p<0.05$*. Significant change vs control $p<0.05^{\#}$. VO_{2peak}, peak oxygen consumption; PPO, peak power output.

Discussion

This study examined the effects of altering the RT component of a 10-week concurrent training program with TUT on inflammation, metabolic homeostasis, body composition and physical capacity. Markers of glucose homeostasis remained unchanged following training, although TNFα decreased within TUT, and IL-6 decreased within CET. Further, load-specific changes in fitness parameters showed increased endurance in TUT, with greater strength gains in CET. Collectively, small training-specific effects existed based on manipulation of the RT portion of CET and have relevant practical implications for stimulus-specific prescription of concurrent training in sedentary populations.

Reduced insulin sensitivity and action are the major physiological disturbances that predicate T2DM (Tripathy et al., 2000), and exercise is purported to improve these parameters across various populations (Inoue et al., 2015). In the present study, no changes were evident in insulin resistance with either training program. Although previous CET-based interventions have been effective to reduce insulin resistance in sedentary populations (Kim et al., 2008a), the weekly volume and/or overall duration of the present program may not have been sufficient to produce a similar training effect. As evidence, Bharath et al. (2018) reported significant reductions in HOMA-IR after a 12-week CET program comprising 5 x 1-hour sessions per week, significantly more volume than that used for the present cohort. Further, HOMA-IR was decreased in overweight adults undertaking CET for 8 months with the greater change caused by either AT or RT alone (Slentz et al., 2011). Thus, it is possible that a longer and/or more volume-dense program would have yielded different outcomes in the current study. Given the majority of participants were already within the normal range for most measures (American

Diabetes Association, 2017), this change may represent inherent variability in the assays used, or indeed a limited potential for change in an apparently healthy population.

Given the inhibitory effect of inflammatory cytokines on glucose control parameters, some authors suggest that changes in the inflammatory milieu may explain changes in insulin resistance (Villareal et al., 2011), although the present study showed inconsistent outcomes across these variables. The present study showed reductions in IL-6 and TNFα, as markers of inflammation, for CET and TUT, respectively. Previous studies have also shown reductions in TNFα and IL-6 following CET across sedentary cohorts (Jorge et al., 2011), although the present study is the first to explore responses to different RT methods (i.e. TUT) within a concurrent training design. The clinical relevance of these findings is a key discussion point, with reduced IL-6 in the training groups indicating a reduction in the relative risk of future T2DM (Pradhan et al., 2001). The greater reduction in TNFα within TUT may reflect a prolonged, metabolically demanding RT stimulus. Compared to conventional RT methods, this type of modified training may entail a greater acute metabolic strain (Scott, 2012), which may contribute to an enhanced endurance stimulus and in turn decreased IL-6 (Hosick et al., 2013). Indeed, Ho et al. (2013) conducted a 12-week high-volume CET intervention in older adults, with results showing a significant reduction in plasma TNFα. Moreover, it is suggested that variation in the within-session energy demands of CET will influence long-term training outcomes (Donges et al., 2013) and further, the intensity of effort should be a primary consideration, perhaps even more important than overall training loads (Villareal et al., 2011). These findings and the stimulus-specific responses add further credibility to concurrent training, but also the potential to further manipulate the CET stimulus to gain more tailored physiological outcomes.

Notably, however, the baseline values for TNFα were ≤ 1.30 $pg \cdot mL^{-1}$ for all groups and do not represent high-risk values. Some authors report that T2DM patients present a typical TNFα concentration >2.5 $pg \cdot mL^{-1}$ (Plomgaard et al., 2007), while Cesari et al. (2003) suggest increased cardiometabolic risk for values above 2.7$pg \cdot mL^{-1}$, and more so for those above 8.7 $pg \cdot mL^{-1}$. Thus, the changes shown here may not necessarily reflect a decreased risk state. To explore the variable inflammatory response between these groups, Ho et al. (2013) reported significant reductions in TNFα with 12 weeks of CET, above that which was achieved through duration-matched single-mode training, though those subjects were obese at baseline. Donges et al. (2013) found decreased TNFα with 12 weeks' CET in sedentary, overweight men, and in this instance the changes coincided with reductions in other cytokine levels and enhanced insulin sensitivity. By comparison, Stewart et al. (2007) observed no changes in TNFα with a 12-week CET regimen in either older or younger sedentary adults, and the overall training prescription was very similar to the present study and the outcome did not differ based on baseline fitness level. Thus, there are a number of factors that may have contributed to the present finding, including the pre-intervention levels of TNFα, the overall training volume, and/or the effect of other cytokines on circulating TNFα.

It is possible that changes in TBFM and/or TBLM mediate changes in inflammatory markers, and some authors suggest fat loss actually precipitates an improved inflammatory profile (Kelly et al., 2007). However, other physiological adaptations unrelated to body composition may affect the inflammatory milieu, such as anti-inflammatory cytokines, lymphocyte characteristics, and various hormonal changes (Gleeson et al., 2011). Interestingly, while TUT showed reduced TNFα and IL-6, it was

inferior with regards to TBLM and TBFM, perhaps reflecting a response independent to changes in fat-mass. Nevertheless, the role of adiposity in the physiological response to training is a relevant topic of discussion. Namely, excessive fat mass and low muscle mass contribute to the development of T2DM (Cameron et al., 2009), and in the present study 10 weeks of CET elicited reductions in TBFM alongside increased TBLM. Although some hypertrophy is expected due to the unaccustomed status of participants, the improvement in previous RT data suggest TUT is equally effective as conventional RT for hypertrophy (Tanimoto et al., 2008; Young & Bilby, 1993). By comparison, Donges et al. (2013) showed reduced TBFM without changes in TBLM after 12 weeks of CET, although this intervention improved insulin sensitivity. That said, other similar studies have incorporated greater AT volume (at least 30 min per session) within training interventions (Bharath et al., 2018). Thus, it is possible that a greater emphasis on AT within the CET framework would provide different body composition, inflammatory and/or metabolic adaptations.

This is the first study to explore TUT within a CET framework and some novel findings were evident with regards to functional fitness parameters. Specifically, TUT appeared to confer a benefit for aerobic fitness, while CET provided superior strength gains. Due to the higher mechanical stress and faster contraction speed of CET, it is possible that greater neuromuscular adaptations occurred within this group (Bottaro et al., 2007) explaining the observed difference in strength outcomes (Young & Bilby, 1993). Although it is established that higher-resistance training will improve strength (Bottaro et al., 2007), the prolonged time exposure in TUT may provide an avenue to target endurance adaptations, or indeed metabolic parameters. Ultimately, the application of a prolonged loading stimulus through slow-speed lifting seems to confer some benefit in the absence of high

mechanical loads in this sedentary population (Tanimoto et al., 2008; Young & Bilby, 1993). Again, the stimulus-specific response highlights the ability to manipulate the stimulus to gain desired physiological outcomes within a concurrent training program.

Limitations

The applied nature of this research provides sound ecological validity, although some methodological limitations are acknowledged. In particular, two additional blood markers (IL-1β and IL-1ra) were to be included in blood panels; however, across the cohort the plasma concentration was below the detectable limit of the measuring device and could not be included in statistical analyses. This pair of immunomodulators contribute greatly to the inflammatory pathway and in their absence, it is more difficult to infer clinical significance. Moreover, the use of older, sedentary populations in the present study limits the application to similar individuals. More data are needed to establish a possible rationale for broader application.

Conclusions

Overall, the effect of training on inflammatory biomarkers showed some benefit of TUT compared to CET. That said, this may be independent of body composition, as CET showed the greatest effect on TBLM and TBFM. Mode-specific adaptations were evident with increased endurance pursuant to TUT and greater strength gains in CET. For older adults seeking to reduce the risk of T2DM, modification of loading strategies through TUT seems to be inferior with regards to body composition; however, there may be a rationale for TUT to reduce inflammatory markers.

Chapter 5

Study 3

As based on the manuscript:

The specificity of concurrent exercise training; relationships between responses in training load, functional capacity, inflammation, and insulin resistance.

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Abstract

Purpose: To assess the relationship of changes in fitness and body composition markers following concurrent training (CET) with the associated changes in the key biomarkers of interleukin (IL)-6, tumour necrosis factor α (TNFα), and insulin resistance (HOMA-IR). Further, to examine the association of training load indices (volume-load and stimulus exposure; SE) on the aforementioned parameters. **Methods**: Thirty-eight sedentary adults underwent 10 weeks of CET. Changes in total-body lean (TBLM) and fat-mass (TBFM), peak oxygen consumption (VO_{2peak}) and peak quadriceps strength were assessed. Plasma concentrations of IL-6, TNFα, and HOMA-IR were also measured in the fasting state. The changes following training were examined in a linear regression model to explain the variance of changes in IL-6, TNFα, and HOMA-IR. Further, volume-load and SE were investigated to explain variance in changes in TBLM, TBFM, VO_{2peak}, and strength. **Results**: The change in IL-6 could be explained by the change in strength and TBLM ($y = 0.423 – (0.035 \times Strength_{change}) + (0.706 \times TBLM_{change})$). $TNF\alpha_{change}$ could be explained by the change in strength ($y = 0.439 – (0.007 \times Strength_{change})$). No predictors were significant in a linear model for HOMA-IR. Volume-load explained the variance of $Strength_{change}$ ($y = 3.24 + (0.137 \times volume\text{-}load)$; $p = 0.023$) and $VO_{2peakchange}$ ($y = 0.925 + (0.013 \times volume\text{-}load)$; $p = 0.022$). TNFα change was significantly correlated with volume-load (rho = -0.404), although this was no longer significant when controlling for $Strength_{change}$. **Conclusions**: During concurrent training with standardised AT, changes in maximal strength best explain the variance in IL-6 and TNFα changes. Overall volume-loads may impact upon strength and VO_{2peak} changes, but any effect on disease biomarkers is more closely related to strength. Individuals seeking to reduce IL-6 and TNFα may benefit from incorporating muscle strengthening activities in a CET design.

Introduction

Engagement in regular exercise training is reported to offset the deleterious effects of chronic physical inactivity, including poor glucose regulation (Halse et al., 2001) and elevated systemic inflammation (Pradhan, 2007). Commonly, aerobic endurance training (AT) is used to enhance aerobic capacity, reduce fat mass, and increase cardiorespiratory function (Petersen & Pedersen, 2005). Conversely, resistance training (RT) provides increased muscular strength and hypertrophy (Braith & Stewart, 2006; Hurley et al., 2011). To maximise the respective adaptive responses, it may be appropriate to combine AT and RT within a training program, termed concurrent training (CET) (Braith & Stewart, 2006; Burton et al., 2017b). Despite potential for interference in trained persons (Fyfe et al., 2014), in untrained individuals there may be a synergistic effect whereby adaptation to both modes is evident when a 50% dose of each modality is provided (Donges et al., 2013; Glynn et al., 2015; Jorge et al., 2011). However, current evidence remains ambiguous as to the relationship between the extent of the training stimulus from CET, and the ensuing functional adaptations in fitness, strength or body composition. Accordingly, further understanding of the relationship between CET training load and ensuing adaptations in functional capacity and inflammatory and metabolic parameters is required to guide more refined exercise prescription.

Disease-related biomarkers such as insulin resistance, and the inflammatory cytokines interleukin (IL)-6 and tumour necrosis factor-α (TNFα), have shown mechanistic importance and are among the most physiologically relevant measures of cardiometabolic risk (Pradhan et al., 2001; Rocha & Libby, 2009). Subsequent to a poor lifestyle-induced health status, elevated levels of IL-6 and TNFα predispose the development of CVD and T2DM (Pradhan, 2007), and show a prognostic relationship with eventual disease onset

(Ajmal et al., 2014). Moreover, cellular resistance to insulin action is among the primary physiological perturbations that leads to metabolic syndrome and T2DM (Tripathy et al., 2000) and amelioration of insulin sensitivity may represent a reduced risk of these diseases. In turn, exercise-induced adaptations of increased aerobic capacity (Hawley, 2002), strength (Hurley et al., 2011), TBLM (Marcotte et al., 2015) and decreased TBFM (Despres et al., 1991) coincide with a reduction in overall cardiometabolic risk factors (Gleeson et al., 2011). Thus, by seeking to simultaneously improve these parameters, CET may be appropriate to decrease the overall risk of CVD and T2DM in untrained individuals (Donges et al., 2013). Although CET can theoretically provide an appropriate dual-mode training stimulus, further understanding of the extent of adaptation in respective functional capacities with ensuing changes in markers predictive of disease risk remain limited (Garber et al., 2011).

Substantial epidemiological evidence indicates that increasing skeletal muscle mass is associated with decreased clinical biomarkers such as insulin resistance (Moon, 2014), and inflammatory cytokines including IL-6 and TNFα (Schaap et al., 2006; Visser et al., 2002). Separately, research suggests cardiorespiratory fitness shows a negative association with inflammatory cytokines (Aronson et al., 2004), and indeed that changes in endurance capacity following CET correlate with a decreased inflammatory profile (Balducci et al., 2012). Thus, CET is reported to improve body composition, strength, and fitness capacity, as well as biomarkers such as IL-6, TNFα, and HOMA-IR; although, the extent to which the changes in these markers can be explained by the aforementioned parameters is unclear.

Given the generic nature of the exercise prescription literature, cross-sectional studies are not necessarily indicative of what is observed following short-term training interventions (Garber et al., 2011). In order to maximise physiological adaptations, practitioners must tailor training variables, such as mode, volume or intensity, to optimise individual outcomes (Burton et al., 2017b). Indeed, overall resistance training volume may be associated with increased hypertrophy (Schoenfeld et al., 2017) and strength (Rana et al., 2008). Moreover, improvements in IL-6, TNF, and HOMA-IR during CET may be specific to the training loads applied (Bruun et al., 2006; Touvra et al., 2011). However, further clarity of the relationship between CET training load and ensuing adaptations in functional capacity is required to allow more appropriate and refined exercise prescription.

Thus, the aims of the present study are twofold; firstly, to quantify the association between changes in primary predictors (lean mass, fat mass, strength and endurance capacity) and clinical disease-related outcome variables (IL-6, TNFα, and insulin resistance) following 10 weeks of training. Secondly, to further examine the association of training loads on subsequent changes in these primary predictors. It is hypothesised, firstly, that increased fitness capacity, alongside reduced adiposity and increased skeletal muscle, will explain reductions in IL-6, TNFα and insulin resistance. Secondly, a larger overall training volume-load is expected to be associated with improved strength and endurance, reduced fat mass, and a reduction in the aforementioned disease indicators.

Methods

Participants

Inclusion criteria required that participants be aged 50-75y, non-smoking, sedentary (< 2 exercise sessions per week) and free from known chronic diseases. Fifty-three participants from within the local region volunteered to take part in the present study, and 38 completed the intervention period. The resulting cohort comprised 26 women and 12 men (age 57 ± 5 y). Institutional research ethics approval was granted (Ref. ETH16-0742) and all participants provided written informed consent for experimental procedures, as well as a formal pre-exercise screening.

Overview

Participants attended testing sessions before and after the 10-week intervention, following an overnight fast and at a standardised time between 06:00-09:00 h. The sessions involved a dual-energy x-ray absorptiometry (DEXA) scan for body composition, venous blood sample for disease biomarkers, strength assessment, and maximal aerobic exercise test. Participants completed a food and activity record for the 24 h preceding baseline testing, and this document was returned before post-testing with instructions to replicate as closely as possible. For reliability of repeated measures, participants were instructed to abstain from vigorous activity for 72 h before both testing sessions. Subsequently, based on baseline age, sex, body mass index, and VO_{2peak}, participants were stratified and randomly allocated to CET (n=18), TUT (n=18) or CRL (n=17). Subjects trained 3 times per week for 10 weeks, and those in CRL were instructed to maintain habitual lifestyle behaviours, which was checked throughout the duration of the study. Final group numbers were CRL (n=13), CET (n=13) and TUT (n=12).

Venous Blood Samples

After an overnight fast, whole blood was extracted from the median cubital vein. Samples were stored in ethylenediaminetetraacetic acid tubes and immediately centrifuged. Supernatants were aliquoted into low-protein-binding tubes and stored at -80ºC until analysis. Plasma concentrations of IL-6, TNFα and insulin were measured using a chemiluminescent immunoassay (Magpix, Luminex Corporation, Texas, USA) and the data produced in the related software. Separately, plasma glucose was measured using an oxidase-peroxidase reagent kit with an inbuilt calibrator (Fisher, Pittsburgh, USA), and insulin resistance calculated using the homeostasis model of assessment (HOMA)-2 computer model (Wallace et al., 2004). The assays used demonstrated intra-assay variability of <13% for IL-6 and TNFα, and <10% for the other analytes, with negligible cross-reactivity. Accordingly, the selected outcome variables used for the present study are IL-6, TNFα and insulin resistance (HOMA-IR).

Body Composition

With no metallic clothing or body fixtures, participants completed a total-body DEXA scan (Lunar Prodigy, GE Medical, Milwaukee, USA). Scanning settings were selected automatically based on subject size, using a resolution of 4.8 x 13mm. Manufacturer software (Encore 16, GE Medical, Milwaukee, USA) calculated lean mass (TBLM) and fat mass (TBFM) for the whole body (Nana et al., 2015).

Fitness Testing

Maximal isometric strength of the right knee extensors was measured using an isokinetic dynamometer (Biodex Medical Systems, Shirley, USA). Following a cycling-based

warm-up (2 min at 50 W) participants were seated on the device with the tibiofemoral joint aligned with the axis of rotation, and the body fastened to minimise movement. Knee flexion was set at 80º and, following an auditory cue, subjects performed a 4 s sub-maximal knee extension. After a brief rest, a second trial was performed, this time at maximum effort. Peak isometric torque (in Nm) was recorded as the highest instantaneous value during the test and used in subsequent analyses.

Participants underwent a maximal graded exercise test on a cycle ergometer (Wattbike, Nottingham, UK) to provide peak oxygen consumption (VO_{2peak}). The test comprised 1-min work periods at 25 W increments and was performed until volitional exhaustion. Oxygen consumption was recorded in a portable gas analyser (Medgraphics, St Paul, USA). Post-test, VO_{2peak} was recorded as the mean value during the 3 highest consecutive 10-s recording periods during the test.

Training Procedures

Training groups trained 3 times per week for 10 weeks. Subjects in the CET group performed 30-40 minutes of full-body RT at a cadence of 1.5-1.5 s (1-sec concentric and eccentric phases) while TUT performed the same volume of repetitions with a cadence of 3-3 sec. During RT, participants were guided using an audible metronome, whereby aural cues dictated movement tempo. Using 0.5 s intervals, CET participants were instructed to lift with 3 counts for both concentric and eccentric phases, while TUT participants lifted with 6 counts for both phases, resulting in 3 and 6 s of time-under-tension per repetition respectively. Constant supervision and verbal feedback ensured compliance and understanding throughout.

To compare between respective RT stimuli, training loads were recorded as the total volume-load and stimulus exposure for the entire 10-week period. Volume-load is defined as [repetitions x weight used] (Schoenfeld et al. (2017) and SE as [volume-load x time-under-tension]. Aerobic training was undertaken using non-load-bearing modalities (cycling and rowing) at an intensity of 65-80% of age-predicted maximal heart rate for 15-20 min, and was identical across both groups. Control subjects were instructed to maintain normal lifestyle behaviours, which was confirmed via a lifestyle questionnaire (Godin & Shephard, 1985) and regular verbal feedback.

Statistical Analysis

Absolute change values between pre- to post-training were used for statistical analyses, with a one-way ANOVA to compare differences between conditions. The selected dependent variables were change values for the biomarkers IL-6, TNFα, and HOMA-IR ($IL\text{-}6_{change}$, $TNF\alpha_{change}$, and IR_{change}), and these were analysed in a correlation matrix with the changes in the independent variables (age, $TBLM_{change}$, $TBFM_{change}$, $Strength_{change}$, $VO_{2peakchange}$, volume-load, and SE) with correlations quantified via Pearson's r for normally distributed variables and Spearman's rho for non-normal variables.

Subsequently, stepwise linear regression analyses were used to investigate the relationship the chosen predictors to variance of changes in IL-6, TNFα, and insulin resistance (HOMA-IR). $TNF\alpha_{change}$ demonstrated heteroscedasticity and thus was log-transformed prior to analysis. A secondary analysis investigated the role of training load (i.e. volume-load rather than SE due to collinearity) in a linear regression model for the relationship with $TBLM_{change}$, $TBFM_{change}$, $Strength_{change}$, and $VO_{2peakchange}$ to quantify the association of training dose with these parameters. Selection of these outcomes was based

on the existing evidence for an association with inflammation and insulin resistance. One additional measure, visceral adipose tissue (VAT) was considered given it shows a strong relationship with IL-6 (Pou et al., 2007a) and impaired glucose homeostasis (Pouliot et al., 1992). However, investigation showed that it did not strengthen statistical analyses, and thus it is not included in the final equations to minimise potential overfitting of regression models.

Highly correlated predictors were removed from the model when tolerance statistics showed values < 0.1, indicating unacceptable collinearity. Partial correlations, unstandardised coefficients, and p-values are reported using a significance level of $p \leq 0.05$. Results are shown for the regression models firstly using all independent variables, and secondly using only those which showed a significant correlation with the dependent variable. Scatter plots for the latter are included to highlight group-specific responses. All analyses were performed using the Statistics Package for Social Sciences (v. 25, IBM, Armonk, USA).

Results

Table 5.1 shows the absolute change values between pre- to post-training for each group. Significant differences existed between CRL and CET and TUT for the change in IL-6 and TNFα, respectively ($p < 0.05$). Further, the change in strength was increased in CET and change in VO_{2peak} in TUT compared to CRL respectively ($p < 0.05$). As shown in Table 5.2, significant correlations existed between IL-6change and $VO_{2peakchange}$ (rho = -0.353, p = 0.041). The change in TNFα correlated with the change in strength (rho = -0.405, p = 0.026), VO_{2peak} (rho = -0.384, p = 0.025), volume-load (rho = -0.404, p = 0.016), and SE (rho = -0.472, p = 0.004). No significant correlations were present for

HOMA-IR ($p > 0.05$). Separately, volume-load was significantly correlated with $Strength_{change}$ (rho = 0.382, p = 0.028), $VO_{2peakchange}$ (rho = 0.380, p = 0.020), and SE (rho = 0.856, $p < 0.001$), while SE correlated with $TBFM_{change}$ (rho = -0.327, p = 0.048), $Strength_{change}$ (rho = 0.363, p = 0.038) and $VO_{2peakchange}$ (rho = 0.496, p = 0.002).

Table 5.1: Changes in physiological parameters following the 10-week intervention. Normally distributed data are shown as mean ± SD, and non-normal variables as median (interquartile range).

	CRL	**CET**	**TUT**
IL-6_{change} ($pg \cdot mL^{-1}$)	0.6 (-0.2, 3.1)	-0.2 (-1.0, 0.2)*	0.0 (-1.0, 0.1)*
$TNF\alpha_{change}$ ($pg \cdot mL^{-1}$)	0.3 (-0.2, 8.6)	-0.4 (-0.9, -0.1)*	-0.6 (-1.1, 0.1)*
$HOMA\text{-}IR_{change}$ (AU)	-0.1 ± 0.5	0.0 ± 0.4	-0.3 ± 0.5
$Strength_{change}$ (Nm)	-1.1 ± 27.3	36.2 ± 35.7*	25.1 ± 21.4
$VO_{2peakchange}$ ($mL \cdot kg \cdot min^{-1}$)	0.7 (-1.2, 2.4)	2.7 (1.5, 3.4)	4.0 (1.6, 5.3)*
$TBLM_{change}$ (kg)	0.5 ± 1.1	1.0 ± 0.8	0.5 ± 0.8
$TBFM_{change}$ (kg)	0.1 ± 1.5	-0.8 ± 1.5	-0.8 ± 0.9
Volume-load (AU)		170 (138, 239)	137 (116, 191)
SE (AU)		510 (414, 716)	823 (696, 1145)#

CRL, control group; CET, concurrent training group; TUT, time-under-tension training group; IL-6, interleukin-6; TNFα, tumour necrosis factor α; HOMA-IR, homeostasis model for assessment of insulin resistance; VO_{2peak}, peak oxygen consumption; TBLM, total-body lean mass; TBFM, total-body fat mass; SE, stimulus exposure.

*denotes significant difference vs CRL in one-way ANOVA.

# denotes significant difference vs CET in one-way ANOVA

There was no interaction between the experimental groups ($p > 0.05$) and accordingly regression models and correlation data are pooled as one group. As described in Table 5.3 and Figure 5.1, regression analysis revealed that IL-6_{change} could be explained by the change in strength and TBLM ($y = 0.423 – (0.035 \times Strength_{change}) + (0.706 \times TBLM_{change})$). Tolerance statistics were > 0.7 for all variables in this model. As shown in Table 5.4 and Figure 5.2, log TNFα_{change} could be explained by the change in strength ($y = 0.439 – (0.007 \times Strength_{change})$). In Table 5.5 and Figure 5.3, for HOMA-IR no predictors were significant in a linear model, and no significant correlations were present with any variable ($p > 0.05$).

For training load variables, as shown in Table 5.4, TNFα_{change} was negatively correlated with total volume-load (rho = -0.404, p = 0.016). However, when controlling for $Strength_{change}$, this correlation was no longer significant (p = 0.148). Separately, in a linear regression model, overall volume-load explained the variance of $Strength_{change}$ ($y = 3.24 + (0.137 \times volume\text{-}load)$; p = 0.023) and $VO_{2peakchange}$ ($y = 0.925 + (0.013 \times volume\text{-}load)$; p = 0.022). Conversely, volume-load did not significantly explain the variance in $TBLM_{change}$ ($y = 0.431 + (0.002 \times volume\text{-}load)$; p = 0.072) or $TBFM_{change}$ ($y = 0.002 – (0.004 \times volume\text{-}load)$; p = 0.076).

Table 5.2: Correlation matrix of changes in biomarkers, body composition, fitness capacity, and training loads following the 10-week intervention. Normally distributed data show Pearson's correlation coefficient denoted by #. Non-normally distributed variables show Spearman's correlation coefficient.

	IL-6c$_{hange}$	Log TNFα$_{change}$	HOMA-IR$_{change}$	Volume-Load	SE
TBLM$_{change}$	0.275	0.122	-0.045$^{\#}$	0.273	0.115
TBFM$_{change}$	0.082	0.093	0.001$^{\#}$	-0.297	-0.327*
Strength$_{change}$	-0.325	-0.405*	0.136	0.382*	0.363*
$VO_{2peakchange}$	-0.353*	-0.384*	0.322	0.380*	0.496*
Volume-Load	-0.257	-0.404*	-0.038		0.856*
SE	-0.290	-0.472*	-0.069	0.856*	

IL-6, interleukin-6; TNFα, tumour necrosis factor-α; HOMA-IR, homeostatic model assessment of insulin resistance; TBLM, total-body lean mass; TBFM, total-body fat mass; VO_{2peak}, peak oxygen consumption; SE, stimulus exposure.

*denotes significance at $p < 0.05$.

Table 5.3: Linear regression models with unstandardised coefficients (β) and significance level (*p*) for predictors of IL-6_{change}. R and p values for regression models also shown. Model A includes all predictors of IL-6 and model B includes only those that were significant in Model A.

	Correlation (r)	**β**	***p***	**Model**
A) IL-6_{change}				*r = 0.761*
Age	-0.003	-0.021	0.684	*p = 0.002*
$Strength_{change}$	-0.598	-0.032	0.002*	
$TBLM_{change}$	0.298	0.902	0.005*	
$TBFM_{change}$	0.264	0.150	0.450	
$VO_{2peakchange}$	-0.239	0.087	0.332	
Volume-Load	-0.387	-0.005	0.101	
B) IL-6_{change}				*r = 0.695*
$Strength_{change}$	-0.598	-0.035	< 0.001*	*p < 0.001*
$TBLM_{change}$	0.298	0.706	0.016*	

IL-6, interleukin-6; TBLM, total-body lean mass; TBFM, total-body fat mass; VO_{2peak}, peak oxygen consumption.

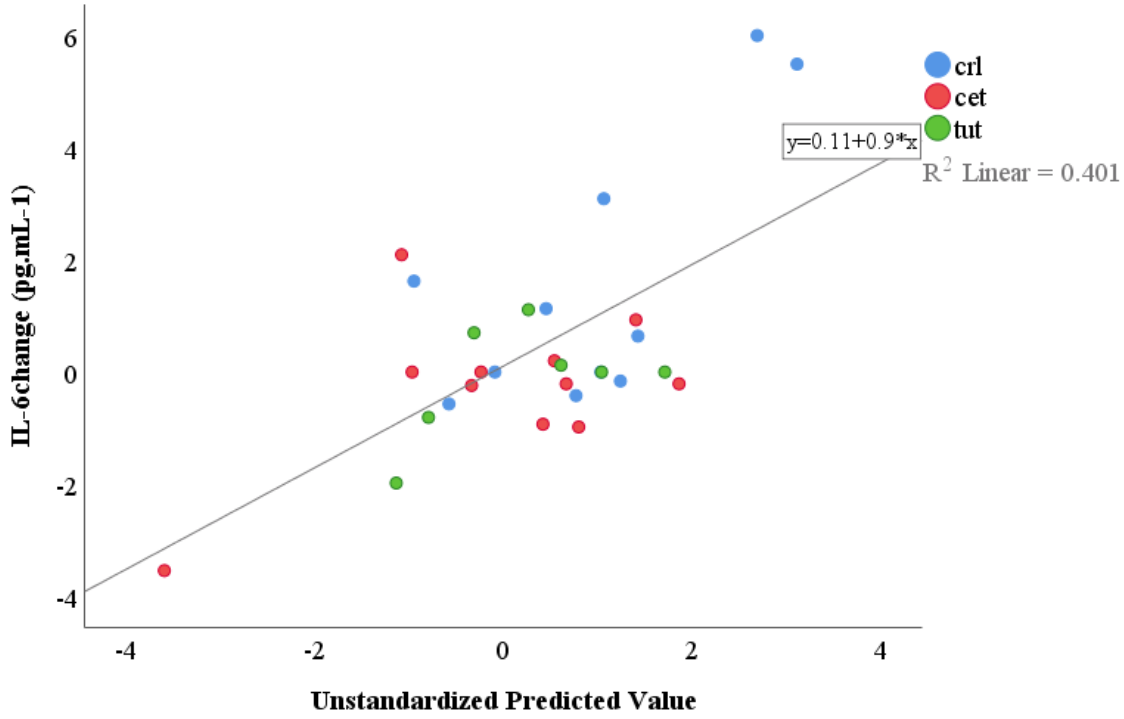

Figure 5.1: Scatter plot of changes in IL-6 against unstandardised predicted values from linear regression model B by group.

Table 5.4: Linear regression models with unstandardised coefficients (β) and significance level (p) for predictors of $TNF\alpha_{change}$. R and p values for regression models also shown. Model A includes all predictors for TNFα and model B includes only those that were significant in Model A.

	Correlation (r)	**β**	***p***	**Model**
A) Log $TNF\alpha_{change}$				*r = 0.675*
Age	0.053	0.006	0.614	*p = 0.019*
$Strength_{change}$	-0.572	-0.006	0.011*	
$TBLM_{change}$	0.093	0.094	0.211	
$TBFM_{change}$	0.280	0.035	0.480	
$VO_{2peakchange}$	-0.215	0.024	0.302	
Volume-Load	-0.433	-0.001	0.084	
B) Log $TNF\alpha_{change}$				*r = 0.572*
$Strength_{change}$	-0.572	-0.007	0.001*	*p = 0.001*

TNFα, tumour necrosis factor α; TBLM, total-body lean mass; TBFM, total-body fat mass; VO_{2peak}, peak oxygen consumption.

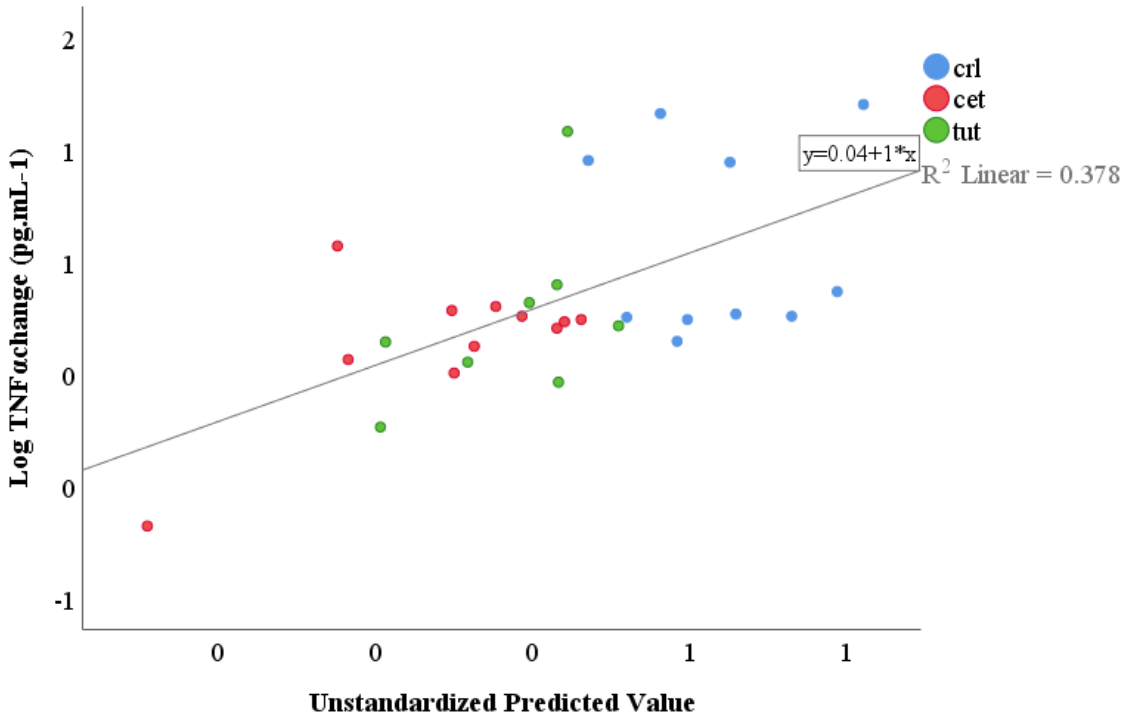

Figure 5.2: Scatter plot of changes in TNFα against unstandardised predicted values from linear regression model B by group.

Table 5.5: Linear regression models with unstandardised coefficients (β) and significance level (p) for predictors of HOMA-IR_{change}. R and p values for regression model also shown.

	Correlation (r)	**β**	***p***	**Model**
HOMA-IR_{change}				*r = 0.304*
Age	-0.056	< 0.001	0.991	*p = 0.889*
$Strength_{change}$	0.194	0.001	0.725	
$TBLM_{change}$	-0.007	0.003	0.978	
$TBFM_{change}$	-0.045	0.002	0.979	
$VO_{2peakchange}$	0.292	0.036	0.274	
Volume-Load	0.071	< 0.001	0.787	

HOMA-IR, homeostasis model of assessment for insulin resistance; TBLM, total-body lean mass; TBFM, total-body fat mass; VO_{2peak}, peak oxygen consumption.

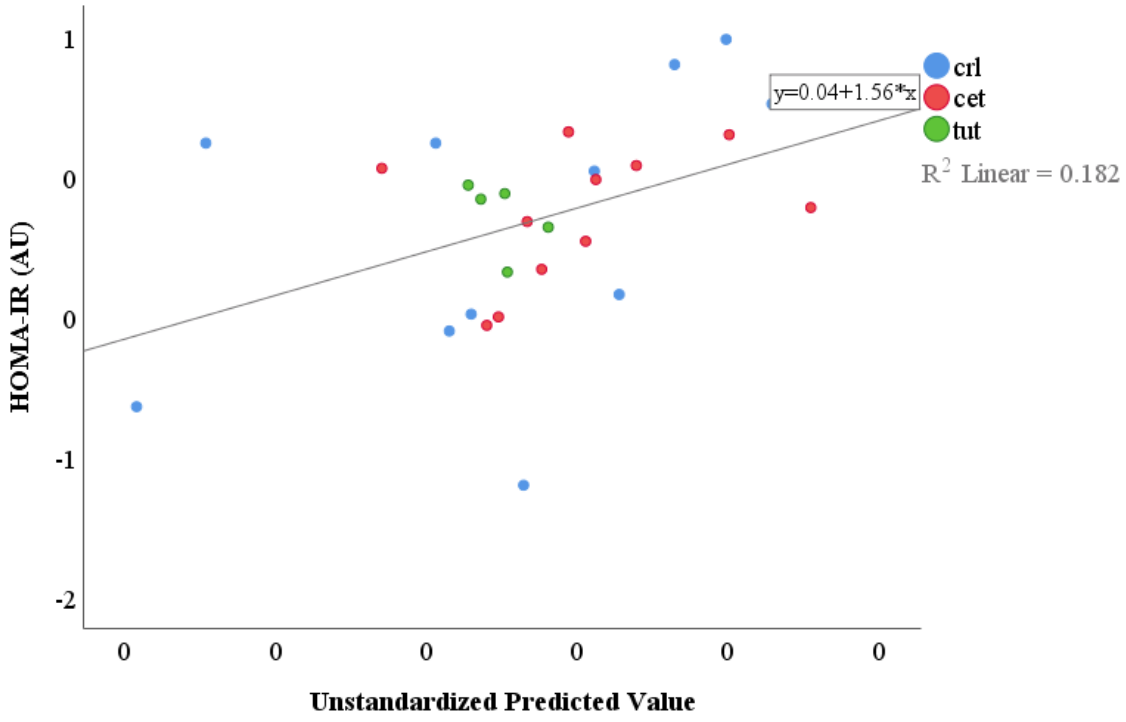

Figure 5.3: Scatter plot of changes in HOMA-IR against unstandardised predicted values from linear regression model by group.

Discussion

The purpose of this study was to investigate the relationships between changes in fasting disease-related biomarkers (IL-6, TNFα, and HOMA-IR) and changes in anthropometrical, fitness, and training load variables following a 10-week concurrent training intervention. The change in IL-6 was explained by changes in strength and TBLM, whilst TNF changes were explained only by a change in strength. Separately, training load variables showed that volume-load was inversely correlated with $TNF\alpha_{change}$ (rho = -0.404, p = 0.016), although this was no longer significant when controlling for changes in strength. Collectively, these results suggest that the strength gains derived from the RT within concurrent training (when AT is standardised) are associated with positive changes in inflammatory cytokines (IL-6 and TNFα).

IL-6 is a key biomarker of systemic inflammation and cardiometabolic risk (Koenig et al., 2006), and a significant association was evident between the change in strength and TBLM and the change in IL-6. This is a novel finding, particularly given that strength outcomes showed a stronger association than either VO_{2peak} or TBFM, both of which have demonstrated a cross-sectional association with systemic inflammation (Fischer et al., 2007; Panagiotakos et al., 2005; Park et al., 2005). Moreover, muscle strengthening activities such as RT are considered inferior to endurance exercise for anti-inflammatory effects (Braith & Stewart, 2006). Older adults have shown an inverse relationship between muscular strength levels and inflammatory cytokines, although this is typically measured cross-sectionally by hand grip strength (Visser et al., 2002). Accordingly, although endurance-based training is typically favoured for reducing cardiometabolic risk factors (Garber et al., 2011), increasing strength via CET showed a stronger association with the corresponding reduction in IL-6.

TNFα shows a mechanistic role in development of CVD and T2DM (Hotamisligil, 2006). Evidence points to a negative relationship of TNFα and muscle hypertrophy (Ogawa et al., 2010), as elevated cytokines are suggested to inhibit functional strength, and thus an increase in strength may accompany decreased inflammation (Pereira et al., 2009). This is supported by studies showing the age-related decline in strength to be associated with increased TNFα in older adults (Bruunsgaard et al., 2004). Substantial evidence demonstrates the association of increased TNFα with increased adiposity (Pedersen et al., 2003) and decreased aerobic capacity (Hosick et al., 2013). However, the present study shows the variance in changes in TNFα could not be explained by either TBFM or VO_{2peak}. In contrast, the strength gains showed stronger explanation of the reduction in TNFα, which may be related to the use of dual-mode CET with only the RT portion modified, especially given AT programs are reported to reduce TNFα (Straczkowski et al., 2001). Further, the reduction in TNFα may permit greater strength gains, providing a reciprocal mechanism for increased adaptation (Pereira et al., 2009). Regardless, considering TNFα was explained mostly by changes in strength, prioritising strength training during CET may be effective in this regard.

Insulin resistance represents a key mechanistic predecessor for metabolic syndrome and T2DM (Alberti et al., 2006). Indeed, reduced insulin sensitivity and action are the major physiological perturbations that predicate this disease (Tripathy et al., 2000), and concurrent training is suggested to improve these parameters in untrained participants (Azarbayjani et al., 2014). However, in the present study there were no significant changes in HOMA-IR following training, and none of the selected predictor variables were significant in a linear regression model. In support, healthy adults performing CET

for 6 months showed no significant relationship between the change in HOMA-IR and any measure of body composition (TBLM, TBFM, or BF%) (Glynn et al., 2015). Conversely, Osuka et al. (2017) reported a significant correlation (r = -0.512) between the change in HOMA-IR and the change in TBLM after 12 weeks of CET in older adults. Interestingly, Glouzon et al. (2015) found that among overweight women who performed 6 months of CET, participants who decreased TBLM showed a corresponding decrease in HOMA-IR, while those who increased TBLM (approximately half the cohort) maintained baseline levels of HOMA-IR. Similarly, the change in HOMA-IR was negatively correlated with the change in VO_{2peak}; however, this was significant only for the lower tertile of VO_{2peak} values. Thus, there may be varying responses depending on whether individuals demonstrate higher or lower changes in aerobic fitness (Glouzon et al., 2015). Collectively, such differences may relate to the participant characteristics, and the specificity of the loads applied (Garber et al., 2011), thus highlighting the need to understand the role of exercise prescription variables.

Appropriate delivery of training modalities and doses is essential to maximise the benefits of exercise (Kraemer & Ratamess, 2004) as volume-matched exercise interventions typically demonstrate equivalent changes in inflammatory cytokines (Balducci et al., 2010; Jorge et al., 2011). Hence, the negative association of volume-load with IL-6 observed here may provide further insight into the specificity of exercise prescription underlying the earlier divergent research findings. In the present study, total volume-load was associated with $Strength_{change}$ and $VO_{2peakchange}$, but not $TBLM_{change}$ or $TBFM_{change}$ in a linear regression model. Overall training volume is considered important for training design and strongly influences physiological adaptations (Schoenfeld et al., 2017). It is generally understood that greater overall volume-loads produce greater strength gains

(Galvao & Taaffe, 2005; McBride et al., 2003). Also, increasing training volumes are related to increased hypertrophy (Schoenfeld et al., 2017) and possibly fat loss during RT, although this is not always the case for the latter (McBride et al., 2003). Whilst significant correlations were shown between SE and $TBFM_{change}$, $Strength_{change}$, and $VO_{2peakchange}$, SE was excluded from regression models due to collinearity with volume-load. Hence, greater exposure to training (i.e. more time spent under load) may favour decreased TBFM., Indeed, this is supported by acute-response data that show greater overall energy expenditure with a prolonged, TUT-style exercise bout (Scott, 2012). However, the collinearity with volume-load (given the method of calculation for SE) makes it difficult to distinguish between volume effects and those related to SE in the current analyses.

Limitations

The applied nature of the present study carries a set of inherent limitations which must be acknowledged. Specifically, for the purposes of the present analysis all participants were pooled, given that interactions of group were excluded from the final regression models. It is possible, for example, that men and women may respond differently to the present interventions, although given the relatively small sample size this was not evident. Similarly, the pooling of the three experimental groups allows for greater statistical power, but the study remains relatively under-powered. Further, although multicollinearity was accounted for in the present analysis by applying a tolerance limit to the regression model, these physiological parameters are often closely related, and may be influenced by other factors. Finally, given this was a CET intervention with the AT component standardised across both training groups, only the RT loads are used in the present analyses. Although this method is more specific to the modalities used (i.e. CET

and TUT), the aerobic portion is likely to influence the overall outcomes, and thus should not be ignored when considering the practical implications of the present findings.

Conclusions

After 10 weeks of concurrent training, the change in quadriceps strength showed the strongest independent association with changes in IL-6 and TNFα. Overall RT training volume demonstrated an inverse relationship with changes in both IL-6 and TNFα, although not independently of the strength change. Thus, within a CET framework, particular attention should be paid to the role of overall training volumes, although this may be less important than the strength adaptations provided. More broadly, emphasising strength gains within a CET design may provide an avenue to decrease IL-6 and TNFα levels. For CET in sedentary populations, exercise prescription should be tailored to individual needs, and the present study provides a possible rationale for focussing upon muscle strengthening exercises within this design. Further, for evidence-based exercise prescription, it is important to consider that cross-sectional data may not always predict the findings of randomised trials. Therefore, more intervention studies are needed to fully understand the practical implications of CET design.

Chapter 6

Discussion

Overview of Aims and Findings

This thesis examined the effects of concurrent exercise training, with modified RT to emphasise TUT, in sedentary individuals. Specifically, the present study compared TUT with conventional CET strategies on inflammatory and cardiometabolic disease markers, body composition, and physical fitness capacity. The objectives were to determine the effects of CET versus TUT on:

1. The response of blood-based inflammatory and cardiometabolic disease indicators.
2. Whole-body and region-specific lean and fat mass, as well as muscle thickness determined by B-mode ultrasound.
3. Functional measurements of maximal strength and aerobic capacity.
4. The relationship between key prognostic indicators and changes in body composition or fitness and, in turn, between specific training load indices and the associated physiological changes following training .

In summary of key results, following the 10-week training intervention, inflammatory cytokines showed a condition-dependent response whereby IL-6 was reduced in CET, TNFα was reduced in TUT, and no exercise-induced change was evident for CRP or MCP-1. However, these changes were accompanied by minimal alteration in glucose homeostasis, including no significant differences in c-peptide, glucagon, and GLP-1. Of note, only fasting glucose was reduced in all groups, including the control group. Further, neither CET nor TUT showed any significant differences for changes in for CVD biomarkers (i.e. adhesion molecules, vWF. The only training-induced improvements were evident for p-selectin, which was reduced in CET.

The clearest group-dependent effect was evident for body composition, which showed that only CET increased TBLM and decreased TBFM. As further evidence, thickness of *m. vastus lateralis* was only increased by CET. In contrast, region-specific measures indicated reduced VAT in CET only, and reduced SAT in TUT. Physical fitness parameters also showed a divergent response, with the greatest strength gains in CET, while both CET and TUT improved PPO, and TUT showed a superior increase in VO_{2peak}.

Finally, in regard to the role of training dose responses, regression analyses revealed that the change in IL-6 could be explained by the change in strength and TBLM, and the change in TNFα could be explained by the change in strength only. The total volume-load correlated negatively with changes in IL-6 and TNFα. These correlations were not significant when controlling for strength changes, suggesting that strength gains were most strongly associated with decreased inflammatory markers, rather than volume-load *per se*.

Accordingly, the following sections will discuss the present findings across a number of particular areas of research, including i) inflammatory biomarkers, ii) glucose homeostasis, iii) CVD biomarkers, iv) body composition, and v) physical fitness. Further investigation is made into the practical considerations of training prescription, and the role of CET modalities.

Effect of CET and TUT on Inflammatory Cytokines

Resulting from chronic inactivity and excessive adiposity, a state of low-grade inflammation elevates the risk of cardiometabolic diseases (Pradhan, 2007), and is characterised by increased concentrations of pro-inflammatory cytokines (Pearson et al.,

2003). In the present thesis, only CET demonstrated reduced IL-6 after the 10-week training intervention. As an explanation, IL-6 is associated with increased adiposity (Park et al., 2005) and low muscle mass (Visser et al., 2002), and the superior changes in TBLM and TBFM from CET may have predicated the change in IL-6. Moreover, the fact that CET showed the largest reductions in VAT provides further credence to the notion that reduced adiposity may have contributed to the contrasting outcomes between CET and TUT (Park et al., 2005). Previous CET studies have shown that in sedentary participants, 12 weeks of CET may be insufficient to produce changes in IL-6 when training volumes are relatively low (Stewart et al., 2007). Hence more training may be needed to differentiate a clearer exercise-induced effect (Nicklas et al., 2008) and the small differences in training load between TUT and CET may hold practical relevance for those aiming to manage the loading issues for sedentary individuals (Van Kan et al., 2009).

Despite significant reductions in IL-6 following CET, the clinical importance of these IL-6 changes is a key focal point. Indeed, Pradhan et al. (2001) reported that among a cohort of healthy women, the relative risk of future T2DM for increasing quartiles of IL-6 was 1.0 (<0.91 $pg{\cdot}mL^{-1}$), 2.5 (0.91-1.38 $pg{\cdot}mL^{-1}$), 4.1 (1.38-2.05 $pg{\cdot}mL^{-1}$), and 7.5 (>2.05 $pg{\cdot}mL^{-1}$) respectively. Within the present study, CET reduced IL-6 from 1.32 (95% CI 0.40-3.47) to 0.46 (0.23-0.64) $pg{\cdot}mL^{-1}$, reflecting a marked decrease in risk in accordance with the data from Pradhan et al. (2001). Thus, this represents a noteworthy finding, both because of the clinically significant result and because CET demonstrated a greater reduction compared to TUT and CRL, and thus may be considered a more appropriate training method for reductions in IL-6.

TNFα is a pro-inflammatory cytokine that contributes directly to development of insulin resistance, T2DM, and atherosclerosis (Hotamisligil, 2006; Kern et al., 2001; Zhang et al., 2006). In the present study, TNFα was decreased within TUT by 0.56 (0.03-0.93) $pg{\cdot}mL^{-1}$, but not in CET or CRL. The reduction in TUT did not coincide with improvements in TBLM, TBFM, or VAT. This is an unexpected finding given that TNFα is typically associated with VAT volume (Ziccardi et al., 2002). Thus, the reduction observed within TUT seems to have occurred independently of these precursors, and instead may have transpired through other physiological mechanisms (Gleeson et al., 2011) as a result of the specific training stimulus used. Namely, prolonged endurance-type exposure (both TUT and AT) seems to have preferentially altered TNFα. Previous acute-response data suggest a slower contraction stimuli increases the metabolic demands compared to slower or higher-resistance contractions (Burd et al., 2012; Scott, 2012). Further, aerobic training as an isolate mode has shown some efficacy to decrease TNFα (Straczkowski et al., 2001). Given this is the first study to identify a role for TUT, it may represent a complementary strategy that provides some endurance-like adaptations when used in conjunction with AT to decrease inflammatory markers of TNFα.

TNFα is known to respond to exercise training when there is an ancillary reduction in fat mass or adiposity, as similar CET studies conducted over 12 weeks show decreased TNFα alongside reduced abdominal adiposity (Donges et al., 2013; Ho et al., 2013). Of note, is that in both these instances the participants were defined as overweight as opposed to the current cohort who were not required to be overweight as an inclusion criterion. In contrast, sedentary men who underwent CET for 16 weeks showed no change in TNFα levels, with no changes in BMI or waist circumferences (Libardi et al., 2012). It is plausible that a number of other mechanisms such as anti-inflammatory cytokines and/or

lymphocyte characteristics may have influenced this outcome (Gleeson et al., 2011; Kasapis & Thompson, 2005), although were not measured in the present study.

Regardless, it is important to consider the clinical significance of the reduced TNFα finding given the low baseline values demonstrated across the participant cohort and large variability in training responses. As evidence, the mean TNFα level at baseline was ≤ 1.30 $pg{\cdot}mL^{-1}$ across all groups, suggesting a relatively low pre-training inflammatory state. According to Cesari et al. (2003) increased cardiovascular risk is present for values above 2.7 $pg{\cdot}mL^{-1}$, and more so for those above 8.7 $pg{\cdot}mL^{-1}$. Thus, although the within-group changes in TUT demonstrate statistical significance, the training-induced reduction in TNFα may not be overly meaningful in terms of modifying disease risk. Further, it has been reported that, above concentrations of 2.8 $pg{\cdot}mL^{-1}$ there is a linear trend between TNFα and the number of metabolic syndrome components present (You et al., 2008). Therefore, despite the positive finding within the present study, it is uncertain whether this represents a significant outcome in the clinical setting for disease risk amelioration.

Forming a key component of the inflammatory cascade, CRP was included in the present study as relevant to cardiometabolic disease prediction (Koenig et al., 2006). That said, CRP was unchanged across all groups following the 10-week training intervention. Given that CRP is closely related to IL-6 (Venugopal et al., 2005), it may be expected that training-induced changes in CRP would parallel those of its mechanistic precursor (Berg & Scherer, 2005). Increased adiposity is considered a key driver of elevated CRP concentrations, which are in turn heavily influenced by the upstream contribution of IL-6 (Kasapis & Thompson, 2005). As evidence, Campbell et al. (2009) found significant

reductions in CRP after 1 year of CET in obese, postmenopausal women, and that the change in CRP correlated with changes in TBFM and waist circumference, with no alteration in IL-6. Despite clear group-specific changes of lean and fat mass observed within this study, CRP was unchanged. In support, changes in CRP after training were not reported alongside changes in adiposity (Donges et al., 2010), despite improving simultaneously with training. Indeed, other mechanisms unrelated to body composition may influence the inflammatory milieu (Kasapis & Thompson, 2005). Previously, short-term CET performed 3 times per week has been effective to improve inflammatory markers such as CRP, although these changes are observed in participants with existing cardiometabolic diseases (Balducci et al., 2010) and further, the effect of CET may not be superior to AT alone within that population (Kadoglou et al., 2013; Kim, 2014).

By comparison, healthy individuals without existing diseases have demonstrated reduced CRP with CET-based interventions, although this is typically observed following longer training periods. For example, Ihalainen et al. (2018) reported decreased CRP alongside reductions in leptin, TNFα, and MCP-1, and this improvement occurred despite participants being recreationally active at baseline, and mean CRP levels being < 2 $mg \cdot L^{-1}$. In this instance, subjects trained 3 times per week for 24 weeks, and results suggested a benefit to completing AT and RT on separate days, with the duration and structure of that training regimen potentially contributing to the positive outcome. Importantly, the change in CRP for that cohort correlated significantly with the change in abdominal fat. Moreover, decreased CRP was observed in conjunction with improvements in insulin sensitivity and leptin levels in overweight adults (Glynn et al., 2015), although those participants were insulin-resistant at baseline and trained for 6 months in total. Overall, it seems that 10 weeks of CET may not be sufficient to produce substantial changes in CRP

in non-diseased individuals. As further evidence, both training groups in the present study demonstrated mean CRP values within the "healthy" range (< 3 $mg \cdot L^{-1}$), and thus there may have been minimal potential for change. This seems to lend credibility to the notion of 'regression towards the mean', whereby CRP values further from the overall mean demonstrate a greater propensity for change (Lakka et al., 2005).

MCP-1 is a marker of systemic inflammation (Niu & Kolattukudy, 2009) showing a mechanistic role in development of CVD (Dawson et al., 1999). In the present thesis, MCP-1 increased only within CRL, and the training groups seemed to provide maintenance of pre-training levels. Given the role of MCP-1 within the inflammatory cascade (Tamura et al., 2008), and the association with obesity and insulin (Simeoni et al., 2004), training-induced reduction typically coincide with improved body composition and/or glucose regulation (Bradley et al., 2008; Trøseid et al., 2004). However, specific training variables may provide small but meaningful changes in the adaptive response. The present 3d/wk, 10 week CET and TUT regimen did not alter MCP-1, and may relate to the non-diseased status and extent of training load encountered.

During exercise, the overall training volume is presented as a possible determinant of clinical outcomes (Bjørnstad et al., 2008; Trøseid et al., 2004), although to date the only CET-specific studies related to MCP-1 have been conducted in diseased populations. For example, heart failure patients showed no change in resting MCP-1 after 20 weeks of CET, but decreased some CVD-related biomarkers, including p-selectin (Bjørnstad et al., 2008). Interestingly, these subjects trained 2h per week using a relatively non-strenuous CET protocol. In contrast, T2DM patients undergoing 12 weeks' CET demonstrated reduced inflammation (MCP-1, IL-8), glucose regulation, and VAT after a training

regimen comprising 3 weekly 1-hour sessions that were, in contrast, closely monitored (Trøseid et al., 2004). The present study involved non-diseased participants training for approximately 3h per week for 10 weeks, and thus it is possible that healthy participants require a longer and/or more intense intervention period to manifest a significant change. Indeed, training programs as short as 2 weeks have shown some effectiveness in this regard, although participants have been typically obese (Leggate et al., 2012). Importantly, although the body composition and fitness measures showed group-specificity in the present study, the overall volume-loads did not reach a statistically significant difference between CET and TUT, and hence greater contrast in modalities and/or training doses may produce divergent responses with regards to MCP-1.

Despite maintenance of pre-training levels within the training groups, some evidence would suggest that these participants were not in the 'healthy' range for MCP-1. Post-intervention values were ≥ 280 $pg \cdot ml^{-1}$ across all groups; however, it is proposed that ostensibly healthy individuals should demonstrate much lower concentrations, with data indicating 159 $pg \cdot ml^{-1}$ (Piemonti et al., 2009), 145 $pg \cdot ml^{-1}$ (Leggate et al., 2012), and as low as 104 $pg \cdot ml^{-1}$ (Valković et al., 2016) as more indicative MCP-1 values across non-diseased populations. That said, the clinical cut-off thresholds for disease risk are not well established for MCP-1; Piemonti et al. (2009) reported that the mean MCP-1 level for T2DM patients was 224 $pg \cdot ml^{-1}$, compared to the abovementioned 159 $pg \cdot ml^{-1}$ for subjects with normal glucose tolerance. In contrast, a sample of 3499 healthy middle-aged adults demonstrated a median MCP-1 concentration of 168 $pg \cdot ml^{-1}$, with the 95th percentile within that cohort showing a median of 381 $pg \cdot ml^{-1}$ (Deo et al., 2004). Separately, Hoogeveen et al. (2005) describe a mean MCP-1 of CVD cases being > 400 $pg \cdot ml^{-1}$, and thus the present cohort may not necessarily possess the typical MCP-1 level of a healthy,

low-risk population, although it would seem the actual disease-related risk may not be clinically relevant. More research is required to verify this hypothesis, however with regards to the present study, the findings do not show a physiologically significant adaptation to the 10-week intervention.

In summary, concurrent training does appear to confer some benefit for inflammatory markers. Specifically, CET reduced IL-6 and TUT reduced TNFα, with no training-induced changes in CRP or MCP-1. Based on the existing literature, it is possible that for healthy individuals who are already within healthy reference ranges for these biomarkers, there is a reduced likelihood of significant changes or indeed, that a longer or more rigorous training intervention is necessary to produce improvements. That said, given the differences between CET and TUT, questions remain as to the effect of the training stimulus itself, and in particular whether altering the load and duration of RT can preferentially target either IL-6 or TNFα. The current data suggest there may be some stimulus specificity with regards to exercise prescription to improve markers of chronic systemic inflammation.

Effect of CET and TUT on Markers of Glucose Homeostasis

In the fasted state, HOMA-IR represents an estimate of insulin resistance (Wallace et al., 2004), and is commonly used to predict future development of T2DM (Alberti et al., 2006). In relation to exercise, concurrent training is suggested to improve glucose homeostasis indicated by reduced insulin resistance and/or glucose (Kim et al., 2008a). In the present study, the within-group changes in IR were not significantly different between groups or over time. In contrast, glucose was decreased in all groups, although again the magnitude of these changes did not result in a clear between-group difference.

Of particular interest is the clinical relevance of these findings; the HOMA model is calibrated such that an IR value of 1.0 is considered normal (Wallace et al., 2004). Considering that participants were predominantly insulin-sensitive before training (as inferred from this index), there may be a reduced likelihood that a short-term exercise regimen will significantly alter insulin resistance. Indeed, there were no significant changes in fasting glucagon, GLP-1 or C-peptide in the present study.

In regard to the training effects of CET on IR, previous studies in sedentary participants have shown no change in proteins related to glucose transport, despite increased insulin sensitivity (Donges et al., 2013). There is some rationale for a longer training intervention period than the current 10 weeks, particularly given that in older adults, an 8-week CET program did not change HOMA-IR (Kraemer et al., 2007), while a longer 4-month program resulted in a significant decrease (Ferrara et al., 2004). However, this finding is not consistent across all studies in healthy populations, with some showing no alteration in HOMA-IR with CET 5 times per week over 6 months (Huang et al., 2007), and others showing clear decreases after having trained 3 times per week for 4 months (Ratel et al., 2011). Accordingly, it is not clear why neither CET nor TUT significantly altered HOMA-IR, and indeed regression analyses in study 3 could not explain the variance shown. Although there were significant changes in inflammatory cytokines and body composition parameters, the lack of change in HOMA-IR may reflect the healthy insulin-sensitive status of participants, but the altered RT stimulus within a CET program had no effect on ensuing changes in insulin sensitivity.

Given the current findings, it is possible that a greater emphasis on AT within the respective programs may provide greater adaptations in insulin sensitivity. Endurance-

based exercise positively impacts glucose transport mechanisms in muscle (Baar et al., 2002), and it is feasible that an AT-focused training regimen would confer a more pronounced change in HOMA-IR and fasting glucose. Indeed, Choi et al. (2007) observed significant reductions in HOMA-IR in overweight women with a protocol comprising 5 weekly sessions of 45 minutes of moderate-intensity AT and 20 minutes of RT per session. Moreover, improved glucose regulatory markers are observed in a majority of studies in which the within-session AT volume is at least 30 minutes (Dâmaso et al., 2014; Duarte et al., 2015; Inoue et al., 2015). That said, the prolonged endurance stimulus of TUT did provide greater changes in aerobic capacity, yet was not superior for improving glucose homeostasis. Thus, although the overall training volume and duration is an important consideration, a greater emphasis on AT may be necessary to provide substantial changes in HOMA-IR and TUT may not be sufficient to drive these improvements in healthy populations.

Leptin is a strong predictor of T2DM (Mcneely et al., 1999) and CVD (Wallace et al., 2001) due to its role in obesity (Mantzoros, 1999), and as a precursor to chronic systemic inflammation development (Iikuni et al., 2008). In the current study, leptin showed no changes in any group after the 10-week intervention. Mechanistically, leptin shows a direct link to impaired insulin signalling (Cohen et al., 1996) and is broadly considered part of the cytokine network in that it demonstrates reciprocal upregulation with IL-1β and TNFα (Sarraf et al., 1997). Previous exercise training studies in sedentary adults have shown mixed results; for example, Mendham et al. (2015) reported significant reductions in fasting leptin alongside improvements in insulin sensitivity but without changes in inflammatory markers. Conversely, in older sedentary women, 16 weeks of CET did not change leptin or any other parameters related to glucose homeostasis (Rossi et al., 2017).

The current study showed no differences for either CET or TUT, despite the fact that CET decreased TBFM and TUT decreased VAT.

To date, the majority of research data relate to overweight or obese individuals, and perhaps more importantly, many involve load bearing AT modalities performed with larger overall volumes. Specifically, Ackel-D'Elia et al. (2014) observed significant reductions in leptin levels using 6 months of CET in obese adolescents, whereby the AT component involved 30 minutes per session of various AT modes including walking and small-sided games. Notably, for that cohort the decrease in leptin was equivalent to a group performing duration-matched AT in isolation. Accordingly, there may be a rationale for prioritising AT strategies (and possibly load-bearing AT) for those seeking to reduce leptin levels. In the present study, participants only completed 15-20 min of AT per session comprising non-load-bearing modalities (cycling and rowing). Although, given TUT imposes greater demands on oxidative metabolism (Scott, 2012), it did not produce superior changes in glucose homeostasis compared to the shorter CET, and thus may not necessarily be comparable with actual endurance training. In support, obese subjects performing CET with 2.5 h per week of moderate-intensity AT demonstrated significant reductions in leptin after 12 weeks (Bharath et al., 2018), while another obese cohort showed unchanged leptin after CET with 1 h per week of AT (Kim et al., 2008a). Evidently, the present training interventions caused minimal changes in glucose homeostasis parameters. This may be related to the specific modalities used, or indeed the target population showing normal metabolic profiles at baseline. Most likely, a longer program is required to elicit positive adaptations in this population, and in particular a greater emphasis on AT volume within a training design seems to be beneficial.

Effect of CET and TUT on Cardiovascular Disease Biomarkers

The acute-phase reactant SAA is associated with future cardiovascular events (Johnson et al., 2004) and shows a mechanistic relationship with systemic inflammation (Berg & Scherer, 2005) and contributes directly to atherogenesis (Artl et al., 2000). Further, epidemiological data show that individuals in the upper tertile of habitual physical activity have a markedly lower (22%) SAA level compared to those in the lower tertile (Panagiotakos et al., 2005). However, following the present training intervention, no within- or between-group differences were evident for SAA. It was hypothesised that the 10-week exercise intervention would decrease basal SAA; although, given the similar volume load between conditions over the 10weeks, it may be a part explanation for the lack of between-group differences in the current study. In comparison to other studies, there are a number of reasons that may explain why this did not occur. Specifically, given that SAA occupies the role of a pro-inflammatory cytokine (Yang et al., 2006), and hepatic SAA catabolism is reduced by other cytokines (Berg & Scherer, 2005), the fact that CRP and MCP-1 were unchanged in the current study may have influenced this outcome. Astengo et al. (2010) reported that neither CRP nor SAA were altered by 8 months' cycling-based training, even with the addition of resistance band-based RT. Moreover, an intensified weight loss protocol over 2 weeks reduced CRP, SAA, as well as other CVD-related risk factors such as ICAM-1 and triglyceride levels (Wegge et al., 2004). Thus, the overall duration of training may be less important than fat loss for improvement of SAA. Separately, among patients with intermittent claudication, SAA levels were reduced after 6 months of training, but not after 3 months (Tisi et al., 1997). Thus, the time course of training adaptations may be longer than could be detected within the present study, and indeed the use of non-diseased subjects in the current study may have limited the potential for SAA changes.

With regards to adhesion molecules, there was little training-induced change and in fact, decreased ICAM-1 and VCAM-1 were evident for CRL. Although there is some evidence for improved adhesion markers following CET in PAD patients (Saetre et al., 2011), there is insufficient research to confirm a role in healthy individuals. The current data are equivocal as to the optimal training design for those seeking to reduce adhesion molecule concentrations. A majority of research pertains to clinical populations, and although CET is demonstrated to decrease ICAM-1 in patients with T2DM (Tönjes et al., 2007), other data in heart failure patients showed no effect of CET after 8 weeks (Niebauer et al., 2005). It would seem that, irrespective of the overall program duration, a reduction in overall or abdominal adiposity may be a key contributor to improved adhesion molecule levels. Indeed, exercise with weight loss interventions have demonstrated efficacy over periods as short as 2 weeks (Roberts et al., 2007; Wegge et al., 2004). That said, CET provided reductions in both TBFM and VAT following the present intervention, without changes in ICAM-1. Thus, a greater AT stimulus may be required, although TUT significantly enhanced VO_{2peak} and PPO, but did not alter ICAM-1 after 10 weeks. Accordingly, more research may be needed, but the present findings suggest fat loss and aerobic stimuli may not be the keys to reducing ICAM-1.

The absence of significant changes pursuant to training within the present cohort may be related to the relatively healthy status at baseline, whereby all groups showed ICAM-1 values $\leq$ 108 $ng \cdot mL^{-1}$. By comparison, other healthy adults have reported significantly higher levels, and disease states are characterised by even higher values. For example, Signorelli et al. (2003) reported that, across a cohort of older adults, healthy subjects showed a mean plasma ICAM-1 concentration of 208 $ng \cdot mL^{-1}$, while a separate group

with diagnosed arterial disease presented a mean value of 317 $ng \cdot mL^{-1}$. Similarly, among 130 adults there was a significant difference between healthy participants and those deemed at risk of developing CVD, showing mean fasting ICAM-1 levels of 132 and 284 $ng \cdot mL^{-1}$ respectively (Blanco-Colio et al., 2007). Other authors have identified an increased risk of cardiac events at concentrations above 502 $ng \cdot mL^{-1}$ (Luc et al., 2003). Thus, although the present study showed no training effect, the potential for a clinically meaningful change may have been low. Evidently, there are insufficient data to elucidate the value of CET within non-diseased individuals; however, beyond the role of ICAM-1 as a prognostic biomarker for CVD, the relevance of training-induced changes within normal physiological ranges is unclear.

VCAM-1, as a biomarker of endothelial dysfunction (O'Brien et al., 1993), did not differ from pre- to post-training, with the only changes being a reduction in CRL. The baseline values across all groups were between 400-500 $ng \cdot mL^{-1}$, which is consistent with previously reported values for healthy (Signorelli et al., 2003) and overweight subjects (Ruel et al., 2008). That said, it is unclear whether these within-group changes are physiologically significant; as some authors have postulated that greater cardiovascular risk is present at concentrations well above 500 $ng \cdot mL^{-1}$ (Semaan et al., 2000), while others have identified a disease-associated mortality risk at levels over 1200 $ng \cdot mL^{-1}$ (Calza et al., 2009). Regardless, in the present study VCAM-1 showed no reductions following the 10-week CET or TUT training program shown here, and thus the unexpected finding requires investigation. Although, since this is the first study to examine the effects of CET on VCAM-1 in healthy sedentary individuals, there are no comparable research studies, though 2 studies in diabetic patients show mixed results. Gibbs et al. (2012) found no changes in adhesion molecules with 6 months of CET,

although reductions in body fat percentage and Hba1c were evident. In contrast, a 4-week CET regimen did reduce VCAM-1, alongside decreased insulin resistance; although, when sub-group analyses were made between subjects with normal glucose tolerance, impaired glucose tolerance, or T2DM, this training effect was only present for the latter two (Tönjes et al., 2007). Thus, to reduce VCAM-1 it is unclear which aspects of training prescription are of most importance; in the Tönjes et al. (2007) study, a significant association was identified between VCAM-1 levels and VO_{2max}, which may provide an avenue for further investigation. That said, specific training variables produced distinct adaptations in the present study, whereby TUT showed superior increases in endurance capacity, without changes in VCAM-1. Therefore, despite the association with aerobic fitness mentioned above (Tönjes et al., 2007), the present findings suggest increased VO_{2peak} may not coincide with reduced VCAM-1.

In summary, the lack of changes in CVD-specific biomarkers may be related to a number of factors. Namely, the use of non-diseased individuals may have minimised the chance to see the magnitude of changes typically seen in clinical populations. Also, many studies that have shown reduced CVD markers with training have incorporated multidisciplinary interventions involving dietary fat loss strategies. It is possible that in order to significantly alter endothelial function and platelet activity in non-diseased subjects, nutritional modification and/or a larger degree of weight loss may be necessary. That said, CET did show superior changes in TBLM and TBFM, and there were greater reductions in VAT and SAT in CET and TUT respectively. There is evidence that an endurance stimulus may preferentially reduce VAT (Thomas et al., 2000), although here the prolonged TUT modality was not as effective in this regard. Thus, despite discrepancies

between CET and TUT for body composition and physical capacity, there was little difference for CVD biomarkers, and thus other mechanisms may explain these responses.

Effect of CET and TUT on Body Composition

Changes in fat and lean mass may precipitate improvements in inflammatory biomarkers and glucose homeostasis (Tack et al., 2012). In the present study, although there was no group x time interaction for TBLM, though there was a significant within-group increase for CET. Given the unaccustomed training status of participants, it may be expected that some muscle hypertrophy will occur due to the novelty of the exercise stimulus (Coffey & Hawley, 2017). That said, although generally homogeneous results are noted across a wide range of lifting speeds (Schoenfeld et al., 2015a), the present findings suggest more conventional, faster-speed strategies may be superior for hypertrophy; possibly, due to the superior effect on muscular strength, and the trend towards increased training volume. In explanation, resistance training with a slow movement tempo is purported to be equally effective as faster, higher-load lifting to drive muscle growth (Burd et al., 2012). Moreover, it is suggested that performing resistance training sets to the point of concentric muscle fatigue will provide a significant adaptive stimulus irrespective of the loads used (Mitchell et al., 2012; Sale, 1987). However, the superior hypertrophy provided by CET was evident in both the TBLM derived from DEXA, and the ultrasound measure of *m. vastus lateralis* thickness. Given the potential for an interference effect with concurrent training (Fyfe et al., 2014), it is possible that the training prescription used for TUT may not have provided a strong enough hypertrophic stimulus to accompany AT. Currently, the literature relating to TUT is resistance training-specific (Keeler et al., 2001; Rana et al., 2008; Tanimoto et al., 2008), and thus the inclusion of TUT within a concurrent design may be inferior for the hypertrophy and strength adaptations seen with TUT as an isolate

mode. This may be an important distinction, given load management is one of the primary considerations of CET (Baar, 2014).

Similarly, although CET produced the greatest reduction in TBFM, there were some mode-specific changes in regional adiposity. Namely, TUT conferred superior decreases in android fat mass and SAT, while CET reduced VAT. Given that a reduction in whole-body and regional adiposity is a key factor in offsetting cardiometabolic risk (Gleeson et al., 2011), such differences in the mode-specific response may have practical implications. Visceral fat accumulation in the abdominal region is an important contributor to a systemic inflammatory state (Park et al., 2005), and hence this region-specific measurement represents a potential target for intervention. Currently, the long-term effect of TUT on fat mass and distribution is unknown; however, short-term data suggest greater TUT provides greater within-session energy expenditure compared to fast-speed RT (Scott, 2012). Although it is problematic to extrapolate acute responses to long-term changes, a differing metabolic stimulus provided by TUT may influence the mobilisation and distribution of fat (Thomas et al., 2000), which in the present study manifested as a reduction in SAT. Importantly, the overall SE within this study was correlated with the change in TBFM, but not the change in VAT. Thus, it does not seem that this type of training can preferentially alter fat mass or distribution.

Currently, the evidence is not sufficient to draw any clear inferences, although high-exposure training of this nature may warrant further investigation. Previously, overweight individuals have demonstrated a superior reduction in TBFM, VAT, and SAT using CET compared to volume-matched AT (Dâmaso et al., 2014). Other studies have also shown efficacy for CET to reduce VAT in obese populations (Davis et al., 2011; de Lima

Sanches et al., 2011), although some suggest it is not different from AT in this regard (de Mello et al., 2011; Slentz et al., 2011). Thus, the intensity of the RT component may provide particular fat loss benefits that are not present with TUT. Furthermore, whether one particular variant of CET preferentially targets fat loss in the subcutaneous or visceral compartments remains unclear. The present findings suggest a prolonged training stimulus (i.e. TUT) may place greater demands on oxidative metabolism (Scott, 2012) and this may impact upon the distribution of adipose tissue (Thomas et al., 2000), however ongoing research is required to confirm this finding.

Effect of CET and TUT on Physical Capacity

Maximal strength is associated with a reduced risk of cardiovascular diseases (Artero et al., 2012) and metabolic dysfunction (Jurca et al., 2004), and hence increases in muscular strength may provide significant health-related benefits. In the present study, the greatest improvement in isometric knee extension strength occurred in CET, which is expected given that higher mechanical loads and faster lifting speeds typically cause greater enhancements in neuromuscular function (Bottaro et al., 2007). When compared to slow-speed lifting, superior strength gains have been observed with controlled, hypertrophy-style RT (Neils et al., 2005) and with high-velocity power training (Bottaro et al., 2007). In addition to the possible neurological adaptations with CET, greater improvements in TBLM and *m. vastus lateralis* thickness observed within CET may have contributed to this result. Indeed, muscle mass correlates with muscle strength in older adults (Reed et al., 1991), and conventional CET seems to improve both parameters concomitantly. For individuals seeking to increase strength and/or power, this is perhaps the most appropriate strategy. In particular, sedentary adults performing CET may benefit from the strength adaptations derived from this type of training.

In contrast, improvements in endurance capacity were observed in TUT, which provided the greatest increase in VO_{2peak}. Increased aerobic fitness is associated with decreased systemic inflammation (Abramson & Vaccarino, 2002) and cardiometabolic disease risk (Jurca et al., 2004), and thus represents a key subclinical biomarker. The mode-specific outcome shown here may provide an avenue for individuals who wish to maximise endurance adaptations from resistance training within the concurrent training paradigm. Indeed, for older adults who may seek to optimise the benefit with minimal training loads, TUT may be an efficient option within a CET design. Given the aerobic training loads were equal across the training groups, the divergent outcomes may be related to specific aspects of TUT in the resistance training design. Specifically, the present findings echo those from Anderson and Kearney (1982) who report that across a spectrum of resistance training loads, skeletal muscle demonstrates both general and specific adaptations to respective exercise stimuli, in that lower-load, longer-exposure modalities favour endurance-related adaptations and higher-load variants favour strength gains. Grgic et al. (2018) propose that greater time spent under load during RT may drive greater acute stress of slow-twitch muscle fibres, and subsequently provide endurance adaptations. This seems to be related to the prolonged stimulus exposure associated with low-load training, and not necessarily the contraction speed (Dankel et al., 2017). Accordingly, although hypertrophic adaptations are mostly similar across the spectrum of RT loads (Mitchell et al., 2012), it seems that changing the load and duration of working sets may provide specific endurance- or strength-related effects (Schoenfeld et al., 2015b). Although increased endurance capacity is observed across many concurrent training studies (Davis et al., 2011; Kadoglou et al., 2013; Ratel et al., 2011), this is the first study to show a superior improvement in VO_{2peak} using TUT in a concurrent training design. Thus,

incorporating TUT may enhance endurance adaptations without necessarily adding to the overall training load.

Modality and Training Load Considerations for Exercise Prescription

Understanding the exercise-induced responses as related to disease risk outcomes is an important avenue for research, though only permits a generic understanding of exercise prescription (Garber et al., 2011). Accordingly, further detailed understanding of the type, volume and exposure of concurrent training provides evidence to guide actual exercise prescription in sedentary populations (Bishop et al., 2019). Presently, study 3 showed the change in quadriceps strength following the 10-week intervention had the strongest association with changes in IL-6 and TNFα. Although previous studies have identified a significant cross-sectional relationship with functional strength and reduced inflammation (Visser et al., 2002), this is the first study to show a significant relationship within a training study context following a CET regimen. Further, although cross-sectional epidemiological data suggest age-related increases in IL-6 are associated with reduced strength (Schaap et al., 2006), the present study is the first to show that the change in strength following concurrent training explained the variance in IL-6 and TNFα changes. Given this is the first study to explore this relationship in a CET design, it raises key questions with regards to exercise prescription. In particular, when prescribing CET it may be appropriate to emphasise strength gains by modifying the load and/or speed of the RT component to provide greater neuromuscular adaptations (Bottaro et al., 2007). In the present study, CET provided the largest improvements in strength and TLBM gains based on more traditional hypertrophic prescription of resistance loads, and despite the purported benefits of TUT, prescription of CET may be beneficial for sedentary populations.

Regardless of the mode of training, the volume or intensity of the training stimulus remain critical for resulting outcomes (Kraemer & Ratamess, 2004). The correlation observed between cumulative volume-loads and the changes in IL-6 and TNFα was significant in a bivariate analysis, however after correcting for strength changes neither correlation was significant. This finding suggests that the strength adaptation derived from either concurrent modality is a key driver of the inflammatory response, and the modality with which training is delivered may be less important. Previous research shows TUT and IL-6 are associated with increased strength in cross-sectional studies (Hosick et al., 2013; Schaap et al., 2006), and these adaptations frequently coincide with strength gains (Azarbayjani et al., 2014), although this is the first study to highlight this relationship within a pre-post CET design. Further, volume-load was also associated with $Strength_{change}$ and $VO_{2peakchange}$, but not $TBLM_{change}$ or $TBFM_{change}$ in a linear regression model. Although greater volume-loads are generally understood to provide greater hypertrophy (McBride et al., 2003), when applied in the present CET model, volume-load did not explain variance in TBLM changes, and hence the training prescription may require further modification if a CET design is used.

Moreover, the association with volume-load and VO_{2peak} was significant, and thus a greater volume during RT may be related to endurance capacity adaptations. Separately, there was a significant correlation between total SE and the change in TBFM, strength, and VO_{2peak}. Thus, although the final regression model did not include SE, increasing the time component of RT (via TUT) may provide appropriate endurance adaptations, although this was not related to changes in IL-6 and TNFα. That said, the AT loads were not included in analyses given they were standardised across both CET and TUT groups.

During concurrent training, the AT component will undoubtedly influence these outcomes, particularly VO_{2peak} (Jones & Howatson, 2019). Therefore, whilst the RT volume presently explained the change in VO_{2peak}, this may be related to the AT dose, and not necessarily the RT itself. However, some evidence in untrained individuals suggests some endurance adaptations can be derived from resistance training (Tanaka & Swensen, 1998), and thus the overall RT volume and modality applied remains a valid consideration for improving aerobic capacity.

In summary, study 3 identified strength capacity as a key factor in the anti-inflammatory response to concurrent training. These results suggest that the strength gains derived from the manipulated RT within concurrent training are associated with positive changes in inflammatory cytokines (IL-6 and TNFα). Further, the overall training volume, regardless of mode, may contribute to these exercise-induced benefits in sedentary populations. Such information leads to better prescription based on dose responses and specific modalities. In particular, individuals seeking to optimise the anti-inflammatory effects of CET may benefit from a greater emphasis on increasing strength performance, and thus the prescription of increased RT loads and/or faster contraction speeds may be appropriate (Bottaro et al., 2007). When prescribing CET, prioritising of muscle strengthening activities may be important for improving inflammatory markers, and when used alongside AT, may provide the greatest overall benefit.

Limitations

The applied nature of this investigation provides ecological validity; however, results in methodological limitations that require acknowledgment. Specifically, participants were instructed to maintain habitual nutrition and activity behaviours outside of the research

environment, and despite the efforts made to ensure compliance, it cannot be guaranteed that participants obeyed these instructions. Thus, the potential confounding effect of individual dietary and/or activity changes external to the study is recognised as a limitation. Indeed, some of the changes observed in CRL for biomarkers such as ICAM-1 and p-selectin may be related to unreported lifestyle changes.

Regarding blood markers, it should be noted that three additional cytokines (IL-10, IL-1β and IL-1ra) were to be included in the data set, but across the participant cohort the values for these markers were outside the detectable range of the measuring device, and thus no data were available for these analytes. These inflammatory mediators would have provided greater insight into training adaptations, and their absence may inhibit the interpretation of the other data. Similarly, although resting glucose, insulin and HOMA indices are used in the present thesis as clinical monitoring tools, it was not practical to conduct functional glucose regulation testing (such as via OGTT or clamp procedures) and thus it is not possible to extrapolate these findings to the postprandial state. Despite the clinical utility of the HOMA, it is cross-sectional in nature and does not directly measure insulin action.

Importantly, although there was a trend for greater training volumes in CET, the between-group differences did not reach statistical significance. Thus, although TUT purportedly entails a decreased load (Watanabe et al., 2013), the protocol used here did not provide such a stimulus for all subjects. In order to fully understand the response of a low-load modality, a lower training load may be required to differentiate TUT from CET. Further, the prescription of non-load-bearing AT modalities was selected for practical reasons, and thus the findings may differ with walking/running training. Also, the within-session

duration of AT was made relatively short in order to focus upon the differing RT stimuli however, CET programs commonly place greater emphasis on the AT component, and in practice this may manifest a divergent outcome.

Chapter 7

Summary, Applications and Future Directions

Summary and Conclusions

The present thesis examined the effects of conventional CET compared to TUT for improvement of subclinical parameters related to chronic systemic inflammation and cardiometabolic disease in sedentary individuals. The three studies aiming to determine the effect of 10 weeks of CET or TUT on:

1. The response of blood-based inflammatory and cardiometabolic disease indicators.
2. Whole-body and region-specific lean and fat mass, as well as muscle thickness determined by B-mode ultrasound.
3. Functional measurements of maximal strength and aerobic capacity.
4. Determine the relationship between changes in key inflammatory and cardiometabolic prognostic indicators with training induced changes in body composition and fitness. In turn, to further explore the relationship between training volumes and changes in body composition and fitness markers.

The three studies that form the present investigation showed both mode-dependent and mode-independent changes in clinical and subclinical parameters. These are outlined below on a study-by-study basis:

- Study 1:
    - CRP was unchanged after training, and MCP-1 increased within CRL, without changes in either training group.
    - CVD markers showed no training-induced changes in adhesion molecules or SAA. Only CET reduced p-selectin, and this was not superior to CRL.
    - CET was superior to reduce TBFM and increase TBLM, while regional measures showed that TUT decreased VAT and CET decreased SAT.

- CET provided the greatest increase in *m. vastus lateralis* thickness.

- Study 2:
  - Inflammatory markers showed a group-dependent response whereby IL-6 decreased in CET only, and TUT decreased TNFα.
  - Markers of glucose homeostasis remained unchanged after training, with the exception of glucose which decreased in all groups.
  - Mode-specific responses were evident for physical fitness parameters, such that CET preferentially improved quadriceps strength
  - TUT provided superior increases in VO_{2peak}, while both CET and TUT increased PPO.

- Study 3:
  - The change in IL-6 could be explained by the change in strength and TBLM, while TNFα changes could be explained by strength only.
  - No significant correlations were evident for HOMA-IR, and none of the selected predictors was significant in a linear regression.
  - For training loads, the overall volume-load was inversely correlated with both IL-6 and TNFα. However, when adjusting for strength neither correlation was significant.
  - Cumulative volume-loads predicted the change in strength and VO_{2peak}, but not TBFM or TBLM.

In conclusion, for untrained individuals seeking to offset age-related decrements in cardiometabolic risk status, performing CET using conventional methods seems to be effective. RT with a conventional, faster cadence used in conjunction with moderate-intensity AT may be most appropriate to enhance body composition and fitness

parameters. Both CET and TUT appear to provide some benefit for disease-specific biomarkers; with CET reducing IL-6 and TBFM and increasing strength and TBLM, Alternatively, for decreased TNFα and increased VO_{2peak}, a prolonged stimulus such as TUT may be more beneficial as the RT component within concurrent training. When prescribing concurrent training, increasing the overall volume-load may provide greater adaptations in IL-6 and TNFα, although the most important aspect of training design seems to be the resulting strength adaptations, when maintaining the AT portion.

Practical Applications

The findings of the present investigation will assist practitioners to prescribe exercise training to older adults with greater precision and specificity of outcomes to be used by exercise and health professionals:

- The present study highlights the efficacy of supervised CET in sedentary and aged populations. For those seeking to achieve a broad range of health-related outcomes through exercise training, CET may be the most pragmatic option.
- Older, untrained individuals who wish to optimise strength gains during CET should incorporate higher-intensity resistance loads and/or faster movement speeds.
- To increase endurance capacity, greater time exposure via TUT within CET may provide greater improvements in aerobic fitness.
- Changes in whole-body lean and fat mass largely favoured conventional CET; however, TUT may provide subtle mode-specific effects, such as improving VAT and aerobic capacity, that will assist in tailoring exercise regimens to individual goals.

- Inflammatory cytokines such as IL-6 and TNFα may respond more positively to different exercise strategies, although more research is needed in order to verify the role of individual training variables.

Directions for Future Research

Based on these findings, possible future research directions are suggested:

- The present study was specific to sedentary older adults without any existing medical conditions, although a potential application exists in clinical populations and those seeking to manage cardiometabolic conditions with exercise. This warrants further investigation.
- In untrained participants, the novelty of exercise may mask the specific effects of divergent exercise modes. It is possible that long-term interventions (> 6 months) would produce different results, although future research is needed to verify this.
- Combining concurrent training regimens with lifestyle modifications such as dietary interventions may confer greater changes in body composition and/or disease biomarkers compared to exercise alone, although at present this is unknown in the context of TUT. Future research should aim to elucidate the effects of fat loss versus muscle hypertrophy on disease-related risk markers.
- Although the current study pooled male and female participants for data analysis, there may be differing responses to training based on sex, and future studies should examine this possibility in a rigorous research framework.
- The present investigation ceased following the intervention period; however, there are a number of long-term factors that may require closer inspection, such as drop-out rates, injuries, and the psychosocial effects of group-based training. Such

matters can influence future exercise behaviours and should be explored with respect to TUT training.

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Appendices

Appendix 1: Institutional Research Ethics Letter of Approval.

Dear Applicant

Thank you for your response to the Committee's comments for your project titled, "Changing the time under tension: effects of different forms of concurrent training on inflammatory, cardiovascular and metabolic disease indicators". Your response satisfactorily addresses the concerns and questions raised by the Committee who agreed that the application now meets the requirements of the NHMRC National Statement on Ethical Conduct in Human Research (2007). I am pleased to inform you that ethics approval is now granted.

Your approval number is UTS HREC REF NO. ETH16-0742.

Approval will be for a period of five (5) years from the date of this correspondence subject to the provision of annual reports.

Your approval number must be included in all participant material and advertisements. Any advertisements on the UTS Staff Connect without an approval number will be removed.

Please note that the ethical conduct of research is an on-going process. The National Statement on Ethical Conduct in Research Involving Humans requires us to obtain a report about the progress of the research, and in particular about any changes to the research which may have ethical implications. This report form must be completed at

least annually from the date of approval, and at the end of the project (if it takes more than a year). The Ethics Secretariat will contact you when it is time to complete your first report.

I also refer you to the AVCC guidelines relating to the storage of data, which require that data be kept for a minimum of 5 years after publication of research. However, in NSW, longer retention requirements are required for research on human subjects with potential long-term effects, research with long-term environmental effects, or research considered of national or international significance, importance, or controversy. If the data from this research project falls into one of these categories, contact University Records for advice on long-term retention.

You should consider this your official letter of approval. If you require a hard copy please contact Research.Ethics@uts.edu.au.

Yours sincerely,

Dr Phillip Newton
Chairperson
UTS Clinical Trials Sub Committee
C/- Research & Innovation Office
University of Technology, Sydney
E: Research.Ethics@uts.edu.au

Appendix 2: Participant Information Sheet and Consent Form

UNIVERSITY OF TECHNOLOGY SYDNEY

Participant Information Sheet and Consent Form

Interventional Research

Title	The effects of muscle time under tension on inflammatory, cardiovascular and metabolic disease indicators
Principal Investigator	Nicholas Allen, PhD student
Site	University of Technology Sydney

Part I – What does my participation in the study involve?

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1 Introduction

You are invited to take part in this research project. Please take time to read the following information carefully and, if you wish, discuss it with friends, relatives and your local doctor. One of our team will go through the information sheet with you and answer any questions you have. Please ask questions about anything that you do not understand.

2 What is the purpose of this research?

This research project is part of PhD research by Nicholas Allen under the supervision of A/Prof Rob Duffield and Dr. Amy Mendham at the University of Technology Sydney (UTS). The aim of this research is to examine the effects of concurrent resistance and aerobic training, using either traditional or 'time under tension' training modes, on a range

of inflammatory, cardiovascular and metabolic disease indicators, as well as body composition and fitness measures.

3 Why have I been chosen?

You have been approached because you meet the criteria for participation in this research. You have indicated that you are aged 50-75y, free from known disease, non-smoking, and currently inactive.

4 Do I have to take part in the research?

It is up to you to decide whether or not to take part in this study. If you do decide to take part you will be given this Participant Information Sheet and Consent Form to sign. You can change your mind later and withdraw from the study at any stage, for any reason.

5 What will happen to me if I take part?

If you choose to take part in this study, I will invite you to:

- *Attend a brief health screening and information session*
- *Participate in a 10-week training program (1 hour, 3 times per week) at the UTS Elite Athlete Gym, Broadway, involving aerobic and resistance training using either:*
    - *Concurrent training (aerobic and resistance exercise)*
    - *Time under tension (TUT) training (aerobic and resistance exercise)*
    - *High-repetition training (aerobic and resistance exercise)*
- *Attend a testing session before and after the training period at the UTS Exercise Physiology Laboratory, involving:*

- *A small blood sample to measure disease indicators. This involves a small amount of blood taken from the forearm (venepuncture)*
- *Measures of height and mass*
- *B-mode ultrasound of arm and thigh muscles to determine muscle thickness, using an external probe and conductive gel*
- *Dual-energy x-ray absorptiometry (DEXA) scan to determine body composition, involving a full-body non-contact scan while participants lay still on a scanning bed. This procedure involves low-dose ionising radiation (similar to the dose associated with domestic air travel)*
- *Measurements of strength and aerobic fitness, including the VO_{2max} cycling test (cycling at increasing intensities until exhaustion) and measures of quadriceps strength (using knee extension movements).*

- *Provide ratings of perceived exertion and fatigue after each training session*

- We recommend that you inform your doctor of your participation in this study -

6 What do I have to do outside of the study?

If you participate in this study, you will be required to attend testing sessions at the UTS Human Performance Laboratory, and 10 weeks of training as described above. If you are allocated to the control group you will be asked to continue your normal nutritional and physical activity behaviours. Irrespective of your group allocation, you must refrain from making any significant changes to your diet or exercise habits outside of the study.

7 After testing, what will happen to my test samples?

With your consent, the investigators will extract approximately 10mL of blood using venepuncture at both the beginning and end of the study. These samples will be stored and later analysed to detect changes in disease biomarkers. The identities of the individuals associated with data will be known only to the researchers, and will not be made public. No photographs or video of you will be taken without your consent, and these will be used for research dissemination purposes only.

8 What are the possible benefits of taking part?

By participating in this research, you will receive 10 weeks' free exercise training under the guidance and supervision of qualified exercise scientists. Further, you will receive a comprehensive health screening, including information about fitness, body composition and disease risk profiles. Finally, following the completion of the study, the research team will offer optional further health/exercise consultation.

9 What are the possible risks involved?

Exercise training of this nature carries an inherent risk; however, the investigators will design and implement training in a manner that minimises risk to participants. Moreover, venous blood collection may cause some temporary discomfort or even minor bruising. Accordingly, only trained researchers will perform this procedure, and will do so in a way that minimises your discomfort. Further, steps will be taken to ensure safety and cleanliness at all times, including sterilisation of venepuncture sites, use of protective gloves, and appropriate disposal of sharp and/or contaminated items. Finally, the fitness testing protocols used in this study are strenuous and fatiguing; however, you are free to

terminate the test at any time and we ask only that you continue until you feel you can no longer meet the demands of the test protocol.

10 Procedures involving ionising radiation

This research project involves exposure to a very small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose from this project is about 0.002mSv. At this dose level, no harmful effects of radiation have been demonstrated and the risk is very low.

11 Can I have other treatments during this study project?

Whilst you are participating in this study project, you may not be able to take some or all of the medications or treatments you have been taking previously. It is important to tell your doctor and the research team about any treatments or medications you may be using, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You must also inform the research team about any changes to these during your participation in the research.

12 What do I do if I wish to withdraw from the research?

If you wish to withdraw from this study please advise the study team. You are free to do so at any time and you will be asked to complete the "Withdrawal of Consent' form included within this information sheet.

13 What happens when the study ends?

Following the completion of the study, the research team will collate and analyse all data. You will be invited to attend a brief informal meeting to discuss the results (both individual and group data) and you will be welcome to ask questions. Additionally, upon request the research team can provide guidelines for you to continue exercising after the study has finished.

Part II – How is the study being conducted?

14 What will happen to information about me?

By signing the consent form you agree to the collection and use of personal information about you for the study project. Any information obtained in connection with this project that can identify you will remain confidential, and your data will be used only for research purposes. Further, it is anticipated that the results of this study will be published in a variety of forums. In any publication or presentation, information will be presented such that you cannot be identified, except with your express permission.

You have the right to request access to the information collected by the study team about you. You also have the right to request that any information with which you disagree be corrected. Please contact the study team if you would like to access your information.

15 What if something goes wrong?

If you suffer any injuries or complications as a result of this study, you should contact the study team as soon as possible, who will assist you in arranging appropriate medical treatment. If you suffer any distress or psychological injury as a result of this study, contact the study team for support and/or referral to a health professional.

16 Who has reviewed the study?

All research in Australia involving humans is reviewed by an independent Human Research Ethics Committee (HREC). This study has been reviewed and given approval by UTS HREC (REF NO ETH16-0742).

17 Further information and whom to contact

If you would like any further information on this study, please refer to the table below. If you would like to talk to someone not directly involved with the study for any further information or should you wish to make an enquiry or complaint to somebody outside of the research team, you may contact the UTS Ethics Secretariat on 02 9514 9772 and quote the HREC reference number ETH16-0742.

Question	Whom to contact	Phone /Email
General questions or concerns during the study	Principal Investigator Nicholas Allen Primary Supervisor A/Prof Rob Duffield	[redacted] Nicholas.Allen@uts.edu.au 02 9514 5294 Rob.Duffield@uts.edu.au

UNIVERSITY OF TECHNOLOGY SYDNEY

PARTICIPANT CONSENT FORM

Title	The effects of muscle time under tension on inflammatory, cardiovascular and metabolic disease indicators
Principal Investigator	Nicholas Allen, PhD student
Site	University of Technology Sydney

1. I have read the attached Participant Information Sheet outlining the nature and purpose of this research study and I understand what I am being asked to do.
2. I have discussed my participation in this study with a member of the study team. I have had the opportunity to ask questions and I am satisfied with the answers I have received.
3. I have been informed about the possible risks of taking part in this study.
4. I freely consent to participation in the research project as described in the Participant Information Sheet.
5. I understand that my participation is voluntary and that I am free to withdraw at any time during the study period.
6. I understand that no photographs or video footage of me will be taken without my consent, and that these will be used for research dissemination purposes only.
7. I understand that if I decide to discontinue my participation in this study, I may be asked to attend follow-up visits to allow collection of information regarding my

health status. Alternatively, the investigator will request my permission to access my data for research and analysis.

Name of Participant	Signature of Participant	Date

Name of Witness to Participant's Signature	Signature of Witness	Date

*Witness is not to be the Investigator or member of the study team nor their delegate

* Please note that in the event that an Interpreter is used, the Interpreter is not a witness to the consent process

ALL WITNESSES MUST BE OVER 18 YEARS OF AGE

Name of Investigator	Signature of Investigator	Date

UNIVERSITY OF TECHNOLOGY SYDNEY

WITHDRAWAL OF PARTICIPATION

Title	The effects of muscle time under tension on inflammatory, cardiovascular and metabolic disease indicators
Principal Investigator	Nicholas Allen, PhD student
Site	University of Technology Sydney

I hereby wish to WITHDRAW my intent to participate further in the above research project and understand that such withdrawal will not jeopardise my future health care.

Participant's Name
(printed) .....

Signature .....

Date .....

If the participant decided to withdraw verbally, please give a description of the circumstances. Coordinating Investigator to provide further information here:

Coordinating Investigator to sign the withdrawal of consent form on behalf of a participant if verbal withdrawal has been given:

Participant's Name
(printed) .....

Signature of Investigator .....

Date .....

Participant will be provided with a copy of this Withdrawal of Consent Form