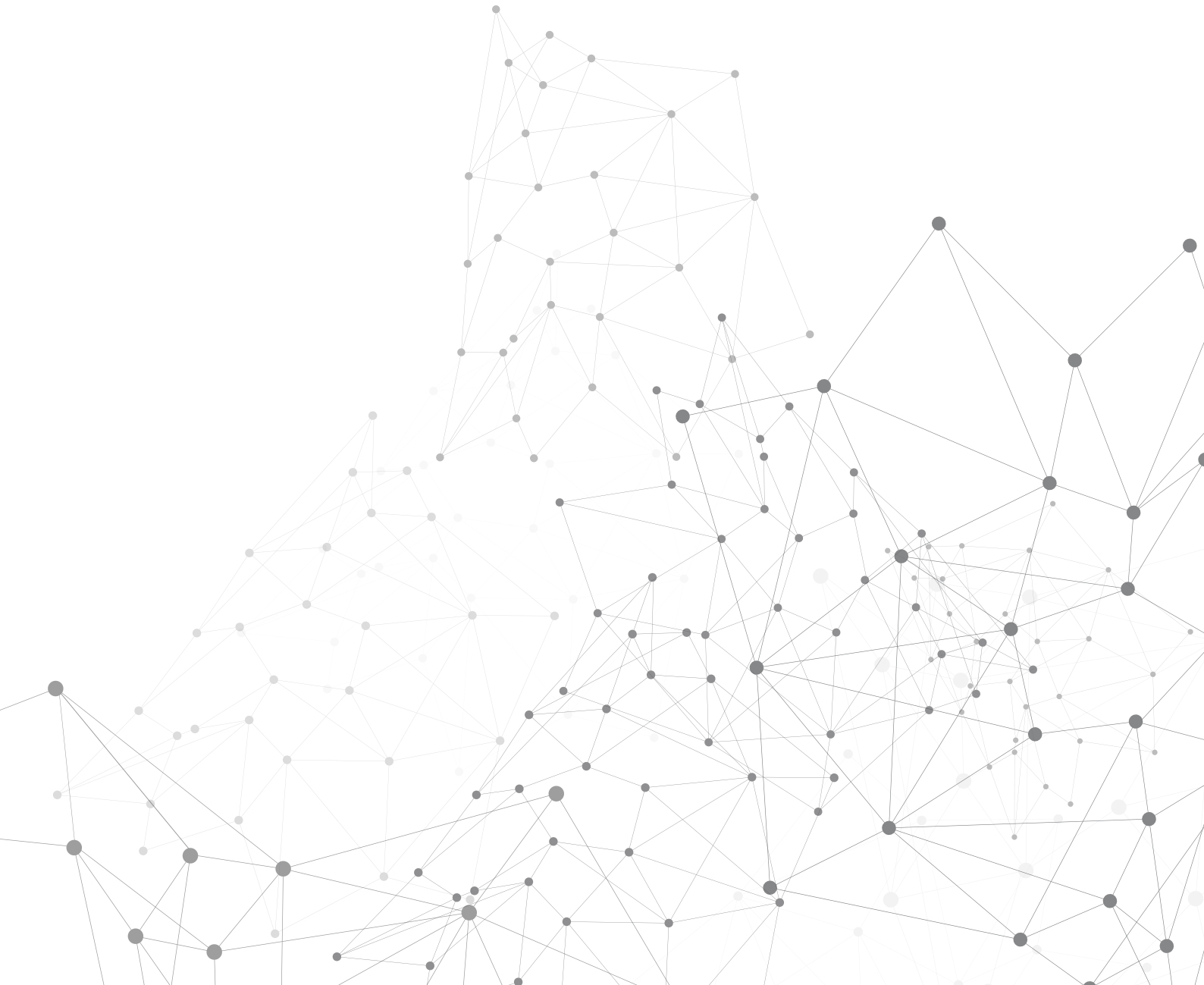
Novel aspects of exercise training to promote human metabolic health

CHAPTER 8

Summary



Summary

The prevalence of obesity has increased exponentially worldwide (1). Obesity is a crucial contributing factor to the development of cardiovascular disorders, type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (2). In fact, obese/overweight individuals are characterized by an impaired whole-body insulin sensitivity (3) and reduced skeletal muscle mitochondrial function (4), which in turn negatively affect plasma glucose homeostasis.
Regular exercise training is a well-recognized lifestyle intervention to prevent and counteract obesity-related metabolic disorders. Classically, exercise volume and intensity are regarded as the main factors determining the benefits of exercise in metabolic health. Hence, exercise volume and intensity provide the physiological rationale of the conventional recommendations of performing at least 150 minutes of moderate intensity aerobic-type combined with resistant-type exercise per week (5). However, the effects of these conventional exercise recommendations differ in magnitude among individuals, showing the need to come up with novel strategies to optimize the effects of exercise.

Many physiological processes in the human body, such as hormone synthesis and glucose homeostasis, exhibit day-night cycles, orchestrated by the central molecular clock which is located in the suprachiasmatic nucleus of the hypothalamus (6). Interestingly, peripheral organs such as liver, adipose tissue and skeletal muscle, contain their own molecular clocks (6). Of note, experimentally induced circadian misalignment causes skeletal muscle insulin resistance in normoglycemic individuals (7), which can be mitigated by performing acute bouts of high intensity interval exercise (8). Such insights that the biological clock, glucose homeostasis and exercise metabolism are tightly intertwined substantiate the hypothesis that the timing of exercise can be used to optimize its insulin sensitizing and metabolic benefits. The link between the skeletal muscle molecular clock and the benefits of exercise on glucose metabolism are reviewed in **chapter 2**. In this chapter, it is discussed how the nutritional status pre-post exercise, as well as the tissue-specific energy depots might influence the effects of exercise timing on glucose metabolism, with special emphasis on insulin resistant and type 2 diabetic individuals. This hypothesis was subsequently tested in **chapter 3**, in which state-of-the-art methodologies are used to investigate the effects of exercise timing on skeletal muscle insulin sensitivity and other clinical parameters in metabolically compromised individuals. We showed that afternoon exercise training confers superior benefits as compared to morning

exercise training in skeletal muscle insulin sensitivity, body composition and exercise performance in obese, metabolically compromised individuals.

Of note, obesity-related metabolic disorders and sedentary aging are often accompanied by exercise intolerance (9), likely explained by a refractory myocellular ATP synthesis via mitochondrial metabolism at the onset of exercise. The delayed responsiveness of skeletal muscle mitochondrial ATP synthesis is known as mitochondrial inertia (10). The responsiveness of skeletal muscle mitochondrial ATP synthesis at the onset of exercise relies on the intramyocellular acetyl-coa availability (10), which is controlled by the mitochondrial enzyme carnitine acetyltransferase (CrAT) (11). In **chapter 4**, the responsiveness of skeletal muscle mitochondrial ATP production at the onset of exercise, its potential underlying mechanisms, and its association with functional read-outs of exercise intolerance were determined in two different cohorts of human volunteers. The responsiveness of skeletal muscle ATP synthesis at the onset of exercise was slower in older, metabolically compromised individuals as compared to young, endurance-trained volunteers as well as in elderly, normally physically active individuals as compared to young, healthy and elderly exercise-trained counterparts. The responsiveness of skeletal muscle ATP synthesis at the onset of exercise was tightly linked to functional outcomes, which coexisted with reduced CrAT activity, low acetylcarnitine levels and elevated ADP concentration in muscle tissue during exercise. These results indicate that mitochondrial inertia at the onset of exercise might emerge as a target for intervention to improve exercise tolerance.

Given the wide variety of methods to assess skeletal muscle mitochondrial function, a direct comparisons and validation of the different markers of mitochondrial function with gold standard measures are needed. In **chapter 5** we determined to what extent different in vitro markers of mitochondrial content and in vivo functional readouts for skeletal muscle and whole-body oxidative capacity reflect muscle mitochondrial respiratory capacity as determined ex vivo, by high resolution respirometry.
Of the in vitro markers, protein content for complex V of the oxidative phosphorylation system and citrate synthase (CS) activity are the most valid surrogate markers of skeletal muscle mitochondrial respiratory capacity. From the in vivo readouts for skeletal muscle and whole-body oxidative capacity, PCr recovery post exercise, maximal aerobic capacity and exercise efficiency are valid reflection of skeletal muscle mitochondrial respiratory capacity. These results are of relevance for researchers to make a good choice from the multitude of techniques

that are available, when determining mitochondrial function. In addition, these findings might benefit researchers aiming to investigate skeletal muscle mitochondrial function but do not posse the gold standard technique to do so, and for studies that may not be able to incorporate muscle biopsies.

Most adults with poor metabolic health fail to meet the recommendations of performing at least 150 minutes of physical activity per week, with a "lack of time" being the most commonly cited barrier (12). In this regard, there has been a flourishing appreciation for the capability of high intensity interval training (HIIT) to improve metabolic health, as this methodology needs at least 50% less time commitment as compared to exercise performed according to the conventional exercise recommendations (13). In **chapter 6**, we investigated if 12 weeks of HIIT prompts beneficial effects on insulin sensitivity, muscle mitochondrial capacity and intrahepatic lipid (IHL) content in obese adults. Given the frequent consumption of carbohydrate rich and insulinogenic sports drinks after a training session, we also explored if co-ingestion of a standardized glucose and casein hydrolysate post-exercise affects the HIIT-mediated metabolic improvements. HIIT enhanced insulin sensitivity, skeletal muscle mitochondrial capacity, decreased intrahepatic lipid content and modified intrahepatic lipid composition in obese adults. These benefits were attained regardless of co-ingesting glucose and proteins after exercise and in the absence of changes in body weight and body composition. Taken together, HIIT is an effective training method to enhance metabolic health in obese adults.

Overall, the results from this thesis provide novel information about exercise timing as contributing factor to optimize the benefits of exercise in metabolic health. Also, the results of this thesis demonstrate that high intensity interval training is an effective training modality to improve whole-body insulin sensitivity, skeletal muscle mitochondrial capacity and to decrease and modify liver fat content and composition in obese adults. In addition, the results of this thesis indicate that skeletal muscle mitochondrial inertia is a novel signature of skeletal muscle mitochondrial function that correlates with markers for daily life activity. Thus, mitochondrial inertia is a putative target of intervention to improve physical function in metabolically compromised and elderly individuals. Furthermore, this thesis shows which markers of mitochondrial content and functional readouts of muscle oxidative capacity reflect muscle mitochondrial respiratory capacity *ex vivo*. Thus, the results of this thesis provide valuable

additions to the current literature about how to exploit the benefits of regular exercise training in human metabolic health.

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