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LEVELS IN YOUNG HEALTHY WOMEN**

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B.Sc. Hon, University of Ottawa, 2001

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Abstract

Adiponectin is a protein secreted exclusively from adipose tissue, which is speculated to increase acute fatty acid oxidation rates. High-intensity exercise has been reported to have a greater capacity to increase absolute fat oxidation rates, as compared to low-intensity exercise. Hence, the objective of this study was to investigate the acute effects of exercise intensity on adiponectin levels in young healthy women. Nine healthy, moderately active women (age = 22 ± 2 years; BMI = 22.1 ± 2.5 kg/m²; VO₂peak = 43.9 ± 4.0 ml O₂/kg/min) performed in a randomized order three experimental sessions: control (C) with no exercise and two equicaloric (350 kcal), low-intensity (LIE) and moderate-to-high-intensity (M-HIE) exercise sessions on a treadmill at 40% and 70% VO₂peak, respectively. Experimental sessions took place during the follicular phase of the participant's menstrual cycle; therefore, sessions were spread out by at least one-month. Plasma adiponectin levels were measured before, at 15-minutes, at 30-minutes, and post exercise session (LI /M-HI) or control session. The results indicated that plasma adiponectin levels were comparable across conditions and remained unchanged over time within each session. These findings suggest that plasma adiponectin levels do not seem to be acutely modulated during and immediately after exercise of varying intensity in young healthy women.

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List of Abbreviations

| | |
|----------------------------|--|
| α | Alpha |
| ACC | Acetyl-coenzyme A carboxylase |
| ACSM | “American College of Sports and Medicine” |
| AMPK | AMP-dependent kinase |
| ANOVA | Analysis of variance |
| β | Beta |
| BMI | Body mass index, kg/m ² |
| CAT-I | Caritine-transferase transport system |
| CHO | Carbohydrate |
| CO₂ | Carbon dioxide |
| CNS | Central nervous system |
| FFA | Free fatty acid |
| FFM | Fat-free mass |
| FM | Fat mass |
| FQ | Food quotient |
| g | Gram |
| gArcrp30 | Adiponectin |
| h | Hour |
| HSL | Hormone-sensitive lipase |
| HI | High-intensity exercise |
| IASO | “International Association for the Study of Obesity” |
| IL-6 | Interleukin-6 |

| | |
|---------------------------------|---|
| IL-8 | Interleukin-8 |
| IOTF | “International Task Force on Obesity” |
| ISO | Isoprenaline infusion test |
| Kcal | Kilocalorie |
| Kg | Kilogram |
| LI | Low-intensity exercise |
| LPL | Lipoprotein lipase |
| m | Meters |
| mL | Milliliters |
| NAASO | “North American Association for the Study of Obesity” |
| NIH | National Institute of Health |
| O₂ | Oxygen |
| PPAR-α | Peroxisome proliferators-activated receptor alpha |
| RER | Respiratory exchange ratio |
| RPE | Ratings of perceived exertion |
| RQ | Respiratory quotient |
| SAT | Subcutaneous adipose tissue |
| SPSS | Statistical package for the Social Sciences |
| TG | Triglycerides |
| TNF-α | Tumor necrosis factor |
| TZD's | Thiazolidinedones |
| VAT | Visceral adipose tissue |
| VO₂ max | Maximal aerobic capacity |
| VO₂ peak | Peak aerobic capacity |

CHAPTER I

Introduction

1.1 Obesity, an epidemic problem:

Obesity is increasing at alarming rates and is closely becoming an epidemic in developed and non-developed countries around the world (<http://www.iotf.org>). This global issue is so troublesome that 'The International Task Force on Obesity' is labeling it by the term "globesity" (<http://www.iotf.org>). The World Health Organization (WHO, 1998, p.87) reported that 'obesity is becoming one of the most important contributors to ill health'. The WHO also addresses the fact that obesity is a major public health concern and highlights that focus should be placed on prevention and management of this health ailment (Seidell, 2000). Obesity is also influenced by factors such as age, gender, race, and socioeconomic class (Bouchard, 2000). More specifically, adult obesity is currently estimated to affect approximately 250 million people worldwide, which is about 7% of the world's population. Subsequently, this number is estimated to increase to ~300 million people by the year 2025 (Seidell, 2000). The American College of Sports Medicine (ACSM, 2001) reported that in the United States alone, 55-60% of adults are considered overweight and 20-25% of adults are thought to be obese. In Canada, it was found that 56% of men and 41% of women had a BMI greater than 25 kg/m² (www.nasso.org). Consequently, the National Institute of Health (NIH) dictates that a BMI of greater than 25 kg/m² is indicative of a need for weight loss measures to be taken (as cited in ACSM, 2001). Unfortunately, less than 5% of adults who lose weight have actually been successful in maintaining weight loss five years later; and approximately 62% return to their initial body weight (Schonfeld-Warden & Warden, 1997). Accordingly, the National Heart, Lung, and Blood Institute (NIH) in collaboration with other NIH organizations attempted to elicit guidelines for the prevention and treatment of obesity and its co-morbidities (Bouchard, 2000). As a

result, a limited amount of research was found outlining the influential role of physical activity in the prevention and treatment of obesity, highlighting the need for subsequent research in this area.

1.2 Health consequences:

Obesity is associated with many health consequences that are recognized as being major contributors to cardiovascular disease, non-insulin dependent diabetes mellitus, hypertension, hyperlipidemia, hyperinsulinemia, and some forms of cancer (ACSM, 2001; Bouchard, 2000). Similarly, obesity causes physical and behavioural problems such as osteoarthritis, sleep apnea, social stigmatization; and, other psychological consequences such as depression and low self-esteem (Bray, 2000). In effect, the estimated cost of the treatment for obesity and its co-morbidities is approximately 2-8% of total sick care costs in Western countries (<http://www.iotf.org>).

1.3 Impact of physical inactivity

There are approximately 300,000 deaths a year attributable at least in part to obesity (Bouchard, 2000). Physical inactivity, as part of a sedentary lifestyle is a known contributor to the increased risk of obesity (Tremblay, Doucet, & Imbeault, 1999). Other health risks associated with inactivity are: heart disease, high blood pressure, adult-onset diabetes, osteoporosis, stroke, depression, and colon cancer (Health Canada, 2003). Conversely, the benefits of regular physical activity are: improved fitness, enhanced posture & balance, improved self-esteem, muscle & bone strengthening, increased energy, reduced stress, and weight control (Health Canada, 2003). The ACSM (2001) suggests that the average adult should spend at least 30 minutes a day of moderate intensity physical activity on most, if not all, days of the week. Health Canada (2003) recommends that sedentary individuals begin with at least 60 minutes of physical activity every day in order to build a healthy foundation. Health Canada (2003) also highlights the importance of continuously improving exercise intensity. Hence, as improvements are made from the minimum set standard, one can adjust time spent in physical activity by increasing the intensity of the exercise. In terms of

weight control, or more specifically, the problems associated with correcting obesity, it is important to consider that exercise is only one important part of the energy balance equation; the other part being energy intake, as discussed below (Tremblay et al., 1999). For weight loss to occur there needs to be a shift in this balance, an increase in energy expenditure (i.e., physical activity/exercise) and/or a decrease in energy intake (Tremblay et al., 1999). Miller, Kocaja, and Hamilton (1997) conducted a meta-analysis over a 25 year period (1969-1994) on the effect of diet and diet plus exercise programs on weight loss. It was found that short-term weight loss occurred with both diet only and diet-exercise groups; thus, manipulations of energy balance. However, due to the limited amount of research available on the long-term effects of weight loss it is recommended that exercise should be part of the maintenance process (Miller et al., 1997; van Baak, 1999).

1.4 Energy balance:

Energy balance occurs when energy intake is equal to energy expenditure (Tremblay et al., 1999). Essentially, when more energy is consumed than is expended, the energy balance becomes positive. The body then stores the surplus of energy mostly as excess fat; however, it can be deposited as protein and glycogen as well. Conversely, when energy expenditure exceeds energy intake there is a negative energy balance, which is ideal for weight loss. Obese and overweight individuals tend to be in a positive energy balance; however, this is not the case in all circumstances. Nonetheless, the goal is to create an energy deficit to promote weight loss. It is also important to consider inter-individual variability in terms of metabolic rate, metabolic efficiency, and appetite control (Brooks, Fahey, White, & Baldwin, 2000). Accordingly, for the obese clientele, much research has focused on the ideal combination of exercise and diet, which ultimately can create a negative energy balance. Specifically, various studies have successfully displayed the positive impact of consuming a low-fat diet and increasing energy expenditure using exercise as a modality for improving energy balance, in both men and women (Dionne, Johnson, White, St-Pierre, &

Tremblay, 1997; Dionne & Tremblay, 2000; Tremblay, Almeras, Boer, Kranenbarg, & Despres, 1994). Further, it has been postulated that increasing exercise intensity from low-to-moderate to high, may actually improve energy balance by stimulating fat oxidation and promoting body fat loss. This notion will be further discussed in the proceeding sections.

1.4.1 Energy intake:

As has been previously stated, in order to maintain stable body weight, it is essential that energy intake match energy expenditure. Energy intake refers to the actual macronutrient intake of dietary foods. Generally, it has been reported that overweight and obese individuals tend to have a diet which contains higher energy density foods, due to the increased fat content, as compared to normal-weight individuals (Tremblay & Almeras, 1995; Westerterp, 2000).

1.4.1.1 Difference in substrate utilization:

It is well known that there are three major macronutrients of food; namely proteins, carbohydrates, and fats that play key roles in energy balance (Tremblay & Almeras, 1995). In terms of energy intake, it is also known that inter-individual variability accounts for a majority of the differences observed among individuals. Additionally, alcohol, which is not considered a macronutrient *per se*, plays a minimal but considerable role in energy balance (Dionne & Tremblay, 2000; Tremblay and Almeras, 1995).

1.4.1.1.1 Proteins:

Proteins represent a small, nevertheless, important part of total daily energy intake that contributes to essential physiological functions of the body. Specifically, proteins are responsible for the maintenance and repair of tissues (Dionne & Tremblay, 2000). Protein intake and protein utilization (via amino acids) are relatively constant in the body. Therefore, the body mainly relies on carbohydrates and fats for body weight maintenance (Flatt, 1995). Further, it has been postulated that proteins display a satiating effect that may in fact reduce energy intake (Rolls, Hetherington, &

Burley, 1988). By definition, proteins are low-density macronutrients that claim a higher thermogenic effect than its counterparts, carbohydrates and fats (Dionne & Tremblay, 2000).

1.4.1.1.2 Carbohydrates:

Similar to proteins, carbohydrate energy balance is well maintained in the body, in terms of intake and oxidation (Flatt, 1995; Schrauwen, 1997; Tremblay & Almeras, 1995). Carbohydrates are known to produce more of a satiating effect with lower energy intake, as compared to fats, but are still less than proteins. Thermogenesis of carbohydrates occurs mainly as a function of increased sympathetic nervous system (SNS) activity and; thus, represents approximately 10% of energy content (Dionne & Tremblay, 2000).

1.4.1.1.3 Fats:

Fats, due to their high-energy densities, display the lowest capacity for promoting satiety and allowing a low energy intake. As well, they supply the lowest ability to increase energy expenditure to support a negative energy balance (Dionne & Tremblay, 2000; Tremblay & Almeras, 1995).

1.4.1.1.4 Alcohol:

Alcohol consumption represents only 5% of total caloric intake of the average person in the United States (Dionne & Tremblay, 2000). Thus, it is clear that alcohol consumption plays a minute role on energy balance. However, even when consumed moderately, alcohol suppresses lipid oxidation and favours fat storage (Dionne & Tremblay, 2000; Suter, Schutz, & Jequier, 1992; Tremblay & Almeras, 1995).

1.4.2 Energy expenditure:

There are three main components that affect energy expenditure; namely, resting metabolic rate (RMR), the thermic effect of food (TEF), and physical activity (EE_{ACT}).

1.4.2.1 Resting metabolic rate:

Resting metabolic rate (RMR) is the minimum amount of energy required by the human body to maintain normal physiological functions in a fasted state at resting conditions. RMR accounts for approximately 70% of total daily energy expenditure in humans (Melby, Ho, & Hill, 2000). There are many variables that are considered to influence RMR such as fat-free mass (FFM), gender, and age. Specifically, the internal organs that proclaim high metabolic activity are the liver, brain, heart, lungs, and kidneys. A gender effect can also be seen in that men tend to have higher RMR values than women, which is increasingly more prevalent with increasing age. Additionally, gender differences have been reported with regard to weight reduction. In a study conducted by Doucet et al. (2000), it was observed that weight loss, in men only, resulted in a significant decrease in resting energy expenditure (REE). No significant differences were found in women even when adjusted for fat mass (FM) and fat-free mass (FFM) loss. However, it was suggested that FM would be the best predictor of any changes in REE, in women. As for the potential role of physical activity on RMR, conflicting literature exists. Some research has shown that trained individuals, as compared to sedentary individuals, display an increased RMR, while others have illustrated no differences between groups. Nonetheless, these conflicting results may be due to methodological weaknesses. As such, various studies differ in the time elapsed between the last exercise bout and the actual RMR measurement consistently ranging from 24-56 hours (Melby et al., 2000).

1.4.2.2 Thermic effect of food (TEF):

The thermic effect of food (TEF) incorporates approximately 8-10 % of daily energy expenditure (Melby et al., 2000). This mechanism involves the energy costs of digestion, absorption, and assimilation of macronutrients, not to mention, the additional costs associated with increased plasma insulin levels, which are caused by increased sympathetic nervous system (SNS) activity (Melby et al., 2000). Further, it has been suggested that carbohydrate-rich diets create a

larger TEF, as opposed to high fat diets (Schrauwen, 1997). Similar to RMR, the effect of physical activity on TEF has not been well established due to further conflicting findings. Nevertheless, it is assumed that the effect would be minimal and that the major benefits exhibited from exercise, as part of weight management approach, would be from increased energy expenditure (Melby et al., 2000).

1.4.2.3 Physical activity:

The energy expended during physical activity (EE_{ACT}) accounts for approximately 15-50% of total energy expenditure (TEE) and is highly variable between and within individuals (Melby et al., 2000). EE_{ACT} depends on habitual exercise performance and efficiency, in addition to the body mass of an individual (Melby et al., 2000).

1.4.3 Impact of exercise as a treatment for obesity:

With the overwhelming prevalence of obesity among the adult population, the challenge in spite of everything remains in determining an infallible yet successful method for prevention and/or treatment. As has been previously stated, one approach to modulating energy balance is to create an energy deficit by increasing physical activity. At this point, it is not clear if exercise alone can produce a substantial amount of weight loss compared to dietary modifications (ACSM, 2001; van Baak, 1999). In effect, there is evidence to suggest that the combination of dietary modifications and exercise can be an effective approach for weight loss (Miller et al., 1997; van Baak, 1999). Nevertheless, it has been shown that exercise can play a prominent role in weight loss maintenance (ACSM, 2001; Tremblay et al., 1999). Further, exercise has shown to be effective in increasing fat oxidation in muscle, which enhances the availability of free fatty acids (FFA) in mitochondria and improves the rate of utilization (Ravussin & Smith, 2002). Other health benefits include cardiovascular fitness, insulin sensitivity, blood pressure, blood lipid profiles, and psychological well being (van Baak et al., 1997).

Currently, the ACSM (2001) recommends a minimum exercise prescription of 150 minutes a week (5 d, 30 min/day) at low-to-moderate intensities. It is recommended that individuals participate in 20-30 minutes of moderate intensity activity (50% VO_2 max), 2-3 times per week (Tremblay et al., 1999). Conversely, some studies have shown that increasing the intensity of exercise may favour an energy deficit and; in effect, may potentially cause weight loss which may in turn be beneficial for the obese clientele (Imbeault, Saint-Pierre, Almeras, & Tremblay, 1997; Tremblay et al., 1999).

Furthermore, research has shown that acute and chronic exercise bouts are beneficial for improving certain metabolic parameters, especially insulin resistance (Henriksen, 2002). This is promising for the overweight and obese population since some of the adaptations to exercise include improvements in insulin action on skeletal muscle glucose transport systems, decreased hormonal stimulation of hepatic glucose production, enhanced blood flow to skeletal muscle, and stabilization of unhealthy blood lipid profiles (Henriksen, 2002). Accordingly, it is clear that energy and fat balance are influenced, in the long term, by increased physical activity and ultimately cause reductions in plasma FFA, leptin and insulin levels (Henriksen, 2002). In addition, it has been stipulated that physical activity may increase resting metabolic rate (RMR) and activate the sympathetic nervous system (SNS) (Tremblay et al., 1999).

Consequently, in the obese and overweight population, when energy expenditure is increased there is always the possibility that the metabolic and hormonal demands placed on the body will be too great and they will want to compensate by increasing energy intake. In other words, they may increase energy expenditure by increasing their physical activity level, but at the same time, they are increasing energy intake and defeating the purpose of creating a negative energy balance. Unfortunately, the only known way to resolve this issue, at the present time, is to impose stricter dietary restrictions to avoid this counteractive cycle (Tremblay et al., 1999).

Moreover, research has shown that the combination of a low-fat diet and physical activity can reduce body weight by as much as 10-15% in obese individuals (Tremblay et al., 1999). This finding is concurrent with the ACSM (2001) recommendations that advocates that a weight reduction of 5-10% will improve health consequences by decreasing blood lipids, blood pressure, and factors related to diabetes mellitus. Therefore, it is abundantly clear that the combination of diet and exercise is an effective method to create a negative energy balance (ACSM, 2001; Tremblay et al., 1999).

1.5 Fat balance:

It is apparent, thus far, from the available literature that there is a parallel relationship that exists between energy and fat balance. This highlights the notion that carbohydrate and fat metabolism are the main physiological mechanisms involved in weight maintenance (Dionne & Tremblay, 2000). In effect, macronutrient intake and oxidation should occur at similar rates, in order for fat balance to be achieved. This notion is well represented by Flatt's RQ/FQ concept, in which RQ represents the respiratory quotient and FQ represents the food quotient expressed as function of VCO_2/VO_2 (Dionne & Tremblay, 2000). As such, macronutrient balance is achieved when energy intake spontaneously corresponds with energy expenditure (Tremblay & Almeras, 1995). In other words, in free living conditions, energy balance occurs when the energy substrate is matched to its oxidation (Tremblay & Almeras, 1995). Collectively, the RQ: FQ ratio is a direct reflection of energy balance, in that, a ratio of greater than 1.0 claims a positive energy balance and a ratio of less than 1.0 represents a negative energy balance (Dionne & Tremblay, 2000). Consequently, when the RQ: FQ is approximately 1.0, it is assumed that proteins, carbohydrates, and fats are in equilibrium; and as a result body weight maintenance should occur (Dionne & Tremblay, 2000).

Unlike carbohydrates and proteins, fat balance is not efficient in its acute regulation in the body. In fact, an increase in certain dietary fats promotes storage rather than oxidation. There is no

known direct regulatory interaction between fat intake and fat oxidation; thus, these variables are largely determined by the fuel utilization from macronutrient intake. As such, fat-containing meals cause lower postprandial insulin release which have less impact on fat oxidation. In effect, due to the lower amounts of carbohydrate intake relative to fat intake, liver and muscle glycogen stores are more likely to be maintained at a lower level. As a result, there is generally a decrease in insulin concentrations and an increased rate of fatty acid release and oxidation between meals (Flatt, 1995; van Baak, 1999). Nonetheless, acute changes in fat balance do occur at minimal rates; however, it is repeated imbalances between fat intake and fat oxidation that are the trigger of increased adipose tissue size.

Accordingly, fat balance is adaptable to body weight changes and is regulated in the long term, as a result of the body's metabolic ability to adjust fat intake and oxidation to equilibrium (Melby, Commerford, & Hill, 1998; Schrauwen, 1997). It should be noted, however, that there is also some support for the notion that those that obese individuals or those susceptible to obesity for genetic and/or lifestyle factors, display an even greater delayed-onset ability to increase fat oxidation, relative to fat intake, as compared to normal-weight individuals (Schrauwen, 1997). Additionally, it has been speculated that obese individuals tend to have impaired fat oxidation rates (Guesbeck et al., 2001; van Baak, 1999). Indeed, Guesbeck et al. (2001) examined substrate oxidation in formerly obese women during a fasted state and during exercise (65%VO₂max). The results revealed that RER values were elevated, indicating more carbohydrate oxidation relative to fat oxidation, in the obese women, in both the fasted state and during exercise. The authors suggest that this may be due in part to an impairment in fat oxidation rates but that further research needs to be completed to fully support this possibility. Nonetheless, it has been shown that obese individuals display higher rates of skeletal muscle glucose uptake, regardless of body weight loss, which indicates higher glucose availability as compared to free fatty acid (FFA) availability (van Baak,

1999). Although the exact mechanism of function with regard to fat oxidation rates in obese individuals are not entirely known, it has been well established that repeated imbalances between fat intake and oxidation will lead to weight gain. Therefore, it is important that weight maintenance approaches for the obese clientele be primarily focused on achieving fat balance (Dionne et al., 1997).

1.5.1 Fat intake:

Fat intake, simplistically, is dependent on the fat content of foods selected and total amount consumed (Flatt, 1995). Accordingly, the main components of carbohydrates are starches and sugars, which are further broken down into glucose. In a similar mechanism, dietary fats, whose main elements are triglycerides, are further catabolized into free fatty acids (FFA) and glycerol constituents. The capacity of the body to store carbohydrates is limited. However, the need for glucose in the body is absolutely essential for daily physiological functions. Carbohydrates are extremely efficient macronutrients because of the rate and low energy cost of oxidation (Dionne & Tremblay, 2000). Furthermore, hepatic *de novo* lipogenesis is the mechanism responsible for accumulating fat in the body (Jequier & Tappy, 1999). In effect, if there is a surplus of carbohydrate intake when the glycogen stores are full, the excess is stored in adipose tissue via this process: *de novo lipogenesis* (which is reflected by a RQ = respiratory quotient > 1.0). Thus, indicating that fat storage exceeds fat oxidation (Dionne & Tremblay, 2000). However, this reaction only occurs in extreme cases of carbohydrate loading (Flatt, 1995). This is notwithstanding the fact that the conversion of carbohydrate and fat in comparison to dietary triglycerides into adipose tissue is not an energy efficient process (~25% energy cost versus ~0-2% energy cost) (Jequier & Tappy, 1999). As such, it must be noted that hepatic lipogenesis is responsible for only a small portion of total fat synthesis, which highlights the importance of adipose tissue lipogenesis (Jequier & Tappy, 1999).

1.5.2 Fat oxidation:

From the available literature, it is evident that protein and carbohydrate intake and oxidation are acutely regulated by the body, which enables amino acids and glucose to adjust oxidation rates to satisfy the degree of intake (Dionne & Tremblay, 2000; Jequier & Tappy, 1999). However, contrary to what seems logical, fat oxidation is not regulated by fat intake. It is actually the function of total energy expenditure minus the amount of energy intake from carbohydrates and proteins, and is dependent on body size and physical activity levels of individuals (Flatt, 1995). Furthermore, it has been stipulated that the body's fat storage capacity is a 100 times larger than that of carbohydrates. Therefore, fat stores are the main energy depots used by humans (Schrauwen, 1997).

Receding to Flatt's RQ: FQ concept, there are two main mechanisms proposed for which increased dietary fat intake causes increased rates of fat oxidation (Jequier & Tappy, 1999; Schrauwen, 1997). First, when there is an increase in dietary fat content of food, relative to carbohydrates, glycogen stores remain in a lower range; thus, decreasing glucose and insulin levels between food intakes. This creates a higher level of plasma fatty acid concentrations in the blood and inevitably increases fat oxidation between meals (Schrauwen, 1997). Additionally, it is known that various tissues in the body such as skeletal muscle breakdown triacylglycerol depots, which eventually increases adipose tissue mass; thus, increasing fat oxidation rates (Schrauwen, 1997). This increase in adipose tissue mass inevitably increases total body fat oxidation rates. However, it is not quite as simple as increasing the quantity of adipose tissue. Those with abdominal obesity tend to have the most pronounced increase in plasma free fatty acids levels. As such, there is elevated lipolysis in visceral adipose tissue (VAT), as opposed to subcutaneous adipose tissue (SAT), due to a reduced sensitivity to the inhibitory effects of insulin, which may be further explained by low density insulin receptors (Jequier & Tappy, 1999). In effect, continual

consumption of a high-fat diet will generally create a positive energy balance and ultimately lead to gains in body fat mass, which cause an increase in fat oxidation (Schrauwen, 1997).

1.5.3 Body fat mass:

Body fat mass is highly influenced by the notion of achieving fat balance. Obesity is associated with increased body fat mass, which is ultimately the result of repeated imbalances between fat intake and fat oxidation (Jequier & Tappy, 1999). As such, adipose tissue mass will increase until it reaches a certain point, after which it will stabilize and a new fat equilibrium will be established. In this regard, fat intake and fat oxidation will be balanced, although it may be at the cost of obesity (Melby et al., 1998). Two mechanisms have been hypothesized: (a) an enlargement of FFM causes an increase in RMR and enhances total energy expenditure; and (b) the increase in FM causes an increased rate of FFA release into circulation, which incites fat oxidation rates (Jequier & Tappy, 1999). Therefore, in order to create a negative fat balance, it is necessary to incorporate either a decrease in fat intake or an increase in exercise induced fat oxidation or more preferably both in combination (Melby et al., 1998). This will be further discussed in the succeeding section.

1.5.2.1 Impact of exercise on fat oxidation:

It has been well established that continuous aerobic exercise can increase fat oxidation rates during and subsequently after exercise training (van Baak, 1999). In support of this concept, Tschritter et al. (2003) compared two different groups of middle-aged women (N=22): endurance-trained (n=9) and untrained (n=13), on the acute effects of exercise in postprandial fat oxidation rates. It was found that both groups of women had increased total fat oxidation rates over a 6-hour period after exercise at 60%VO₂max for 90 minutes, in comparison to their fasted state. Thus, it is apparent that the women were oxidizing subsequently more free fatty acids (FFA) and triglycerides (TG) in skeletal muscle.

Moreover, other training effects of exercise on substrate utilization that have been reported are: a) that there is an increased number of mitochondria in skeletal muscle, b) increased oxidative enzymatic activation; c) increased β -oxidation; d) increased fatty-acid binding-protein content; e) skeletal muscle LPL changes; and f) changes in malonyl-CoA to favour fat oxidation rates. Not to mention the fact that exercise training improves lipolytic response to catecholamines of adipocytes most probably via increased levels of hormone-sensitive lipase (HSL) (van Baak, 1999).

As has been previously discussed, the size of adipose tissue mass plays a pivotal role in increasing FFA mobilization and oxidation in normal-weight and obese individuals. As such, research has shown that a reduction in body fat mass results in a subsequent decrease in relative fat oxidation rates (Tremblay & Almeras, 1995). This of course counteracts the optimal situation, which would be to lose excess body fat mass without decreasing fat oxidation rates. This vary notion was explored by Leijssen et al. (1998), in which it was found that low-intensity exercise without body weight loss, increased relative fat oxidation rates in obese individuals. This finding was further corroborated by Aggel-Leijssen, Saris, Hul, and van Baak, (2001), who found that caloric energy restriction in addition to low-intensity exercise training, with weight loss, could actually counteract the decline in relative fat oxidation in obese men. A similar trend with a comparable protocol had also been previously found in women (Nicklas, Rogus, & Goldberg, 1997). It has been speculated that this may be due to increased levels of HSL (van Baak, 1999).

Additionally, it is logical to assume that trained individuals, due to lower body fat mass, would possess lower relative fat oxidation rates; however, this is not the case when examining absolute fat oxidation rates. Trained individuals actually display a higher functional capability for mobilizing and oxidizing fat, due to the stimulatory effects on the sympatho-adrenal system (Tremblay & Almeras, 1995). Specifically, these functions include the activation of catecholamine release (Poehlman, Gardner, Arciero, Goran, & Calles-Escandon, 1994) and stimulation of the beta-

adrenergic receptors (Tremblay & Almeras, 1995; Tremblay, Coveney, Despres, Nadeau, & Prud'homme, 1992). Thus, exercise does have an impact on fat oxidation via the sympatho-adrenal system as long as exercise training dominates over the reducing effects of body fat loss. Unfortunately, if regular training is severely impaired or terminated an increase in fat mass may be the cost associated with restoring fat balance. Moreover, it has been suggested that an increase in exercise intensity from low-moderate (40-50% VO_2 max) to moderate-high ($\geq 70\%$ VO_2 max), may also have a positive impact on fat oxidation (Achten, Gleeson, & Jeukendrup, 2002; Imbeault et al., 1997). It is thought that this is due, in part, to the increased ability of the skeletal muscle in the body to oxidize fat (Tremblay, Simoneau, & Bouchard, 1994). More specifically, the malonyl-CoA mechanism has been suggested to play a pivotal role in regulating fat oxidation rates in animals and humans (Jeukendrup, Saris, and Wagenmakers, 1998) (see Figure 1). This process can be seen in the liver, heart, and skeletal muscle in humans. In effect, the accumulation of malonyl-CoA in the outer space of mitochondrial cells blocks entry of fatty acids to enter the inner space of mitochondria via carnitine-transferase transport system (CAT-I), to further undergo β -fat oxidation (Jeukendrup et al., 1998). During exercise, AMP levels are increased and act on AMP-dependent protein kinase (AMPK). This leads to the phosphorylation of acetyl-CoA carboxylase, $\text{ACC}_{\beta}\text{-OH}$ (active) to $\text{ACC}_{\beta}\text{-P}$ (inactive) and reduction in its activity. As a result, malonyl-CoA is not formed and FA's are oxidized from plasma FFA's or intramuscular triglycerides (Jeukendrup et al., 1998).

The effect of exercise on malonyl CoA levels

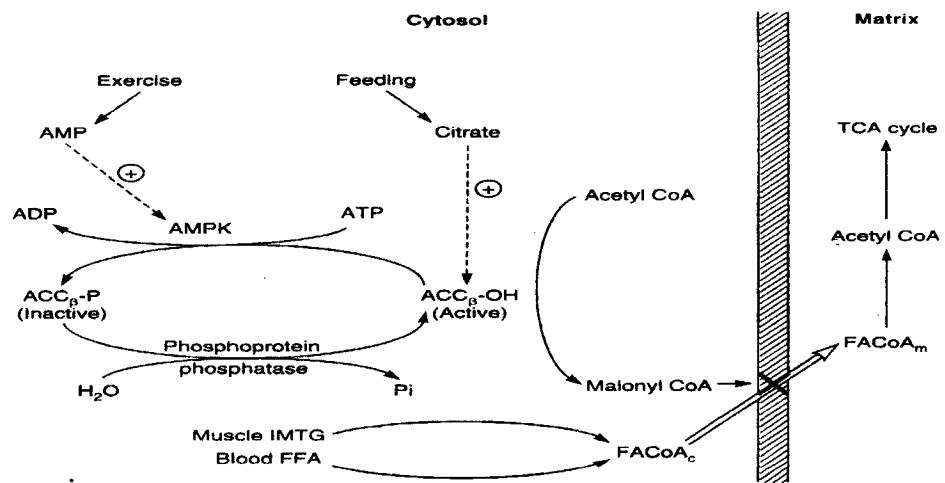


Figure 1. The effect of exercise on malonyl CoA levels. *Adapted with permission from Houston, (1995).*

1.5.2.2 Impact of exercise intensity on fat oxidation:

In general, health professionals recommend low-intensity exercise prescriptions to obese clientele as one method for weight loss. It has been well documented that low-intensity exercise is thought to be associated with increased relative and absolute fat oxidation rates, in both men and women (van Aggel-Leijssen, Saris, Wagenmakers, Senden, & van Baak, 2002). However, more recent literature has focused on the potentially more favorable effects of increasing exercise intensity on improving absolute fat oxidation and enhancing fat loss (Achten et al., 2002; Imbeault et al., 1997; Tremblay, Simoneau et al, 1994; Tremblay et al., 1999). Indeed, absolute fat oxidation rates seem to be optimal between 50 and 70% VO_2max (Jeukendrup et al., 1998). Clearly, one of the more obvious benefits of performing high intensity exercise is that the same amount of kilocalories can be expended in both low and high intensity exercise, but the time spent in high-intensity exercise is diminished substantially. To date, a limited amount of research is available on the impact of high intensity exercise on fat oxidation rates in humans. There is an even greater gap in the literature regarding the acute effects of exercise on fat oxidation rates.

1.5.2.2.1 The acute effects versus chronic effects of exercise intensity on fat oxidation rates:

In order to completely understand the widespread application of the long-term consequences of exercise (ie: chronic), it is necessary to regard the outcome measure(s) of a single bout of exercise (ie: acute effects). Establishing immediate short-term implications of certain physiological parameters provides a minimum exercise effect that can help to explain certain metabolic functions. Thus, the response to exercise training under short-term conditions is an important variable to consider (Thompson et al., 2001). For the obese population, because of their usually untrained state, it is important that a minimal standard be set in order to create benchmarks for which exercise interventions can be built upon (Thompson et al., 2001).

Thus far, it has been established that long-term high intensity exercise is associated with decreased adiposity and improved RMR (Tremblay, Simoneau et al., 1994; Tremblay et al., 1999). Several studies have reported that the acute effects of high-intensity exercise (70% VO_2max) after one week of daily exercise intervention were that insulin sensitivity improved. This is supposedly accounted for by the greater reductions in muscle glycogen content (Thompson et al., 2001). Conversely, other studies have shown that high-intensity exercise creates an inverse relationship between muscle triglyceride levels and insulin sensitivity, and thus relates to improving insulin resistance (Thompson et al., 2001). Research has also shown that the long term effects of high intensity exercise tend to be associated with increased absolute fat oxidation rates (Tremblay et al., 1999). In fact, van Aggel-Leijssen et al. (2002) examined that long-term effects of exercise training (LI=low-intensity 40% VO_2max and M-HI=high-intensity 70% VO_2max) on beta-adrenergic stimulation of fat metabolism in obese (n=23) and lean men (n=6) *in vivo*. As such, it was found that neither the low-intensity nor high-intensity exercise group improved in beta-adrenergic mediated relative fat oxidation rates. However, the results did indicate that the high-intensity group displayed increased glycerol rates. Thus, the authors contend that high-intensity-training may increase beta-adrenergic mediated lipolysis (van Aggel-Leijssen et al., 2002). Interestingly, the authors did not find impaired β -adrenergically mediated fat oxidation changes in obese participants when infused with isoprenaline (ISO) in incremental doses (a known stimulator of beta receptors), contrary to what has been stipulated in past studies. Indeed, fat oxidation rates were not impaired in this sample of obese participants. Nonetheless, the authors contest that this may be due to the variability in fitness levels between participants (van Aggel-Leijssen et al., 2002). Additionally, high-intensity exercise has been linked to decreased relative fat oxidation rates in men (Achten et al., 2002; Imbeault et al., 1997). Further, it was found that continuous moderate-to-high intensity exercise bouts (70% VO_2max) resulted in successive reductions in post-exercise energy intake resulting in a

negative energy balance (Imbeault et al., 1997). Nevertheless, these results have only ever been examined in men and; thus, further need to be investigated in women.

As such, Kanaley, Weatherup-Dentes, Alvarado, and Whitehead (2001) examined the acute effects and long term moderate-to-high-intensity exercise (65% VO_2 max) in lean ($n=8$) and obese women ($n=23$) on fat oxidation rates. The participants were required to complete a short-term exercise session of 30 minutes on a treadmill at 70% VO_2 peak, followed by a 16-week exercise-training program of aerobic training (3 times per week at 70% VO_2 peak). The results of the short-term exercise session indicated that fat oxidation rates increased up to 15 minutes of exercise which was significantly different from rest. However, fat oxidation rates did not increase substantially more at 30 minutes. Comparing the lean versus obese women, it was shown that obese women had a 30% higher relative fat oxidation rates by 30 minutes of acute exercise. Interestingly, no differences were observed at rest but group differences were apparent during exercise even when corrected for fat-mass (FM). The authors suggest that there may be differences between lean and obese in terms of intramuscular triglyceride utilization (Kanaley et al., 2001). With regard to the 16-week aerobic training, there were no resting or exercise induced fat oxidation rates changes in the obese women. Although the authors contend that the training program may not have been long enough to observe substantial results. Further, as would be expected, the authors did find a significant increase in CHO oxidation rates over the long-term (Kanaley et al., 2001).

Accordingly, Achten et al. (2002) further expanded on the acute effects of high intensity exercise on fat oxidation by examining various exercise intensities in order to determine a specific maximal fat oxidation rate in twenty healthy moderately active men ($N=20$). In addition, three interesting concepts were explored; namely, maximal fat oxidation (Fat_{max}), minimal fat oxidation, (Fat_{min}) and the optimal fat oxidation zone, (Fat_{max} zone). Fat_{max} is defined as being the highest rate of fat oxidation that can be observed during exercise. Fat_{min} is defined as being the exercise intensity

in which the fat oxidation rate is zero (i.e., $RER \geq 1.0$). Fat_{max} zone is a range of 10% (high and low) of exercise intensities with fat oxidation rates taken from Fat_{max} . Using these concepts Achten et al. (2002) observed that the average Fat_{max} was $0.60 \text{ g} \cdot \text{min}^{-1}$ at $64\% \pm 4\% VO_{2max}$ (range 42-84) and the Fat_{max} zone was between 55 ± 3 and $72 \pm 4\% VO_{2max}$. Further, it was found that above the highest value for Fat_{max} , fat oxidation decreased substantially and became negligible at $89 \pm 3\% VO_{2max}$ (range 71-99). This further corroborates the findings of Jeukendrup et al. (1998), in which it was found that exercise intensities over 85% VO_2 max decrease the body's use of plasma FFA's and muscle triglycerides. This decrease in available FFA's may be due to lower rates of appearance of FA's into blood plasma. Jeukendrup et al. (1998) contend that this, along with minimal reductions in lipolysis, is ominous of FA's entrapped in the adipose tissue. However, the exact mechanism for which a reduction in FFA oxidation during high-intensity exercise is observed is not yet known (Jeukendrup et al., 1998). These results further support the notion that the acute effects of high intensity exercise are that relative fat oxidation rates decrease as exercise intensity increases above moderate levels; however, absolute fat oxidation rates are increased. Additionally, the cumulative effects of increased high intensity exercise bouts over the long-term are that it may potentially create a negative energy balance and further increase absolute fat oxidation rates, which may inevitably lead to body fat loss (Imbeault et al., 1997). Moreover, it has also been established that maximal fat oxidation rates depend on an individual's capacity to oxidize free fatty acids (FFA) and can be improved with training (Achten et al., 2002). This is particularly promising, in particular, for the obese clientele in terms of the potential benefits of exercise. Thus, by continuously improving exercise frequency, intensity, and duration it is possible to ameliorate fat oxidation rates (Tremblay et al., 1999). As such, there is limited research available on this concept; thus, it would be warranted to further explore these trends. As a result, these promising findings may set a future precedent for weight loss alternatives. In addition, it should be noted that the acute effects of high intensity

exercise have mainly been examined in men; therefore, it is also warranted to investigate if these same observations can be corroborated further in women.

1.6 Adipose tissue as an endocrine organ:

In the past, adipose tissue was thought only to act as an energy reservoir or an inert depot for fat storage (Fruhbeck, Gomez-Ambrosi, Muruzabal, & Burrell, 2001; Saltiel, 2001). However, in more recent years, adipose tissue has been thought to act as an endocrine organ and actually be heavily involved in the metabolic and neuro-endocrine functions related to energy balance and fat metabolism (Berg, Combs, & Scherer, 2002; Fruhbeck et al., 2001; Havel, 2002). This implicates the importance of the sympathetic nervous system (SNS) in regulating fat oxidation rates, body weight, and insulin sensitivity (Ravussin & Smith, 2002) (see Figure 2).

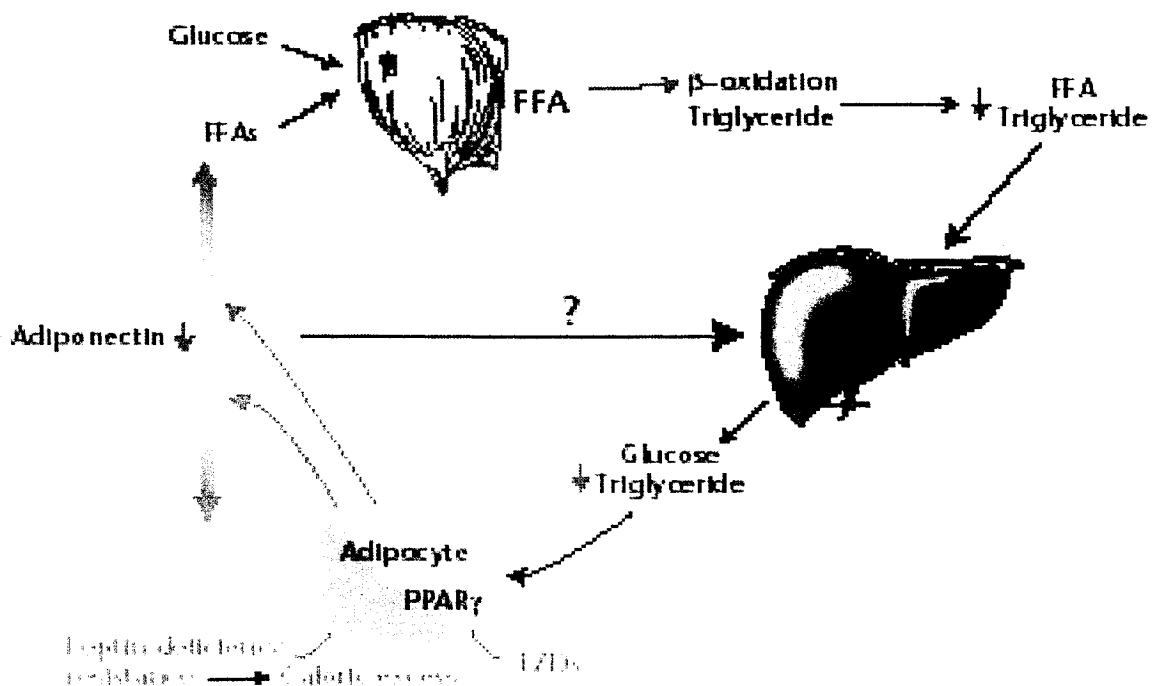


Figure 2. A hypothetical model for the mechanism of adiponectin. *Adapted from (Saltiel, 2001).*

It is well known that adipocytes play a vital role in endocrine, paracrine, and autocrine functions that affect important tissues such as the hypothalamus, pancreas, liver, skeletal muscle, kidneys, endothelium, and the immune system (Fruhbeck et al., 2001). It is also well established that one of the central roles of adipocytes is to store triglycerides when energy intake exceeds energy expenditure (Fruhbeck et al., 2001). Functionally, adipocytes secrete a number of enzymes and regulatory proteins, such as tumor necrosis factor (TNF)- α , leptin, adiponectin, interleukin (IL-6), interleukin (IL-8) (Bruun et al., 2003), and adiponectin, which carry out some of the most basic metabolic processes such as lipolysis and lipogenesis (Fruhbeck et al., 2001) (see Appendix A). The focus of much of the research over the last couple of years, with regard to proteins secreted by adipose tissue, has largely been on determining their specific structural and functional roles, in terms of energy metabolism. Undoubtedly, associations and cross-links can be made between these proteins and there is still much information that remains to be unfolded. For the scope of this text the main focus will be placed on the adipose-derived protein adiponectin and its effects on energy metabolism.

1.6.1. Adiponectin and metabolic parameters in humans:

It is clear that adipose tissue secretes a number of key hormones that contribute to energy metabolism; however, the one of particular interest is adiponectin. Adiponectin has been linked to acute fatty acid oxidation, which is said to play an intricate role in important metabolic functions associated with fat metabolism (Saltiel, 2001). Adiponectin is secreted exclusively from adipose tissue; normal concentrations range from 5-30 $\mu\text{g/ml}$ in plasma (Nishizawa et al., 2002). Adiponectin is also said to have the capacity to improve insulin sensitivity and correct hyperglycemia in obese individuals (Berg et al., 2002; Saltiel, 2001).

To date, it has not been given to humans in synthetic form. According to epidemiological studies, adiponectin is present in lower amounts in obese, compared to lean individuals (Berg et al., 2002; Saltiel, 2001). A gender dimorphism is also apparent, in that, women tend to have higher levels of adiponectin than men (Berg et al., 2002). It has been suggested that this gender difference may be the result of the presence of androgens in men. In effect, research has shown that androgens may decrease the production of adiponectin in mice. This highlights the notion that the presence of androgens, specifically, testosterone may have the capacity to cause hypoadiponectinemia, which may greatly increase the potential risk factors associated with insulin resistance and atherosclerosis in men (Nishizawa et al., 2002). Interestingly, the same group also reported that plasma adiponectin concentrations were not significantly different between pre-and post-menopausal women (Nishizawa et al., 2002). Thus, it is clear that sex hormones play a key role in regulating adiponectin concentrations; however, the exact mechanism for which this occurs is not yet known.

Adiponectin seems to be associated with various metabolic parameters that could potentially provide a link between insulin resistance, obesity, and its associated co-morbidities. Ryan et al. (2003) examined a cohort of 148 women aged 18 to 81 years with a BMI range of 17.2-44.3 kg/m² for certain physiological parameters that could be correlated with adiponectin concentrations. The women were broken down into different age groups: young (< 40 years), middle (40-59 years), and older (over 60 years). The results indicated that, as expected, that the women predisposed to diabetes (n=18) and actually diabetic women (n=23) displayed lower levels of adiponectin than normal glucose-tolerant women (n=108). Using univariate correlation analysis, it was found that plasma adiponectin concentrations were negatively associated with: BMI, percent body fat, visceral adipose tissue (VAT), and subcutaneous abdominal tissue (SAT), insulin, and leptin concentrations. There was also a positive correlation between adiponectin and glucose utilization across the age span (Ryan et al., 2003). As such, lower levels of adiponectin have been found in individuals with health

ailments other than diabetes mellitus, such that there have also been reports that hypoadiponectinemia is also related to coronary heart disease (CHD) (Berg et al., 2002).

As discussed, low adiponectin levels seem to be associated with various health ailments: diabetes mellitus, coronary artery disease, and most notably for this discussion, obesity. Interestingly, it has been stipulated that a decrease in BMI of 10% can induce an increase in circulating levels of adiponectin and improve insulin sensitivity (Berg et al., 2002). In support of this notion, Esposito et al. (2003) performed a randomized weight-loss control trial with obese women (N=120). After two years, adiponectin levels remained significantly increased ($2.2\mu\text{g/ml}$; $p = 0.01$) with continued weight maintenance. These results were independent of insulin sensitivity ($p = 0.007$). This provides support for the notion that weight reduction and maintenance, potentially through diet and exercise, may play a significant role in improving adiponectin levels. This will be elaborated on in the following sections.

1.6.2 Hormonal and non-hormonal regulation of adiponectin.

Over the past couple of years adiponectin has been linked to many hormonal and non-hormonal factors that may potentially affect, at least partially, its up-or downregulation via certain receptors. Indeed, factors such as TZD's, (Yu et al., 2002) β -agonists (Fasshauer, Klein, Neumann, Eszlinger, & Paschke, 2001), TNF- α (Fasshauer, Klein, Neumann, Eszlinger, & Paschke, 2002), ghrelin (Ott et al., 2002), and insulin all have distinct functions that notably seem to influence adiponectin gene expression (see Table 1).

Table 1. Studies reporting hormonal and non-hormonal regulation of plasma adiponectin concentrations

| Variable | Sample | Method | Conclusion(s) | Reference |
|-------------------|--|--|--|-------------------------|
| TZD's/ Insulin | N=27 lean, obese, & non-diabetic | Hyper-insulinemic- euglycemic glucose clamp pre & post 3 month Tr with TZD's | TZD Tr ↑ adipo levels in <u>all</u> subjects; insulin inhibited adipo (∴ adipo & insulin are ⊥) | (Yu et al. 2002) |
| β-agonists | 3T3-L1 adipocytes, <i>in vitro</i> | Adipo mRNA measured. Treatment of cells with isoproterenol* | Adipo gene expression was inhibited by β-adrenergic agents ∴ adipo may play a role in catecholamine-induced IR | (Fasshauer et al. 2001) |
| TNF-α | 3T3-L1 adipocytes, <i>in vitro</i> | Adipo mRNA measured.* Treatment of cells with insulin, TNF-α, and dexamethasone for 16H | Adipo gene expression was reversibly DR by insulin, TNF-α, and dexamethasone. ∴ adipo selectively controlled modulator of SI | (Fasshauer et al. 2002) |
| Ghrelin | Using brown AT model to test ghrelin mediated affects on adipo | Chronic ghrelin stimulation | Adipo gene expression was severely impaired, acutely and for several hours. ∴ ghrelin may possess selective effects on adipocyte signaling & function | (Ott et al. 2002) |
| IL-6 | 3T3-L1 adipocytes, <i>in vitro</i> | Adipo mRNA measured.* Treatment of cells with forskolin, TNF-α, and dexamethasone | Adipo gene expression is reversibly DR by IL-6 ∴ adipo selectively controlled modulator of SI | (Fasshauer et al. 2003) |

*Measured using quantitative real-time reverse transcription-polymerase chain reaction.

AT=Adipose tissues; DR=downregulated; H=Hour Tr=treatment; adipo=adiponectin; SI=insulin sensitivity; IR= insulin resistance; TZD's= thiazolidinedones

1.6.3. The role of adiponectin on fat oxidation:

Due to the novelty of this relatively new hormone secreted from adipose tissue and the modest amount of literature available, it is imperative to highlight some of the fundamental findings that preface the potential role of adiponectin on fat oxidation rates. Accordingly, in mice it has been found, *in vivo* that regular injections of gAcrp30, which are a proteolytic fragments inserted by dialysis, prevents high-fat diet induced weight gain without any changes in food consumption (Berg et al., 2002). It has been postulated that this may be due to the fact that gAcrp30 causes an acute increase in fatty acid oxidation in isolated muscles via the increased stimulation of beta-oxidation (Berg et al., 2002). Similar effects can be seen with regard to the administration of full-length adiponectin homologues in mice. As a result, it has been found that in resting conditions, adiponectin levels exhibit an insulin-sensitizing effect on hepatocytes, resulting in the suppression of hepatic glucose output (Berg et al., 2002).

Due to the promising findings in mice concerning the possible link between adiponectin and obesity related functions, in more recent years, naturally the focus has shifted from animals to humans (see Table 2). As such, English, Coughlin, Hayden, Malik, & Wilding (2003) found that postprandial plasma adiponectin concentrations increased over a 180 minute period in obese individuals (n=11) reaching eminent proportions at 60 minutes (2.9 [range 2.1 to 4.1] to 12.1 [range 8.5 to 17.4] µg/ml) after a fixed breakfast. However, there were no significant increases in adiponectin levels in lean individuals (n=13) over the same time-span. These particular results highlight the potential effects of postprandial lipid metabolism in obese patients, which may provide a link between adiponectin concentrations and acute fat oxidation that has been shown in mice. The authors also contend that these results may offer a solution to those obese individuals that are insulin resistant because there seems to be beneficial effects in terms of glucose and lipid metabolism with a rise in adiponectin, in particular, on maintaining normal glucose tolerance (English et al., 2003).

Table 2. Selected studies reporting relevant findings, with regard to plasma adiponectin levels, in humans.

| Authors Year | Design | # Subjects | Results |
|-------------------------|-----------------|--|--|
| English et al. (2003) | Cross-sectional | n=11 obese; n=13 lean | Postprandial adipo ↑ in obese over 180 min; adipo did <u>not</u> ↑ in lean, at rest |
| Gavrilla et al. (2003) | Cross-sectional | N=6, healthy, normal weight men | Adipo displays ultradian & diurnal variation with a ↓ at night, reaching nadir early in the morning 24-H variations similar to cortisol, suggesting a potential relationship Out-of-range with leptin diurnal variations |
| Peake et al. (2003) | Cross-sectional | n=24 normal weight; n=20 prone-Type II diabetes (29F:15M); healthy & sedentary | Adipo did not change in response to a high-fat meal Fat meal did not activate adipo proteolytic conversion |
| Ryan et al. (2003) | Longitudinal | N=148 women (18-81 years) | Adipo does not Δ with age; neg associated with: % body fat, VAT, SAT, insulin, & leptin, in women Positively correlated with glucose utilization |
| Stefan et al. (2002) | Correlational | N=93 [18W (14 men & 4 women) and 75 Pima Indians (55 men & 20 women); healthy | Adipo were neg correlated with WTR & %body fat, no correlation b/w adipo & 24-hour RQ, no correlation b/w adipo & 24-H EE |
| Tschitter et al. (2003) | Correlational | n=262 using euglycemic-hyperinsulinemic clamp & n=636 using OGTT, healthy non-diabetic men & women | Adipo neg correlated with fasting TG & FFA concentrations in both men & women; thus insulin-sensitizing effect present |
| Yang et al. (2003) | Correlational | N=66 non-diabetic healthy obese women, undergoing elective abdominal surgery | Subcutaneous relative adipo mRNA correlated with omental relative adipo; adipo in omental tissue was related to TG metabolism No regional difference with respect to adipo mRNA levels |

Adipo=plasma adiponectin; H=hour; F=female; M=male; Δ=change; WRT=waist-to-hip ratio; VAT=visceral adipose tissue; SAT=subcutaneous adipose tissue; TG=triglycerides; FFA=free fatty acids; EE=energy expenditure; OGTT=oral glucose tolerance test; neg=negative.

With this idea in mind, it would be warranted to investigate if adding the stimulatory effects of exercise to a similar protocol would elicit a similar outcome in the pattern of adiponectin, in both lean and obese individuals.

In accordance, it appears that a relationship exists between elevated adiponectin levels and increased lipid metabolism. Specifically, it has been found that adiponectin levels are associated with decreased liver and muscle triglycerides, in addition to decreased triglyceride and FFA concentrations in plasma (Berg et al., 2002). Indeed, Peake, Kriketos, Denyer, Campbell, and Charlesworth (2003) explored the possible relationship between adiponectin levels and plasma fatty acid concentrations after consumption of a high-fat, low CHO-meal (N=44 [20F; 15M] healthy, sedentary, non-smokers). Additionally, the authors attempted to establish if postprandial activation of adiponectin via the development of proteolytic fragments was occurring, which has been shown in mice. The results indicated that there was no significant change in postprandial plasma adiponectin concentrations over a 6 hour period. These results were concurrent with a previous study that examined an undefined meal (Hotta et al., 2000). Furthermore, there was no evidence of the production of proteolytic fragments in the postprandial stage. The substantiation from this particular study determined that, unlike mice, adiponectin may not acutely regulate circulating fatty acid metabolism in humans. However, the authors did not collect calorimetric data in order to examine relative fat or CHO oxidation rates. As a result, only absolute circulating plasma triglyceride and plasma NEFA [mmol/L] were shown. It would have been interesting had the authors included this type of data, in order to determine if adiponectin concentrations, in fact, do not influence fatty acid metabolism at the cellular level. Thus, it would be warranted to measure individual respiratory quotients in order to identify specific CHO and fat oxidation rates. Certainly, more research is needed in this particular area in order to draw definitive conclusions.

In a recent study by Yamauchi et al. (2002) it was speculated that adiponectin increases phosphorylation and activity of 5'-AMP-activated protein kinase (AMPK) (see Figure 3). As well, it simultaneously increases glucose uptake and lactate production in myocytes in skeletal muscle in addition to reducing glucose levels, *in vivo*. Further, adiponectin promotes an increase in phosphorylation of acetyl coenzyme A carboxylase (ACC) and fatty-acid oxidation in myocytes and hepatocytes mediated by AMPK (Yamauchi et al., 2002). Thus, it is apparent that AMPK is activated by adiponectin and plays a key role in regulating glucose metabolism and insulin sensitivity, *in vitro* and *in vivo*. The authors also contend that adiponectin does not necessarily increase AMP kinase activity (AMPK); however, it may increase cellular AMP levels by an unknown mechanism. It is suggested that this may be due to mitochondrial uncoupling or activation of adenine nucleotide phosphates. Interestingly, the authors also mention that other key factors in the activation of AMPK in addition to adiponectin are leptin and exercise, which seemingly may play a substantial role in the regulation of energy expenditure and glucose and lipid metabolism. It has also been elucidated that the AMPK pathway may possess useful targets for therapeutic agents intended to decrease 'lipotoxicity' in patients with obesity and type II diabetes. Thus, at this point, it is clear that there seems to be an acute effect of fat oxidation that is prevalent in mice. These findings were further corroborated by Tomas et al. (2002), in which they found a 30% decrease in the concentration of malonyl-CoA; thus, eliciting an increase in fatty acid oxidation in mice, *in vitro* and *in vivo*. Further, Chen et al. (2003) unveiled that ACC- β phosphorylation was highly responsive to increased exercise intensity and AMPK signaling; in addition to following the same general pattern of fat oxidation rates during acute exercise. Nevertheless, it would seem that AMPK activation is not reliant on AMPK kinase activation during exercise (Chen et al. 2003). In this sense, it may potentially elude to the fact that another mechanism may be involved, namely

The effect of exercise on malonyl CoA levels

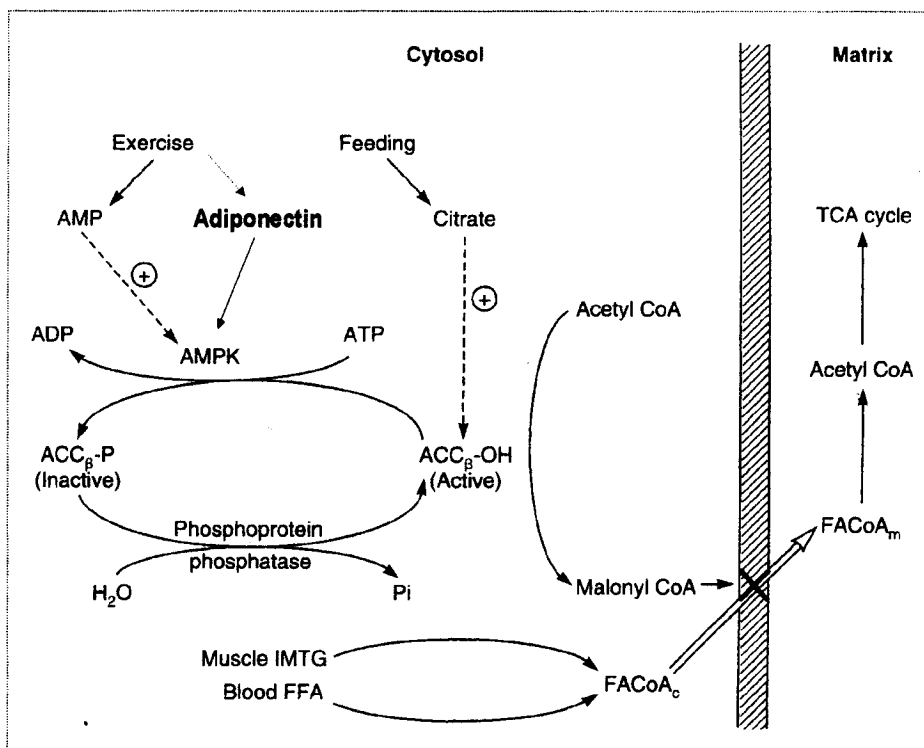


Figure 3. The effect of adiponectin on exercise and malonyl CoA levels. *Adapted from Houston, (1995).*

adiponectin.

Accordingly, Stephan et al. (2002), to the best of our knowledge, were the first to examine if an increase in fat oxidation rates using 24-hour energy expenditure (EE) were present in humans. More specifically, plasma adiponectin concentrations of 75 healthy, non-diabetic Pima Indians were measured using a 24-hour energy expenditure chamber in resting conditions only. The results illustrated that fasting plasma adiponectin levels did not play a role in the whole-body regulation of fat oxidation and energy expenditure. Indeed, it should be noted that a 24-hour energy expenditure respiratory chamber is not the ideal tool to be used to measure acute changes in substrate utilization, due to free-living conditions such as spontaneous activities and postprandial states.

Moreover, in humans, adiponectin levels have been found to be negatively correlated with body weight, fat mass and resting insulin levels (Berg et al., 2002). Zietz et al. (2003) found that serum adiponectin levels were correlated to HDL-cholesterol ($r = .86$; $p < .001$; $n = 523$) independent of age, gender, BMI, and fasting insulin concentrations. In terms of weight reduction, Yang, Wang, Hu, and Yang (2001) examined 22 obese individuals and found that weight loss caused plasma adiponectin levels to increase by a mean of 46 %. In effect, research has also shown that a strong positive correlation exists between adiponectin levels and insulin-stimulated glucose uptake (an indicator of insulin sensitivity). Specifically, Weyer et al. (2001) found, while comparing Caucasians and Pima Indians, that a decrease in plasma adiponectin levels (hypoadiponectemia) was more closely related to the degree of insulin resistance and hyperinsulinemia, rather than the degree of adiposity and glucose intolerance.

Furthermore, studies have shown a possible link between adiponectin levels and insulin resistance by using thiazolidinedones (TZD's), an insulin-sensitizing drug that improves insulin resistance and lowers plasma levels of both glucose and insulin in several genetic models of obesity (Berg et al., 2002; Yu et al., 2002). It was found that TZD's significantly increases plasma

adiponectin concentrations in insulin-resistant humans, suggesting that there is an inverse relationship between plasma adiponectin and insulin levels. However, at this point, it is not known if decreased adiponectin levels are the cause or effect of any abnormal metabolic conditions (Berg et al., 2002; Yu et al., 2002).

1.6.3.1 Impact of acute exercise and adiponectin concentrations on fat oxidation:

Given the fact that weight reduction in obese individuals seems to cause an increase in plasma adiponectin concentrations, it is plausible to believe that exercise may exhibit similar effects. In essence, this is due to the fact that exercise is one component that can potentially lead to an increase in weight reduction and improvements in absolute fat oxidation rates. Nevertheless, it has yet to be seen if adiponectin is related to adaptive responses to exercise, acute and chronic, which exist for such events as a shift in fuel oxidation (see Table 3). This would further facilitate lipid flux and favour beta-oxidation of fatty acids rather than carbohydrates as the primary energy source (Berg et al., 2002). At this point, only one study has examined the acute effects of adiponectin and exercise. In particular, Kraemer et al. (2003) investigated the acute effects of continuous and progressively intermittent high-intensity exercise on adiponectin levels. The participants included a group of young healthy moderately-active men (n=6) and a group of highly trained male runners (n=7). Moderately-active men ran on a treadmill at 79% VO_{2max} for 30 minutes continuously. Well-trained runners completed intermittent exercise on a treadmill for 60, 75, 90, and 100% VO_{2max} . The results indicated that the moderate-trained group of male participants did increase adiponectin levels, however, when the results were adjusted for plasma volume shifts the results failed to show significance. In the highly-trained group, it was shown that there was also an increase in adiponectin levels over time but when compared to the control the values were not significant. The authors concluded that despite the obvious trend of increasing adiponectin levels after 30 minutes of high-intensity continuous and intermittent running the results were not statistically

significant. The authors preclude that the increase may have been produced by increased plasma volume shifts (Kraemer et al., 2003). Similarly, only one study to date has been published that examines the potential relationship between adiponectin concentrations and chronic exercise (Hulver et al., 2002). Subsequently, it was found that adiponectin was not affected by long term regular aerobic exercise training (6 months of exercise training, 4 day/wk for ~45 min at 65-80% VO_2peak), with no loss of body mass or fat mass, regardless of improvements on insulin action (Hulver et al., 2002).

In sum, the literature has shown that there seems to be a relationship between elevated adiponectin levels and increased fat oxidation in mice. In humans, the specific role(s) of adiponectin are not as clear; however, it has been shown that weight loss in obese individuals can improve adiponectin levels. Only one study to date has examined the acute effects of exercise on fat oxidation rates and adiponectin levels. More specifically, limited information is available on the acute effects of low versus high intensity exercise on fat oxidation rates with regard to adiponectin concentrations. Further investigations need to be made primarily because acute high intensity exercise has been associated with increased absolute fat oxidation in humans (Achten et al., 2002; Imbeault et al., 1997) as has been previously discussed. This will further contribute to our understanding of whether or not an adipose tissue derived protein such as adiponectin is acutely influenced by a low and/or high intensity exercise session in terms of substrate utilization. From a clinical perspective, this knowledge may be particularly beneficial for the obese clientele because adiponectin may provide a link to explaining the associated consequences of obesity, whether it is insulin resistance and/or impairments in fat oxidation rates.

Table 3. Studies reporting the effect of exercise on plasma adiponectin concentrations in humans.

| Authors | Year | Design | # Subjects | Acute/Chronic | Results |
|-----------------------|------|--|---|--|---|
| Kraemer et al. (2003) | | Acute exercise: 30 min (MI) continuous Intermittent: using 4 different intensities (60, 75, 90, 100%) VO _{2max} | Acute: 6 healthy males Intermittent: 7 trained runners | Acute/intermittent | Acute: ↑ adipo, not sig. after correction plasma volume shift Intermittent: Δ's adipo over time, but not sig. b/w exercise responses & C |
| Hulver et al., (2002) | | EG & WL group, pre-post 6 months exercise training | EG: 11, sedentary, healthy subjects [3F, 8M] WL: n=14 morbidly obese[3M, 11F], via gastric surgery | Chronic, 6months (4 days/wk for ~45 min @ 65-80% VO _{2peak}) | Adipo not altered with exercise training, despite ↑ insulin action |
| Ryan et al. (2003) | | Longitudinal, WL group, WL + AE, and WL +RE | N=40[WL=15, AE=16, AR=9], sedentary, overweight/obese, post-menopausal women | Chronic (3x/wk), 6 months | Plasma adipo did not Δ with a 6 month MI exercise training |
| Yatagai et al. (2003) | | Longitudinal | N=20, healthy non-obese men | Chronic (5 days/wk; 60min/day at LT intensity) | Adipo pos. correlated with SI Normal values resumed after 1-wk ∴ ET-induced ↑ SI not dependent on ↑ in adipo |

MI=moderate-intensity exercise; Adipo=adiponectin; EG=exercise-group; WL=weight-loss group; F=female; M=male; wk=week; AE=aerobic exercise; RE=resistance exercise; Δ= change; SI=insulin sensitivity; ET=exercise training; C=control; b/w=between

CHAPTER II

PART I

Justification for Research

Obesity has reached epidemic proportions in North America and around the world. Highlighting the need for effective interventions to treat and prevent this ailment and reduce the impact of its associated co-morbidities (www.iotf.org). It has been well established that weight reduction is achieved by modifying energy and fat balance to negative deficits (Dionne & Tremblay, 2000). Accordingly, exercise is a commonly used modality for improving energy and fat balance in obese individuals, as part of a weight-reducing program (Dionne & Tremblay, 2000). In the past, exercise regimes have focused on low-intensity aerobic exercise in order to amplify fat oxidation rates. However, more recently, it has been found that increasing exercise intensity may actually be more beneficial for the obese clientele (Imbeault et al., 1997). Unfortunately, research in this area has generally focused on men; no studies to date have examined the potential impact of low versus high intensity exercise on fat metabolism in young healthy women. Therefore, evaluating the potential role of varying exercise intensities (low versus moderate-to-high) on fat oxidation rates in women is warranted.

From the modest amount of available literature, it has become abundantly clear that the once believed stagnant qualities of adipose tissue are no longer viable. In recent years, numerous regulatory proteins have been discovered that are secreted from adipose tissue in response to specified extra cellular stimuli or changes in the metabolic state (Berg et al., 2002; Fruhbeck et al., 2001; Saltiel, 2001). Much research has focused on defining the structural and functional roles of each. The one of particular interest is adiponectin, which is said to play an intricate role in fat oxidation rates. As such, it has been established that adiponectin levels are lower in individual with

diabetes mellitus and coronary heart disease (CAD) (Berg et al., 2002). Conversely, adiponectin can be seen in higher proportions in lean versus obese individuals, and in women as compared to men (Berg et al., 2002; Saltiel, 2001). Research has also shown that increased concentrations of plasma adiponectin are involved in the amelioration of fat oxidation, at least in mice (Berg et al., 2002). However, the role of adiponectin in humans is not as clearly defined, which further highlights the need for more research in this area. This will heighten our understanding of the functions of this protein in humans, and its subsequent role in the treatment of obesity.

Moreover, although weight loss is not the direct focus of this research, its significance is still imperative to our understanding of the role of adiponectin in terms of weight reduction for a clinical perspective. At present, it is apparent that there is a limited amount of research available on the impact of weight reduction on increasing adiponectin levels in humans. Therefore, it is essential that research be conducted to identify if more conventional methods for weight loss (by creating a negative energy balance) would have a greater impact on improving adiponectin levels and; thus, increasing fat oxidation rates.

Similarly, another known way to create an energy deficit is to increase energy expenditure, which can be accomplished by using exercise as a modality. Again, limited research is available on the impact of exercise on adiponectin levels. Therefore, given that adiponectin may play a composite role in acute fat oxidation rates, which is central to creating a negative fat balance to satisfy weight loss in obese individuals, it would be noteworthy to discover if there is link between the acute effects of exercise on adiponectin levels and fat oxidation rates. More specifically, it would be advantageous to view the acute effects of low versus high intensity exercise on fat oxidation, in order to identify if adiponectin is associated with short-term changes in fat oxidation rates.

Finally, it has been previously stated that no studies have been conducted to evaluate the impact of varying exercise intensities (LI versus M-HI) on fat oxidation rates in women. In the same

respect, research has shown that gender differences are apparent in plasma adiponectin levels, triglyceride content in muscle and the liver, and percent body fat (Matsubara, Maruoka, & Katayose, 2002a). Therefore, due to the modest amount of available literature the decision was made to examine women exclusively.

CHAPTER II

PART II

Research aims & hypotheses

2.1 Primary research question:

The general research question examined the acute effects of exercise on changes in adiponectin levels and fat oxidation rates in young healthy women.

2.2 Specific research question:

The specific research question examined the acute effects of low versus high intensity exercise on fat oxidation, in order to determine whether adiponectin levels are associated with changes in fat oxidation rates in young healthy women between the ages of 20 and 35 years.

2.2.1 Research hypotheses:

- 1- Given this, we hypothesized that there would be an acute adiponectin level rise concurrent with increased absolute fat oxidation with higher exercise intensity, as compared to lower-intensity exercise in young healthy women.

2.2.2 Limitations

To narrow the scope of our study we decided to limit our sample population to only women. This is due to the fact that similar results have already been determined in men. Because we only studied women, it was imperative that we test them during their follicular phase of their menstrual cycle to limit the interaction with other circulation hormones. The original number of participants to be recruited was approximately ten. The results on nine participants are presented. This number was based on budgetary constraints. We controlled the participants' diet with a standardized diet three days prior to each experimental testing session (this will be described in the subsequent section). The three experimental sessions were completely randomized, however, each session

followed the same time line with the exception of which exercise or control session was being performed (i.e., LI exercise, M-HI exercise, or control). All exercise sessions were performed on a standardized treadmill. The Moxos Gas Analyzer was used to determine energy expenditure using the principles of indirect calorimetry. Based on the values obtained during the VO_2 peak exercise test, each individual participant's exercise sessions (LI and M-HI) were calculated in order to expend a total of 350 kcal per session. Therefore, the exercise sessions were isocaloric.

2.2.3 Delimitations:

The potential weaknesses of the research are deemed to be minimal. However, we were limited to the available equipment in the laboratory. In terms of the blood sampling, it would have been more accurate had we been able to use a tracer method, rather than relying on a single blood sample at a particular point. Ideally, it would have been interesting to view the appearance and disappearance rates of adiponectin levels to establish more definitively if adiponectin did or did not fluctuate at all during the exercise (control) sessions. Further, CHO and fat oxidation rates could have been more precisely measured had we used urinary excretion values to more accurately measure protein oxidation. Instead it was estimated to be ~10% of energy expenditure. As well, it is most probable that it would have been better to measure participants in a fasted state, rather than in a postprandial condition for this particular research question. This is due to the fact that this would have elicited greater fat oxidation rates and would have given us a better indication of the movement pattern of adiponectin. However, this research question was part of a larger study and thus these factors were not amendable.

CHAPTER III

Methodology & Techniques

3.1 Description of study

Participants were informed that the study involved identifying the impact of varying exercise intensities on adiponectin levels in the body. Candidates that accepted to participate in this study were asked to complete three different experimental protocols: two at pre-determined exercise intensities (low and high), and one in a resting condition.

3.2 Selection of participants

Nine pre-menopausal women between the ages of 20-35 years were recruited using advertisement flyers at the University of Ottawa (see Appendix B). All nine women had a normal BMI (ranging from 20 to 25 kg/m²) and were weight stable (± 2.0 kg) for 6 months. Participants were non-diabetic, non-smokers, and between the ages of 20 and 35 years. Only women with a normal regular menstrual cycle were recruited (i.e., 28-35 days), including those using oral contraceptives with the exception of the use of deprovera (due to the lack of a regular menstrual cycles). Participants were moderately active women: active 3-5x/week at moderate-intensity (less than or equal to 45 minutes a training session). Information was obtained by phone from those that responded to the flyer. Participants that satisfied the inclusion criteria from the phone screen were asked to present themselves to the laboratory for the first initial visit, in which the pre-test evaluation took place.

3.3 Research design

This study was a crossover approach.

3.4 Protocol and procedure for data collection

Participants were asked to partake in a pre-test evaluation followed by three different experimental sessions including a resting session, exercise at low-intensity (40% VO_2 peak), and exercise at moderate-to-high-intensity (70% VO_2 peak).

3.4.1 Pre-test evaluation:

The pre-test evaluation was the first formal contact between the participant and investigators of this research project. One of the major goals of this session was to inform the participant on how the study would proceed. Other variables were collected such as morphological information about the participant. Please refer to Appendix C for the exact objectives of this baseline evaluation.

3.4.1.1 Objectives of the pre-test session:

As is outlined in the breakdown of the pre-test session, the participants were asked to present themselves to the laboratory at 09:30am. It is at this time that the participants were explained the proceeding events surrounding the study. After the participants were explained all necessary information and provided the opportunity to ask any questions, the informed consent documentation were signed by the participants and the respective investigators (see Appendix B). After which, the participants were asked to fill out a medical history questionnaire (see Appendix B). This was to ensure that all-extraneous pathological variable or allergies were known prior to the commencement of the study. Participants were scheduled for the first experimental session, which had to take place during the follicular phase of their cycles. The participants had to be tested in the follicular phase, which was within the first 8 days of their menstrual cycles. The reason for this is that sex hormones are at their lowest values. This was important because research has shown that variations in estrogen and progesterone affect energy expenditure and substrate oxidation (Matsuo, Saitoh, & Suzuki, 1999). Anthropometrical measurements followed by the bioelectrical impedance to determine percent body fat were obtained. The finally stage was to complete the maximal aerobic capacity test

using the Jean Jobin protocol (Boulay et al., 1984). The information obtained from this session was tabulated in order for a patient profile to be created and certain parameters calculated (i.e., 40% VO_2 peak & 70% VO_2 peak) using the Weir equation (Weir, 1949). The Weir equation measures the relationship between oxygen consumed (VO_2), carbon dioxide (VCO_2) produced and energy expenditure.

3.4.2 Three experimental session modality's

The three experimental conditions were rest, exercise at low-intensity (40% of VO_2 peak), and exercise at moderate-to-high-intensity (70% of VO_2 peak). The rest session acted as a control condition. For each experimental session the participants were asked to present themselves to the laboratory at a pre-arranged time. The participants were asked to follow a 3-day standardized diet prior to each experimental session. The low-intensity exercise session was at 40% of the VO_2 peak obtained from the first session (pre-test). At this time, timed efforts were calculated so that the participants expended 350 kilocalories in the exercise session. Likewise, moderate-to-high-intensity exercise was at 70% of VO_2 peak. In the same manner, the timed efforts were calculated so that the participants expended 350 kilocalories as well. It was hypothesized that the protocol at moderate-to-higher-intensity exercise would be completed faster than low-intensity; thus, it took less time to complete. Participants were allowed to drink water as desired to remain hydrated. Further, a heart rate monitor was used throughout the experimental sessions to calculate heart rate (bpm). In each exercise experimental session, both moderate-to-high and low intensity, the participant expended approximately 350 kilocalories on a treadmill, which was pre-determined by the initial VO_2 peak test. A fixed period of one month separated each experimental session. From the VO_2 peak test, the calculation of the 40% and 70% VO_2 peak was tabulated, which corresponded to a value of VO_2 , heart rate, and RQ (respiratory quotient); these values were calculated for low and moderate-to-high intensity using the Weir equation (Weir, 1949). Also, we were able to calculate energy expenditure for the 350 kilocalories from the intensity of exercise given. For all three experimental sessions the same protocol was followed and the same time line was respected. The only difference was which condition they completed: rest, low-intensity, or moderate-to-high-intensity. Please refer to Appendix C where a simulated time line is provided.

3.4.2.1 Protocol for experimental sessions

Participants arrived to the laboratory at approximately 8h00 in the morning (see Appendix C). Participants were told to follow a 3-day standardized diet and to be fasted from 19h00 the night before. In addition, they were asked to refrain from physical activity and alcohol consumption for at least 48 hours prior to the testing sessions. Insertion of the catheter took place at 8h05; by a qualified registered nurse (RN). At this point the first blood (fasting state) sample was taken. Participants rested until approximately 8h30. Resting metabolic rate (RMR) was determined by a 15-minute interval sample using indirect calorimetry. During this time the participants remained in a rested condition and were allowed to do work quietly at a desk, if desired. At 9h45, another blood sample was taken. After this was completed, the experimental condition of either exercise (low or high intensity) or rest commenced. It was not possible to calculate exactly the duration and the speed of the exercise sessions because these values were to be determined based on participant's individual results from the VO_2 peak. However, it was hypothesized that the moderate-to-high-intensity exercise would take ~40 minutes to complete, and that the lower-intensity exercise would take approximately 1 hour. The resting condition (control) was one hour in length. Blood samples were taken during fasting, pre-exercise, at 15-minute intervals during the exercise bout, and immediately post-exercise.

3.5 Compulsory criteria for experimental sessions

Results were obtained for nine women with a normal range for BMI (20 to 25 kg/m²). All participants met the inclusion criteria defined in the pre-test and were required to participate in all three experimental sessions. The order of these sessions was randomly assigned.

3.5 Statistical analyses

Analysis of variance (ANOVA) for repeated measures (condition and time) was used to determine the effect of treatment (high and low-intensity exercise) on the dependent variables,

plasma adiponectin concentrations (Time: F = fasting, BEX = before exercise or control; 15-min during exercise or control; and PEX = post-exercise or control). ANOVA for repeated measured were used to evaluate fat oxidation and carbohydrate rates for a condition and time effect. Statistical package for the Social Sciences, SPSS version 10.0, (Chicago, IL, USA) was used for all other analysis. $P < .05$ was considered statistically significant. All values were means and standard deviations (SD) for tables and mean and standard estimate of error (SE) for figures.

3.6 Description of measures

3.6.1 Pre-test

3.6.1.1 Anthropometrical measurements

Height was measured by using a standard stand-up scale (± 0.1 cm). Weight was measured using a standard scale (± 0.1 kg), and waist circumference with a standard tape measure (± 0.1 cm). The waist circumference was measured from the mid-distance between the iliac crest and the widest portion of the waist.

3.6.1.2 Bioelectrical impedance

Bioelectrical impedance was used to determine percent body fat using Tanita (TBF-300, Snoqualmie, WA). This method works on the principle that a weak electrical current circulates through the body, which determines values of resistance for fat mass (FM) and fat-free mass (FFM). The software calculated FM, FFM, and percent body fat among other variables.

3.6.1.3 Aerobic capacity test (VO_2 max)

A VO_2 max test was administered during the pre-test. The goal of this test was to determine the low and high-intensity exercise protocols that would be followed in the proceeding experimental sessions. The protocol used was the Jean Jobin (Boulay et al., 1984) using a treadmill as the exercise modality. An example of the protocol is available in the following table. This test is

considered ideal for untrained participants (Boulay et al., 1984). Intraclass variability 0.99 for total work performed (KJ/kg) and 0.93 for mean HR (Boulay et al., 1984).

Jean Jobin protocol for VO₂ max

| Time (minutes) | Speed (mph) | Incline (%) | Blood pressure (mmHg) | Heart rate (bpm) |
|-----------------------|--------------------|--------------------|----------------------------------|-----------------------------|
| 0 | 3.4 | 0 | | |
| 3 | 3.4 | 4 | | |
| 6 | 3.4 | 8 | | |
| 9 | 3.4 | 12 | | |
| 12 | 3.4 | 16 | | |
| 15 | 4.0 | 14 | | |
| 18 | 4.0 | 16 | | |
| 21 | 5.2 | 12 | | |
| 24 | 5.2 | 15 | | |
| 27 | 6.0 | 14 | | |
| 30 | 6.0 | 16 | | |

Heart rate and blood pressure were measured at rest and during specific intervals throughout the exercise test. Heart rate was measured every minute, and blood pressure was measured at the end of each stage. Ratings of perceived exertion (RPE) were monitored using the Borg's scale (Borg, 1982). Termination criteria for graded exercise testing were followed. Participants stopped the test if they met at least two of the following criteria: (1) RER > 1.15, (2) a plateau in O₂ consumption despite increases in workload, (3) reached 85% for age-predicted heart rate (ACSM, 2001). The Moxus oxygen analyzer (AEI technologies, Pittsburgh, Pennsylvania; model S-3A/II; ± 0.1% O₂ accuracy) was used to measure the data during the exercise test for variables such as VO₂, VCO₂,

and RER by indirect calorimetry. Substrate oxidation values (FAT & CHO) were determined using an adapted version of the Frayn, (1983) equations, taking into account 10% protein oxidation from total energy expenditure under the exercise conditions (LI and HI).

3.7.2. Experimental sessions

We asked that the participants arrive at the laboratory at around 8h00 in the morning, after a 12 hour fast. They were provided a standard breakfast at 8h30. The breakfast contained 2 pieces of whole-wheat toast, 20 g of peanut butter and 20 g of jam, one 20 g piece of cheese, and an orange juice of 250 mL. This breakfast was at a fixed composition mixture (FQ= 0.85), which represents ~570 kcal. The participant had 15 minutes to eat the breakfast. This same breakfast mixture was given at every experimental session.

3.7.2.1 Blood sampling and analysis

Blood samples measurements for plasma adiponectin were drawn into 1/10 volume EDTA-aprotinin tubes, and immediately placed on ice. All tubes were centrifuged at 4° C for collection of plasma and stored at -80° C until required for analysis (Matsubara, Maruoka, & Katayose, 2002b). Blood samples were measured for adiponectin concentrations using RIA kit. This method is a valid measure using a radioimmunoassay technique that determines fasting plasma adiponectin concentrations. More specifically, RIA assay utilizes ¹²⁵I-labeled murine adiponectin and a multispecies adiponectin rabbit antiserum to determine the level of adiponectin in serum, plasma or tissue culture media by the double antibody/PEG technique. The adiponectin standards are prepared using recombinant human adiponectin and can be used to determine the circulating levels of adiponectin in human serum/plasma samples. This method employs adiponectin-specific antibody (intra-assay and inter-assay coefficients of variation 1.78 and 9.25%, respectively). Again, blood samples were measured: when the catheter was first inserted ~8h05 (pre-breakfast), at pre-exercise

or control (~9h45), during exercise or control at fifteen minute intervals, and after exercise or control (~11h00).

CHAPTER IV

Results & Discussion

Results

Table 1 represents the characteristics of the women participants (N=9). Body weight (kg) and waist circumference (cm) remained stable between experimental sessions (data not shown). Table 2 shows the energy expenditure (EE) expressed in kilocalories (kcal), duration (min), and percentage of VO_2peak for the low-and high-intensity exercise sessions. As was stated previously, participants expended the same amount of kilocalories in each session of low-and high-intensity exercise. The subjects took approximately 66.0 ± 8.46 minutes to complete low-intensity exercise at $40.9\% \pm 1.39 \text{ VO}_2\text{peak}$ and spent approximately 37.0 ± 4.56 min in high-intensity exercise at $69.4 \pm 2.77 \text{ VO}_2\text{peak}$.

To investigate the nature of carbohydrate (see Figure 1a), and fat oxidation rates (see Figure 1b) a repeated measures ANOVA with two within-factors (time: at 15 and 30 minutes) was used to evaluate a condition, time, and/or condition x time interaction. Irrespective of time, CHO oxidation during exercise was significantly higher during the high-intensity exercise session, as compared to the low-intensity exercise session. CHO oxidation decreased significantly over the low-intensity and high-intensity exercise sessions ($p < .05$). Fat oxidation rates were significantly higher during the high-intensity exercise session, as compared to the low-intensity exercise session $p < .05$ (see Figure 1b). However, there was not a statistically significant time effect, although it was apparent that at least during low-intensity there seemed to be a slight increase in absolute fat oxidation rates. No condition versus time interaction effect was found.

Figure 2 displays adiponectin levels at rest (during a fasted state), before exercise or control session, at 15 minutes of exercise or control session and immediately post-exercise or control session. Plasma adiponectin levels were comparable between conditions and did not change over

time $p > .05$. When comparing the trend in adiponectin and fat oxidation rates, it is apparent that fat oxidation rates over a 30-minute period during low and high-intensity exercise remained static.

Table 1. Descriptive characteristics of participants (N=9)

| Variables | Mean (\pm SD) | Range |
|----------------------------------|-----------------------------------|--------------|
| Age (years) | 22.4 \pm 2.06 | 19.0-26.0 |
| Body weight (kg) | 63.8 \pm 7.25 | 49.3-76.3 |
| Height (m) | 1.70 \pm 6.54 | 159-183 |
| BMI (kg/m ²) | 22.1 \pm 2.41 | 19.5-27.2 |
| Waist circumference (cm) | 77.2 \pm 6.38 | 65.0-89.0 |
| Body fat (%) | 24.8 \pm 5.75 | 14.4-34.7 |
| VO ₂ peak (ml/kg/min) | 43.9 \pm 4.60 | 35.0-52.7 |
| VO ₂ peak (L/min) | 1.66 \pm 6.09 | 1.34-2.23 |

Note: Values are expressed as mean and standard deviations (SD). Data represents mean values for all experimental sessions, with the exception of VO₂peak (ml/kg/min), VO₂ peak (L/min), and Body fat (%), which were determined during the pre-test only.

Table 2. Energy expenditure and duration of the low- and high-intensity exercise sessions (N=9)

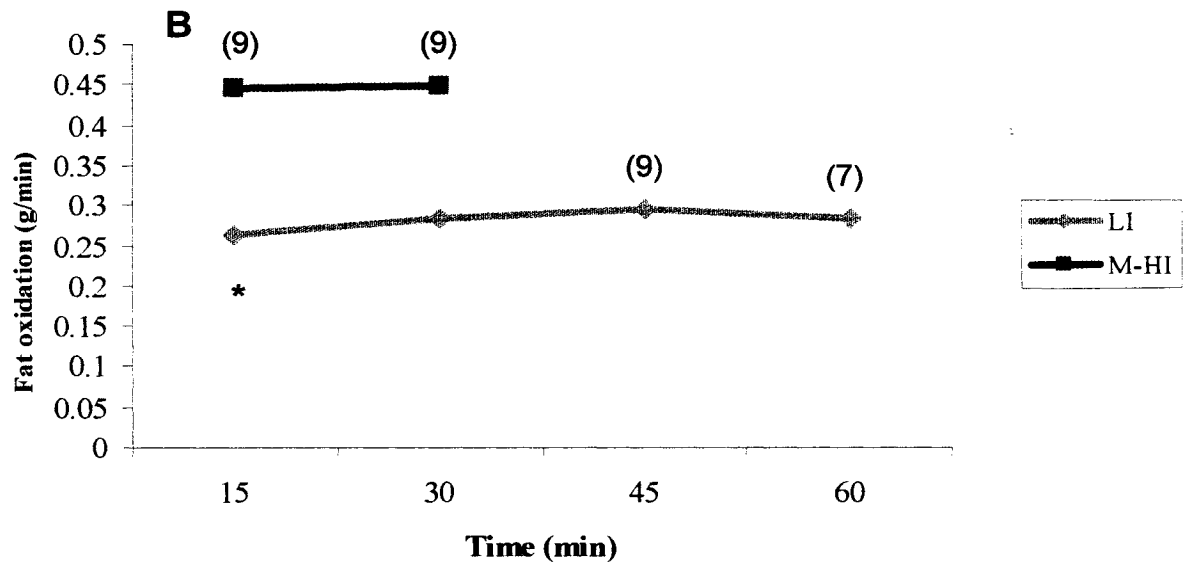
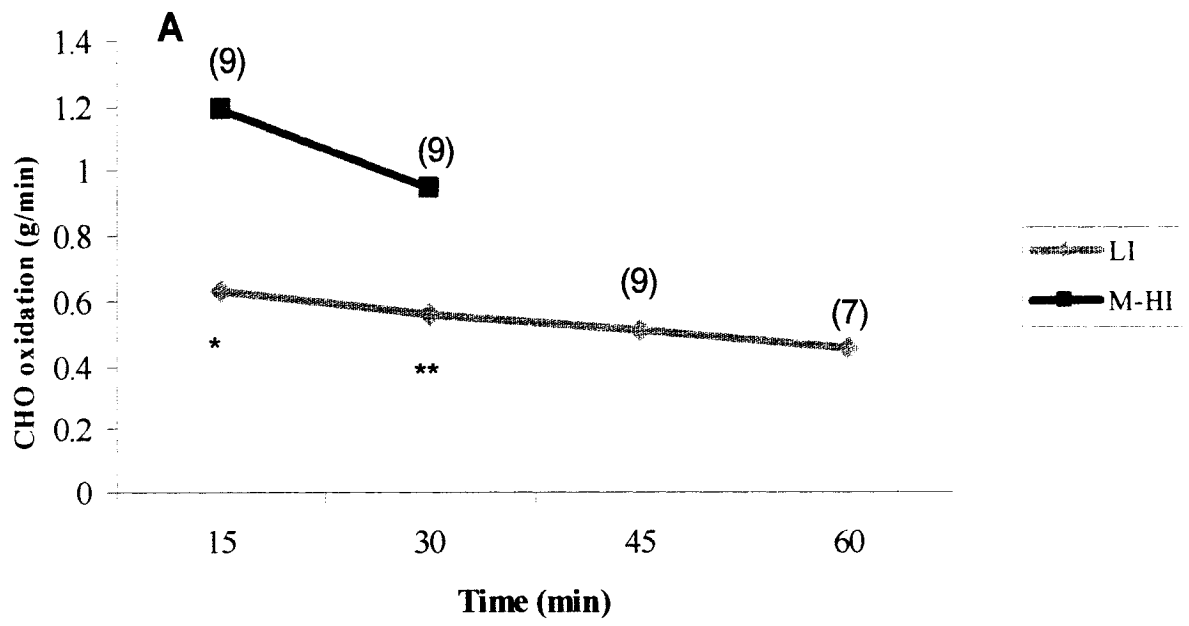
| | Low-intensity | | High-intensity | |
|-----------------------------------|---------------|-------|----------------|------|
| | Mean | SD | Mean | SD |
| Energy expenditure (kcal) | 350.5 | 10.62 | 348.6 | 10.3 |
| Duration (min) | 66.0 | 8.46 | 36.9 | 4.56 |
| Intensity (%VO ₂ peak) | 40.9 | 1.39 | 69.4 | 2.77 |

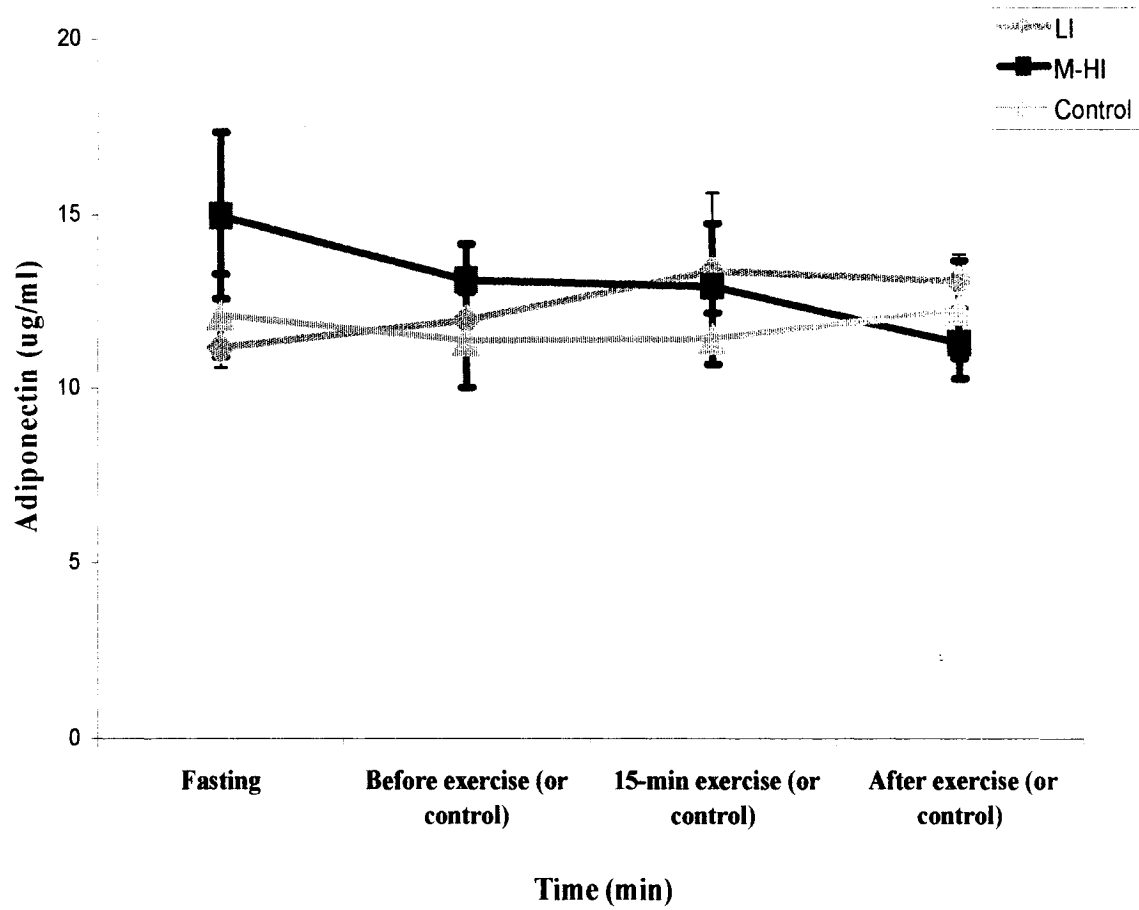
Note: Values are expressed as mean and standard deviations (SD).

Figure Legend

Figure 1. Changes in (a) carbohydrate (CHO) oxidation (g/min) and (b) fat oxidation (g/min) over time in women (N=9) undertaking (●) low-intensity (LI) and (■) moderate-to-high-intensity (M-HI) exercise sessions. Numbers in parentheses refer to the number of participants who had to exercise at this time to expend 350 kcal. Values are expressed by mean \pm SE. For CHO oxidation, a significant effect was observed between conditions (LI versus M-HI); in addition to a time effect at $p < .05$. For fat oxidation, only a significant difference was observed between conditions (LI versus HI) $p < .05$.

Figure 2. Adiponectin ($\mu\text{g/ml}$) levels in participants (N=9) during a fasted state (LI=●, M-HI=■, and rest=▲), postprandial before exercise or control, at 15-minutes during exercise or control, and immediately post-exercise or control. Values are expressed by mean \pm SE.





Discussion

The purpose of this study was to investigate the acute effects of exercise intensity on plasma adiponectin levels in young healthy women. The major finding was that plasma adiponectin levels were similar during acute low-and high-intensity exercise and this occurred, despite the fact that a greater absolute fat oxidation pattern was observed during high-intensity exercise.

In the past, weight loss regimes for overweight and obese clientele have generally focused on prescribing low-intensity exercise training to maximize fat oxidation rates. However, more recent literature has focused on the potentially more favourable effects of moderate-to-high-intensity exercise on fat oxidation rates (Achten et al., 2002). Indeed, absolute fat oxidation rates are thought to be increased in men via moderate-to-high-intensity exercise (70%VO₂max) (Achten et al., 2002; Imbeault et al., 1997). Similar trends were hypothesized to occur in women under equivocal conditions. In our study, as expected, fat oxidation rates were significantly higher during moderate-to-high-intensity exercise, as compared to low-intensity exercise. For both carbohydrate and fat oxidation rates, there were significant differences between low-and moderate-to-high-intensity exercise. This corroborates the findings of Imbeault et al. (1997), who also found that carbohydrate and fat oxidation rates were significantly higher during moderate-to-high-intensity exercise.

Circulating concentrations of adiponectin have been linked to acute fatty acid oxidation in mice, *in vitro* and *in vivo* (Berg et al., 2002). The link has yet to be established in humans. Research has shown that a variable such as weight loss (Esposito et al., 2003; Ryan et al., 2003; Yang et al., 2003) and administration of TZD's (Berg et al., 2002; Yu et al., 2002) have been shown to increase plasma adiponectin levels and improve insulin sensitivity in humans (Berg et al., 2002). Furthermore, it has already been well established that exercise training has the capacity to improve insulin sensitivity (Havel, 2002). However, a minimal amount of information is known

about the effects of exercise on plasma adiponectin concentrations in blood. We, in turn, hypothesized that acute exercise would increase circulating adiponectin concentrations and absolute fat oxidation rates with varying exercise intensities. Accordingly, to the best of our knowledge, Kraemer et al. (2003) were the first and only group to examine the acute effects of continuous aerobic exercise (79% VO_2max for 30 min) on circulating adiponectin levels. Our results were concordant with those of Kraemer et al. (2003), in that, exercise did not seem to increase the plasma adiponectin concentrations. However, Kraemer et al. (2003) did observe a 10% increase in adiponectin concentrations post-exercise (1-hour post-exercise), but when corrected for hemoconcentrations (increase in plasma volume shift) the results were no longer significant. These results are interesting because Kraemer et al. (2003) administered an exercise intensity of 79% VO_2max , which is almost 10% higher than our study (70% VO_2peak). This raises the question as to whether an increase in exercise intensity is ominous of increases in adiponectin concentrations because our results for adiponectin remained stable throughout the exercise sessions (both low-and high-intensity).

In the second part of their experiment Kraemer et al. (2003) examined the effect of intermittent aerobic exercise at 60, 75, 90, and 100% VO_2max on plasma adiponectin concentrations. The results indicated that moderate increases occurred after 10 minutes at 60% VO_2max , but then values descended thereafter before reaching 100% VO_2max , and finally rebounded upwards again during recovery (one-hour of recovery was monitored). Thus, the authors concluded that exercise was not a stimulant for increased plasma adiponectin concentrations in both continuous and intermittent aerobic exercise. It is possible that intermittent exercise may have elicited a completely different response to adiponectin due to the mechanism of this type of exercise. The discrepancy between our results and those of Kraemer et al. (2003) are noteworthy. In fact, Kraemer et al. (2003) only examined men, whereas our study only considered women. Nevertheless, initial circulating levels of adiponectin could simply explain the differences

al., 2002; Hulver et al., 2002). As such, Kraemer et al. (2003) showed an increase in insulin concentrations post-exercise, but this was independent of adiponectin concentrations. Similarly, Hulver et al. (2002) found that long-term exercise training (6 months, 4-days/wk for ~45min at 65-80%VO₂peak) did improve insulin sensitivity, but did not ultimately have an effect on plasma adiponectin concentrations. Thus, insulin and adiponectin were shown to be independent of each other at least in response to exercise.

Conversely, in a weight-loss subgroup in the same study, it was found that a rise in plasma adiponectin was the result of weight loss and improvements in insulin sensitivity; but yet again the relationship between adiponectin and insulin sensitivity was mutually exclusive. The overall conclusion of this study was that adiponectin did not influence exercise-induced insulin sensitivity.

In addition to the inverse relationship between insulin and adiponectin there has been speculation that an inverse relationship exists between adiponectin and leptin (Matsubara et al., 2002b). It is warranted to briefly review the effect of acute exercise on leptin concentrations because analogous trends are apparent. Leptin is another hormone that is secreted primarily from white adipose tissue, which stimulates lipid oxidation and increases energy expenditure (Hulver & Houmard, 2003). In contrast to adiponectin, circulating leptin levels are increased in those that suffer from obesity, which is indicative of either reduced leptin clearance and/or increased secretion. Additionally, plasma leptin concentrations seem to be highly influenced by alterations in energy balance, and more specifically, by creating an energy deficit, by caloric restriction and/or exercise (Hulver & Houmard, 2003). Similarly to adiponectin, a decrease in adipose tissue mass results in a subsequent shift in circulating plasma concentrations, in that, leptin levels are decreased (Hulver & Houmard, 2003) and adiponectin concentrations are increased (Matsubara et al., 2002b). Hulver and Houmard (2003) published a review article on the influence of acute and chronic exercise on plasma leptin levels. Unequivocally, the research has shown that acute exercise does not alter plasma leptin concentrations in non-exhaustive bouts of exercise lasting less

than one hour. As such, plasma leptin levels seem to only be altered with acute exhaustive exercise when a substantial amount of energy is expended. This trend seems to increase with greater exercise intensity and duration (minimum of one hour) (Hulver & Houmard, 2003). Additionally, there seems to be similarities in the acute response to short-term exercise between plasma leptin and adiponectin concentrations. Thus, perhaps it would be beneficial to examine the acute effects of plasma adiponectin levels in conditions of greater exercise intensity and duration as was previously suggested in our discussion concerning fat oxidation rates. This modification may create different results.

Hulver and Houmard (2003) further contend that exercise-induced decreases in plasma leptin levels may be due to adjustments in nutrient availability or nutrient flux at the cellular level, where secretion and production takes place via the hexosamine biosynthetic pathway (Hulver & Houmard, 2003). This pathway further mediates the effects of glucose on the gene expression of leptin. Although it is difficult to speculate about whether adiponectin may potentially be regulated by this mechanism, or something similar to it, further research needs to be conducted. This raises the question as to whether there is a link between leptin and adiponectin responses to acute exercise, other than the fact that they are inversely related (Matsubara et al., 2002b). As has been previously mentioned, adiponectin does not seem to increase postprandially in lean individuals, but has been shown to increase in obese individuals (English et al., 2003). Similarly, plasma adiponectin concentrations did not change in response to a high-fat meal, highlighting the notion that adiponectin may not acutely regulate lipid oxidation in humans after all (Peake et al., 2003). Moreover, plasma adiponectin levels were not associated with fat oxidation rates, in that, there was no correlation between plasma adiponectin concentrations and 24-hour RQ, at rest (Stephan et al., 2002). To date, there is a limited amount of research that has addressed this potential relationship between plasma leptin and adiponectin concentrations. Further research needs to be conducted in order to entertain any further notions.

between men and women. Research has shown that men tend to have lower levels of adiponectin, as compared to women (Berg et al., 2002). Hence, theoretically men start exercise with lower initial concentrations and thus there is even more opportunity for adiponectin levels to change. Accordingly, a plausible explanation may be that there is a gender dimorphism, which has been speculated in other studies (Berg et al., 2002; Nishizawa et al., 2002). The extent of this explanation resides on the fact that there may be an affect as a result of androgens in men. Indeed, androgens in mice have been reported to decrease circulating plasma adiponectin concentrations (Nishizawa et al., 2002). Whether there is an additive effect with exercise remains to be seen in both men and women. Further research would need to be conducted to further elaborate on this link.

Although in our study we did not examine glucose and insulin concentrations during the exercise sessions, it may have been warranted to be able to comment on its affect on plasma adiponectin concentrations. It is well established that exercise has the capacity to improve acute insulin sensitivity (Goodyear & Kahn, 1998; Hulver et al., 2002; Reaven, 1988; Reaven, 1993; Yatagai et al., 2003). In effect, Kraemer et al. (2003) did examine these variables and found that concurrent with much of the literature glucose and insulin levels remained relatively stable throughout acute aerobic exercise, but increased substantially post-exercise. Conversely, it was revealed that glucose rates and insulin sensitivity were increased significantly during the intermittent stage of 100%VO₂max. This is a plausible finding since it is known that exercise, especially, higher intensity exercise elicits greater catecholamine release into the blood with increased stimulation from exercise (Brooks et al., 2000; Purdon, Brousson, Nyveen, & al., 1993). Thus, at an exercise intensity of 100%VO₂max it would be expected that glucose and insulin responses would also increase dramatically. This increase in glucose production can be accounted for by the stimulation of hepatic glycogenolysis (Brooks et al., 2000). Accordingly, with respect to plasma adiponectin, research has shown that adiponectin and insulin are inversely related. (Berg et

More recently, another hormone has been speculated to have an inverse relationship with plasma adiponectin, namely, cortisol. Fernandez-Real, Lopez-Bermejo, Casamitjana, and Ricart (2003) contend that adiponectin levels display anti-inflammatory effects. This may be due to a direct association between fasting cortisol and adiponectin. Indeed, serum cortisol has been previously linked to the development of insulin resistance and is increased with the severity of obesity. Thus, cortisol is considered an anti-inflammatory molecule that seems to exhibit an additional inverse relationship with BMI and insulin levels. In fact, low fasting cortisol (which is observed in obesity) is speculated to lead to decreased adiponectin secretion and insulin resistance. Thus, it is logical to theorize that the inverse nature between adiponectin and cortisol would allow for an indirect compensatory mechanism that would regulate the degree of insulin resistance and allow it to remain stable (Gavrilla et al., 2003). This notion is interesting because another recent article has attempted to further link adiponectin, leptin receptor (sOB-R), and cortisol by examining their diurnal and ultradian patterns at rest, over a 24 hour period (Gavrilla et al., 2003). In effect, it was found that circulating adiponectin and the leptin receptor (sOB-R) displayed a similar ultradian pulsatility and diurnal variations with a significant decline at night, while reaching lowest values in the early morning. In fact, the 24-hour variations in serum adiponectin followed the same trend as this leptin receptor (sOB-R), but not leptin concentrations itself. Gavrilla et al. (2003) speculate that the two proteins (adiponectin and sOB-R) may be regulated by a common factor. Further, adiponectin displayed a similar pattern to cortisol with a small lag time of two hours to reach its lowest proportions. Although the authors contend that cortisol may, in effect, play an intricate role in inhibiting adiponectin concentrations in humans (Gavrilla et al., 2003).

Additionally, another hormone has been hypothesized to have an affect on adiponectin concentrations. In particular, thyroid hormones are speculated to regulate adiponectin expression as well (Fernandez-Real et al., 2003; Yoda et al., 2001). Further, adiponectin is thought to play a

role in adaptive thermogenesis, which may be elicited in a direct or indirect manner; it is not yet known (Fernandez-Real et al., 2003). Thus, it is apparent that the novelty of this relatively new hormone, adiponectin, has led to exciting and intriguing investigations with regard to discerning links in its potential endocrine functions.

From a clinical perspective, the link between plasma adiponectin, exercise intensity, and fat oxidation rates cannot be made at this time. Further research needs to be conducted to elaborate on the mechanistic role(s) of plasma adiponectin levels. It would seem that a number of other variables may contribute to our understanding of the exact mechanism(s) of adiponectin (ie., insulin, leptin, and cortisol). Thus, further research needs to be conducted for more links to be drawn. With regard to obesity, research has consistently shown that weight loss increases adiponectin concentrations (Berg et al., 2002; Esposito et al., 2003). Moreover, English et al. (2003) found that postprandial plasma adiponectin did increase significantly in obese participants in a resting condition; however, no effect was shown in lean individuals. This highlights the notion that adiponectin may act in a more pronounced manner in overweight and obese individuals. It would be interesting to view results of plasma adiponectin levels with a similar protocol to our study, thus including exercise, to establish if it would elicit a different response.

In summary, it is apparent that there are no acute effects of exercise intensity on plasma adiponectin levels and fat oxidation rates in young healthy women. Moreover, we are fundamentally in agreement with Kraemer et al. (2003) that a longer exercise duration and amplified exercise intensity; in addition to post-exercise assessment may be required to magnify any hormonal alterations that may be discernable by acute moderate-to-high-intensity exercise.

CHAPTER V**Article in submission**

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The acute effects of exercise intensity do not influence plasma adiponectin levels in young healthy women.

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Running Head: Adiponectin & exercise intensity in women

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Keywords: adiponectin, exercise intensity, substrate metabolism, young healthy women

Abstract

Adiponectin is a protein secreted exclusively from adipose tissue, which is speculated to increase acute fatty acid oxidation rates. High-intensity exercise has been reported to have a greater capacity to increase absolute fat oxidation rates, as compared to low-intensity exercise. Hence, the objective of this study was to investigate the acute effects of exercise intensity on adiponectin levels in young healthy women. Nine healthy, moderately active women (age = 22 ± 2 years; BMI = 22.1 ± 2.5 kg/m²; VO₂peak = 43.9 ± 4.0 ml O₂/kg/min) performed in a randomized order three experimental sessions: control (C) with no exercise and two equicaloric (350 kcal), low-intensity (LIE) and moderate-to-high-intensity (M-HIE) exercise sessions on a treadmill at 40% and 70% VO₂max, respectively. Experimental sessions took place during the follicular phase of the participants' menstrual cycle; therefore, sessions were spread out by at least a one-month. Plasma adiponectin levels were measured before, at 15-minutes, at 30-minutes, and post exercise session (LI /M-HI) or control session. The results indicated that plasma adiponectin levels were comparable across conditions and remained unchanged over time within each session. These findings suggest that plasma adiponectin levels do not seem to be acutely modulated during and immediately after exercise of varying intensity in young healthy women.

Introduction

Obesity is increasing at alarming rates and has already reached epidemic proportions (27). It is well known that obesity is associated with many health consequences such as cardiovascular disease, non-insulin-dependent diabetes mellitus, hypertension, hyperlipidemia, hyperinsulinemia, and some forms of cancer (5) (2). Weight reduction is primarily achieved by modifying energy and fat balance to negative deficits (8). Exercise is one known approach to increase energy expenditure and create this deficit, yet the most effective way to do this remains unclear. In the past, exercise regimes have focused on continuous low-intensity aerobic exercise in order to amplify fat oxidation rates. However, more recently, it has been suggested that increasing exercise intensity may actually be more beneficial, due to its potential effects on increasing absolute fat oxidation rates (1). Unfortunately, research in this area has generally focused on men. To our knowledge, no studies to date have examined the potential impact of low versus high intensity exercise on fat metabolism in young healthy women. And only one study exists detailing the acute effects of high-intensity exercise ($65\%VO_2\text{max}$) in women, in which it was found that fat oxidation rates increased significantly in as little as 15 minutes (15). Therefore, evaluating the potential role of varying exercise intensities (low versus high) on fat oxidation rates in women is warranted.

Over the last couple of years, it has become abundantly clear that the once believed stagnant qualities of adipose tissue are no longer valid. Numerous regulatory proteins such as leptin, TNF- α , adiponectin, resistin, and adiponectin have been discovered to be secreted from adipose tissue in response to specified extra cellular stimuli or changes in the metabolic state (11). Ever since the discovery of leptin, adiponectin unequivocally has been the subject of much research. Adiponectin is exclusively secreted from adipose tissue and normal concentrations range from 5-30 $\mu\text{g/ml}$ (19). Indeed, it has been established that plasma adiponectin concentrations are lower in individuals with diabetes mellitus, coronary heart disease (CAD), and obesity (3). A gender

dimorphism is also suggested in that women seemingly display higher concentrations, as compared to their male counterparts (3, 24). Additionally, in mice, it has been shown that increased concentrations of plasma adiponectin are involved in the amelioration of acute fatty acid oxidation (3). However, the role of adiponectin in humans is not clearly defined. Adiponectin has been shown to increase with weight loss (3) (9) in both men and women. In fact, a decrease in BMI by 10% can induce a significant increase in circulating levels of plasma adiponectin in humans (3). This notion creates intrigue, in that plasma adiponectin concentrations may create a potential link between obesity and the regulation of energy metabolism.

Moreover, adiponectin is speculated to play an intricate role in lipid metabolism and has displayed characteristics of improving insulin sensitivity (3) (11) (24) (25). Indeed, Tschitter et al., (2003) (25) found that adiponectin was negatively correlated with fasting triglyceride (TG) and free fatty acid (FFA) concentrations in both men and women, further emphasizing that adiponectin may be responsible in some manner for improving fat oxidation rates. Thus, there may be a link between fat oxidation rates and plasma adiponectin levels. This raises the question as to whether, exercise, as a means of increasing energy expenditure, would provide any additional acute effects on increasing plasma adiponectin concentrations and/or improving fat oxidation rates. Even more specifically, is it plausible to hypothesize that increasing exercise intensity would cause additional increases in the same variables. To the best of our knowledge, only one study to date has examined the acute effects of 30-minutes of continuous aerobic high-intensity exercise (79% VO_2max) on adiponectin levels in young healthy men (16). As expected, adiponectin increased significantly, but when corrected for the plasma volume shift, results were no longer considerable.

In summary, a very limited amount of research is available on the impact of exercise on plasma adiponectin levels. We hypothesize that there may be link between the acute effects of exercise on adiponectin levels and fat oxidation rates. Thus, the aim of this study was to

investigate the acute effects of exercise intensity on plasma adiponectin concentrations and fat oxidation rates in young healthy women.

Methods

Subjects

Nine young moderately trained women mean age 22.4 ± 2.06 years were recruited using advertisement flyers at the University of Ottawa. All nine women had a normal BMI 22.1 ± 2.41 kg/m^2 and were weight stable (± 2.0 kg) for 6 months. Participants were healthy, non-diabetic, and non-smokers. Only women with a normal regular menstrual cycle were recruited (i.e., 28-35 days), including those using oral contraceptives. Participants were moderately active women: active 3-5x/week at moderate-intensity (less than or equal to 45 minutes a training session). Participants that satisfied the inclusion criteria from the phone screening were informed that the study involved identifying the impact of varying exercise intensities on physiological parameters in the body. Candidates that accepted to participate in this study were asked to complete three different experimental protocols: two at pre-determined exercise intensities (low and moderate-to-high), and one in a resting condition. When all criteria were met the participants were asked to present themselves to the laboratory for the initial visit, in which the pre-test evaluation took place. The University of Ottawa Ethics Board approved this study.

Experimental design and protocol:

This study was a crossover approach. Participants were asked to partake in a pre-test evaluation followed by three randomly assigned different experimental sessions including a resting session, exercise at low-intensity (40% VO_2 peak), and exercise at moderate-to-high-intensity (70% VO_2 peak). The exercise sessions were equicaloric, in that, participants expended a total of 350 kcal during each session.

Pre-test evaluation:

The participants were invited to the laboratory where the study was explained at ~09:30am. Written informed consent was obtained by the participant and witnessed by the research assistant. The participants were then asked to fill out a medical history questionnaire. The participants were then scheduled for the first experimental session, which had to take place during the follicular phase of her menstrual cycles. The participants had to be tested during the follicular phase that is within the first eight days of her menstrual cycle. The reason for this is that sex hormones are at their lowest values and research has shown that variations in estrogen and progesterone affect energy expenditure and substrate oxidation (18).

Anthropometrical measurements:

Height (± 0.1 cm) and weight (± 0.1 kg), were measured using standard scales. Waist circumference was measured with a standard tape measure (± 0.1 cm). The waist circumference was measured using a standard tape measure (± 0.1 cm) from the mid-distance between the iliac crest and the widest portion of the waist.

Body composition:

Bioelectrical impedance was used to determine percent body fat using Tanita (TBF-300, Snoqualmie, WA) to determine variables such as fat mass (FM), fat-free mass (FFM), and percent body fat.

Aerobic capacity test ($\dot{V}O_{2max}$):

$\dot{V}O_{2max}$ test was conducted using a continuous treadmill protocol. From the $\dot{V}O_{2max}$ test, 40% and 70% $\dot{V}O_{2peak}$ were calculated, which corresponded to values of $\dot{V}O_2$, heart rate, and RQ (respiratory quotient); these values were calculated for low and high intensity using the Weir equation (26). The Jean Jobin protocol (6) was used, in which stages increased by three-minute intervals (6). Participants started with a warm-up with a speed of 3.4 mph and 0% incline. The following four stages remained at the consistent speed of 3.4 mph and increased only in incline

from 4%, 8%, 12%, and 16%. After which the speed increased and the incline varied from 12 to 16%. This test is considered ideal for untrained participants (6). Heart rate (bpm) (Polar monitors, Woodbury, NY, USA) and blood pressure (mmHg) were measured at rest and at each three-minute interval throughout the exercise test. Specifically, heart rate (bpm) was measured every minute, and blood pressure (mmHg) was measured at the end of each stage. Ratings of perceived exertion were monitored using the Borg's scale (4). Termination criteria for graded exercise testing were followed. Participants stopped the test if they met at least two of the following criteria: (1) RER > 1.15, (2) a plateau in O₂ consumption despite increases in workload, (3) reached 85% for age-predicted heart rate (2). The Moxus oxygen analyzer (AEI technologies, Pittsburgh, Pennsylvania; model S-3A/II; ± 0.1% O₂ accuracy) was used to measure the data during the exercise test for variables such as VO₂ and VCO₂ using indirect calorimetry. Substrate oxidation values (FAT & CHO) were determined using an adapted version of the Frayn et al. (1983) (10) equations, taking into account 10% protein oxidation from total energy expenditure under the exercise conditions (LI and M-HI).

Three experimental sessions:

The three experimental conditions were rest, exercise at low-intensity (40% of VO₂ peak), and exercise at moderate-to-high-intensity (70% of VO₂ peak). The rest session acted as a control condition. For each experimental session the participants were asked to present themselves to the laboratory at a pre-arranged time. At this point, a timed effort was calculated so that the participant expended 350 kilocalories in the exercise session. Further, a heart rate monitor was used throughout the experimental sessions to view the participants' heart rate (bpm). A fixed period of one month separated each experimental session.

Protocol for experimental sessions:

Prior to arriving at the laboratory participants had followed a 3-day standardized diet. Participants arrived to the laboratory at approximately 8h in the morning after a 12-hour fast: they were abstained from physical activity and alcohol consumption for at least 48 hours prior to testing. Anthropometric measurements were taken such as height, weight, and waist circumference. A catheter was then inserted at ~8h05 by a qualified registered nurse. At this point the first blood sample (fasting state) was taken. The participant rested until approximately 8h30 during which resting metabolic rate (RMR) was determined by a 15-minute interval sample using indirect calorimetry. During this time the participant remained in a rested state in a supine position. Following RMR the participant was served a standard breakfast. The breakfast included 2 pieces of whole-wheat toast, 20 g of peanut butter and 20 g of jam, one 20 g piece of cheese, and an orange juice of 250 mL. This breakfast was at a fixed composition mixture (FQ= 0.85), which represents 570 kcal. The participant was given 15 minutes to eat the breakfast. This same breakfast mixture was given at every experimental session. The participant then had one hour to rest in a seated position at a table in the laboratory. At ~9h45, another blood sample was taken (BEX=before exercise) or control. After this was completed, the experimental condition of either exercise (low or moderate-to-high intensity) or rest commenced. Moderate-to-high-intensity exercise took 40.0 ± 1.39 minutes to expend 350 kcal and the lower-intensity exercise took 66.0 ± 8.46 minutes to expend 350 kcal. The resting condition (control) was 75 minutes in length. During the exercise bout (or control) blood samples were taken at 15-minute intervals. Another blood sample was taken 5 minutes after exercise or control (after 75 minutes).

Blood sampling and analysis

Blood samples measurements for plasma adiponectin were drawn into 1/10 volume EDTA-aprotinin tubes, and immediately placed on ice. All tubes were centrifuged at 4° C for collection of plasma and stored at -80° C until required for analysis (17) Blood samples were measured for

adiponectin concentrations using a commercially available radioimmunoassay kit (Linco Research, St-Charles, MO, USA).

Statistical analyses:

Analysis of variance (ANOVA) for repeated measures (condition and time) was used to determine the effect of treatment (high and low-intensity exercise) on the dependent variables, adiponectin concentrations in plasma (Time: F=fasting, BEX=before exercise or control; 15-min intervals during exercise or control; and PEX=post-exercise or control). ANOVA for repeated measured were used to evaluate fat and-carbohydrate oxidation rates for a condition and time effect. SPSS version 10.0 from SAS Institute (Chicago, IL, USA) was used for all other analysis. $P < 0.05$ was considered statistically significant. Values in tables expressed in terms of means and standard deviations (SD) and all values in figures are means and standard estimate of error (SEE).

Results

Table 1 represents the characteristics of the women participants (N=9). Body weight (kg) and waist circumference (cm) remained stable between experimental sessions (data not shown). Table 2 shows the energy expenditure (EE) expressed in kilocalories (kcal), duration (min), and percentage of VO_2 peak for the low-and high-intensity exercise sessions. As was stated previously, participants expended the same amount of kilocalories in each session of low-and high-intensity exercise. The subjects took approximately 66.0 ± 8.46 minutes to complete low-intensity exercise at $40.9 \pm 1.39\%$ VO_2 peak and spent approximately 37.0 ± 4.56 min in moderate-to-high-intensity exercise at $69.4 \pm 2.77\%$ VO_2 peak.

To investigate the nature of carbohydrate (see Figure 1a), and fat oxidation rates (see Figure 1b) a repeated measures ANOVA with two within-factors (time: at 15 and 30 minutes) was used to evaluate a condition, time, and/or condition x time interaction. Irrespective of time, CHO oxidation during exercise was significantly higher during the high-intensity exercise session, as compared to the low-intensity exercise session. CHO oxidation decreased significantly over the

low-intensity and moderate-to-high-intensity exercise sessions ($p < .05$). Fat oxidation rates were significantly higher during the moderate-to-high-intensity exercise session as compared to the low-intensity exercise session $p < .05$ (see Figure 1b). However, there was not a statistically significant time effect, although it was apparent that at least during low-intensity exercise there seemed to be a slight increase in absolute fat oxidation rates. No condition versus time interaction effect was found.

Figure 2 displays adiponectin levels at rest (during a fasted state), before exercise or control session, at 15 minutes of exercise or control session and immediately post-exercise or control session. Plasma adiponectin levels were comparable between conditions and did not change over time $p > .05$. When comparing the trend in adiponectin and fat oxidation, it is apparent that fat oxidation rates over a 30-minute period during low and moderate-to-high-intensity exercise remained unchanged.

Discussion

The purpose of this study was to investigate the acute effects of exercise intensity on plasma adiponectin levels in young healthy women. The major finding was that plasma adiponectin levels were similar during acute low-and high-intensity exercise and this occurred, despite the fact that a greater absolute fat oxidation pattern was observed during high-intensity exercise. In the past, weight loss regimes for overweight and obese clientele have generally focused on prescribing low-intensity exercise training to maximize fat oxidation rates. However, more recent literature has focused on the potentially more favourable effects of high-intensity exercise on fat oxidation rates (1). Indeed, absolute fat oxidation rates are thought to be increased in men via moderate-to-high-intensity exercise ($\sim 64\% \text{VO}_2\text{max}$) (1, 14). Similar trends were hypothesized to occur in women under equivocal conditions. In our study, as expected, fat oxidation rates were significantly elevated during high-intensity exercise, as compared to low-intensity exercise. For both carbohydrate and fat oxidation rates, there were significant differences

between low-and high-intensity exercise. This corroborates the findings of Imbeault et al. (14), who also found that carbohydrate and fat oxidation rates were significantly higher during high-intensity exercise.

Circulating concentrations of adiponectin have been linked to acute fatty acid oxidation in mice, *in vitro* and *in vivo* (3). The link has yet to be established in humans. Research has shown that variables such as weight loss (9) (23) (28) and administration of thiazolidinediones (TZD's) (3) (29) have been shown to increase plasma adiponectin levels in humans (3). However, a minimal amount of information is known about the effects of exercise on plasma adiponectin concentrations in blood. We, in turn, hypothesized that acute exercise would have increased circulating adiponectin concentrations and absolute fat oxidation rates with varying exercise intensities. Accordingly, to the best of our knowledge, Kraemer et al (2003) (16) were the first and only group to examine the acute effects of continuous exercise (79% VO_2max for 30 min) on circulating adiponectin levels. Our results were concordant with those of Kraemer et al., (2003) (16), in that, exercise did not seem to increase plasma adiponectin concentrations. However, Kraemer et al. (2003) (16) did observe a 10% increase in adiponectin concentrations post-exercise (1-hour after), but when corrected for hemoconcentrations (increase in plasma volume shift) the results were no longer significant. These results are interesting because Kraemer et al. (2003) (16) administered an exercise intensity of 79% VO_2max , which is almost 10% higher than our study (70% VO_2peak). This raises the question as to whether an increase in exercise intensity is ominous of increases in adiponectin concentrations because our results for adiponectin remained stable throughout the exercise sessions (both low-and moderate-to-high-intensity).

In the second part of their experiment Kraemer et al., (2003) (16) examined the effect of intermittent exercise at 60, 75, 90, and 100% VO_2max on plasma adiponectin concentrations. The results indicated that moderate increases occurred after 10 minutes at 60% VO_2max , but then values descended thereafter before reaching 100% VO_2max , and finally rebounded upwards again

during recovery. Thus, the authors concluded that exercise was not a stimulant for increased plasma adiponectin concentrations in both continuous and intermittent aerobic exercise. Nonetheless, it is possible that intermittent exercise may have elicited a completely different response to adiponectin due to the mechanism of this type of exercise. The discrepancy between our results and those of Kraemer et al. (2003) are noteworthy. In fact, Kraemer et al. (2003) (16) only examined men, whereas our study only considered women. Nevertheless, initial circulating levels of adiponectin could simply explain the differences between men and women. Research has shown that men tend to have lower levels of adiponectin, as compared to women (3). Hence, theoretically men start exercise with lower initial concentrations and thus there is even more opportunity for adiponectin levels to change. This is addition to the possibility of there being a potential affect by sexual hormones. Accordingly, a plausible explanation may be that there is a gender dimorphism, which has been speculated in other studies (3) (19). This explanation resides on the fact that there may be an effect as a result of androgens in men. Indeed, androgens in mice have been reported to decrease circulating plasma adiponectin concentrations (19). Whether there is an additive effect with exercise remains to be seen in both men and women. Further research would need to be conducted to further elaborate on this link.

Although in our study we did not examine glucose and insulin concentrations during the exercise sessions, it may have been warranted to be able to comment on its effect on plasma adiponectin concentrations. It is well established that exercise has the capacity to improve insulin sensitivity acutely (21) (22) (12) (13). Kraemer et al. (2003) (16) did examine these variables and found that concurrent with much of the literature glucose and insulin levels remained relatively stable throughout acute exercise, but increased substantially post-exercise. Conversely, it was revealed that glucose rates and insulin sensitivity were increased significantly during the intermittent stage at 100%VO₂max. This is a reasonable finding since it is known that exercise, especially, higher intensity exercise elicits greater catecholamine release into the blood with

increased stimulation from exercise (7) (20). Thus, at an exercise intensity of 100%VO₂max it would be expected that glucose and insulin responses would also increase dramatically. This increase in glucose production can be accounted for by the stimulation of hepatic glycogenolysis (7) With respect to plasma adiponectin, research has shown that adiponectin and insulin are inversely related. (3) (13). As such, Kraemer et al. (2003) (16) showed an increase in insulin concentrations post-exercise, but this was independent of adiponectin concentrations. Similarly, Hulver et al. (2002) (13) found that long-term exercise training (6 months, 4days/wk for ~45min at 65-80%VO₂peak) did improve insulin sensitivity, but did not ultimately have an affect on plasma adiponectin concentrations. Thus, insulin and adiponectin were shown to be independent of each other at least in response to exercise.

In summary, it is apparent that there are no acute effects of exercise intensity on plasma adiponectin levels and fat oxidations rates in young healthy women. Moreover, we are fundamentally in agreement with Kraemer et al. (2003) (16) that a longer exercise duration and post-exercise assessment may be required to magnify any hormonal alterations that may be discernable by acute high-intensity exercise.

Table 1. Descriptive characteristics of participants (N=9)

| Variables | Mean \pm (SD) | Range |
|----------------------------------|-----------------------------------|--------------|
| Age (years) | 22.4 \pm 2.06 | 19.0-26.0 |
| Body weight (kg) | 63.8 \pm 7.25 | 49.3-76.3 |
| Height (m) | 1.70 \pm 6.54 | 159-183 |
| Body fat (%) | 24.8 \pm 5.75 | 14.4-34.7 |
| VO ₂ peak (ml/kg/min) | 43.9 \pm 4.60 | 35.0-52.7 |
| VO ₂ peak (L/min) | 1.66 \pm 6.09 | 1.34-2.23 |
| BMI (kg/m ²) | 22.1 \pm 2.41 | 19.5-27.2 |
| Waist circumference (cm) | 77.2 \pm 6.38 | 65.0-89.0 |

Note: Values are expressed as mean and \pm standard deviation (SD)

Table 2. Energy expenditure and duration of the low- and moderate-to-high-intensity exercise sessions (N=9)

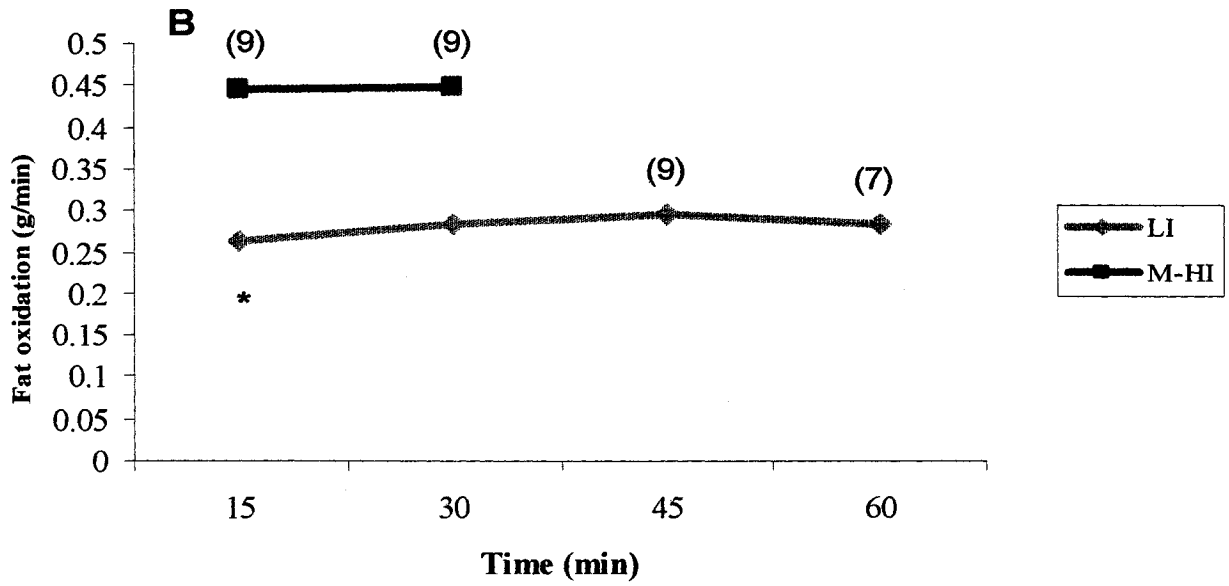
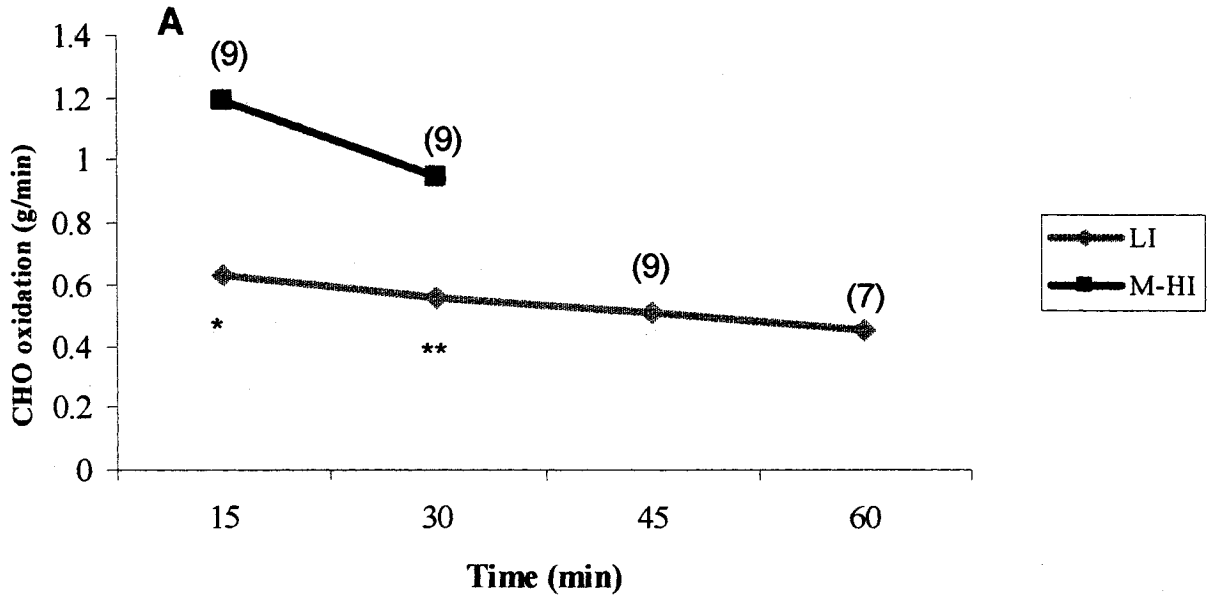
| | Low-intensity | | High-intensity | |
|-----------------------------------|---------------|-------|----------------|------|
| | Mean | SD | Mean | SD |
| Energy expenditure (kcal) | 350.5 | 10.62 | 348.6 | 10.3 |
| Duration (min) | 66.0 | 8.46 | 36.9 | 4.56 |
| Intensity (%VO ₂ peak) | 40.9 | 1.39 | 69.4 | 2.77 |

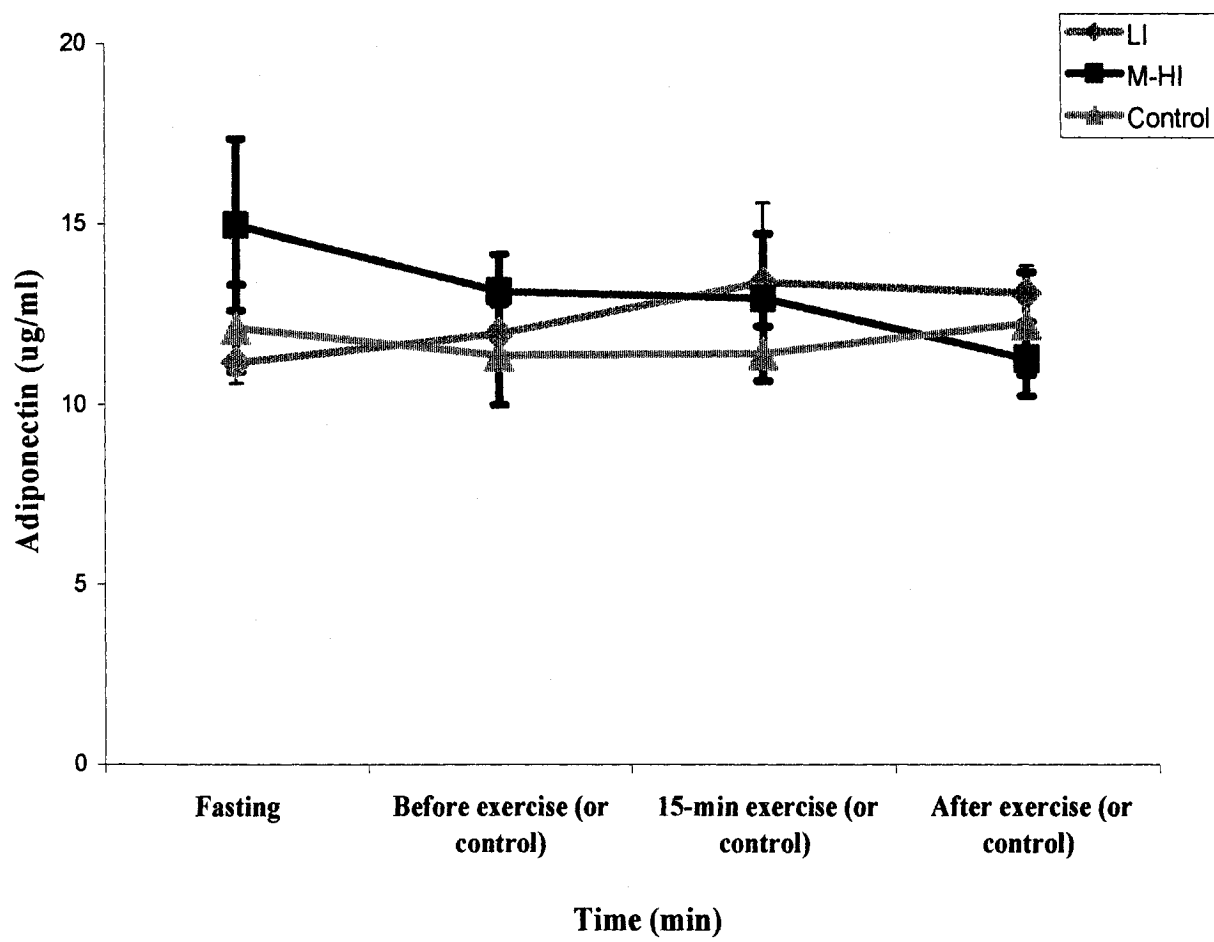
Note: Values are expressed as mean and \pm standard deviation (SD)

FIGURE LEGEND

Figure 1. Changes in (a) carbohydrate (CHO) oxidation (g/min) and (b) fat oxidation (g/min) over time in women (N=9) undertaking (●) low-intensity (LI) and (■) moderate-to-high-intensity (M-HI) exercise sessions. Numbers in parentheses refer to the number of participants who had to exercise at this time to expend 350 kcal. Values are expressed by mean \pm SE. For CHO oxidation, a significant effect was observed between conditions (LI versus M-HI); in addition to a time effect at $p < .05$. For fat oxidation, only a significant difference was observed between conditions (LI versus M-HI) $p < .05$.

Figure 2. Adiponectin ($\mu\text{g/ml}$) levels in participants (N=9) during a fasted state (LI=●, M-HI=■, and rest=▲), postprandial before exercise or control, at 15-minutes during exercise or control, and immediately post-exercise or control. Values are expressed by mean \pm SE.





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CHAPTER VI

Conclusion & Perspectives

In conclusion, it is apparent that there are no acute effects of exercise intensity on plasma adiponectin levels and fat oxidations rates in young healthy women. These results are contrary to what was originally projected, which was that adiponectin levels would rise with increasing exercise intensity and fat oxidation rates. Due to the novelty of this hormone adiponectin and the relatively small amount of literature available on its mechanistic role(s), especially in humans, it is difficult to speculate whether we could have adjusted our protocol to elicit a different response.

To the best of our knowledge, we are the second group to examine the acute effects of exercise on adiponectin concentrations in blood and coincidentally reported similar findings. In accordance, we are fundamentally in agreement with Kraemer et al. (2003) (who were the first to report the acute effects of exercise on adiponectin levels) that a longer exercise duration may have elicited a different result. We further believe that perhaps an increase in exercise intensity, in addition to evaluating a post-exercise assessment (recovery period) may be required to magnify any hormonal alterations that may be discernable by acute exercise and/or higher-intensity exercise.

In hindsight, in terms of amending our protocol to potentially obtain a more favourable response, there are certain parameters that could have been altered. For instance, a more precise measurement tool for obtaining fat and CHO oxidation would have been by examining the exact values for urinary nitrogen excretion; however, we did not have the equipment necessary to support this technique. Nonetheless, since we did obtain dietary intake for three days prior to each experimental session, we could have estimated more precisely urinary nitrogen excretion by calculating protein intake for the individual subjects. This is instead of assuming protein oxidation rates occur at 10% of energy expenditure. In support of this notion, Ferrannini (1988) found that

the estimated error could be as high as $\pm 4\%$. Additionally, the ultimate evaluation for fat and CHO oxidation rates would have been to use a tracer method. However, we did not have access to tracer method equipment. As well, it is most probable that it would have been better to measure participants in a fasted state, rather than in a postprandial condition because this would have elicited greater fat oxidation rates and would have given us a better indication of the movement pattern of adiponectin. Thus, future studies measuring the movement pattern of adiponectin and fat oxidation rates should probably measure participants in a fasted condition.

Furthermore, we could have taken more frequent blood samples to display a more precise overview of the trends during exercise. For instance, Kanaley et al. (2001) used 10-minute blood sample intervals for their protocol, as compared to ours which were 15-minute intervals. Although we speculate that this would not make a large difference in terms of the overall display pattern of any particular trend.

Finally, it would be interesting to determine if a similar protocol would present diverse findings in an obese population. Indeed, studies have shown that weight loss initiates an increase on plasma adiponectin concentrations in overweight and obese individuals (Berg et al., 2002; Esposito et al., 2003). Moreover, as stated previously, English et al. (2003) did find that plasma adiponectin levels did significantly increase in obese individuals in a postprandial state, contrary to what was found in lean individuals. Furthermore, to the best of our knowledge, no studies to date have examined the effect of exercise on adiponectin levels in the obese population. Thus, future studies should evaluate if adiponectin changes, due to exercise, are more pronounced in obese individuals.

CHAPTER VII

Statement of contribution of collaborators

Torrey Parker:

I was one of the Master's student of co-supervisors, Dr. Pascal Imbeault and Dr. Eric Doucet. I was the first author of my thesis, journal article submission, and presentations associated with completing the requirements for the Master's of Arts program at the University of Ottawa. All corrections and feedback came from the co-supervisors, mentioned above. I was responsible for collecting all the data in the laboratory with Marjorie Pomerleau. I was further responsible for entering and analyzing the data that pertained to my thesis topic.

Dr. Eric Doucet:

Dr. Doucet was my co-supervisor for my Master's project. He and Marjorie Pomerleau designed the protocol together prior to my participation. He further supervised Marjorie and me in the laboratory for data collection. He provided me with feedback on my thesis and journal article submission.

Marjorie Pomerleau:

Marjorie developed the project in collaboration with Dr. Doucet. She prepared all the supporting documentation (ie., patient profiles, obtained ethics approval etc...). She was responsible for completing data collection in the laboratory along with data inputting.

Dr. Pascal Imbeault:

Dr. Imbeault acted as my co-supervisor on this project. His responsibilities included supervising the data collection in the laboratory and providing financial support for this project. He further guided me in developing my thesis paper and helped me prepare my proposal defense presentation. He also helped me write an abstract for submission to the North American Association for the Study of Obesity (NAASO) conference in Fort Lauderdale, Florida (October,

2003). He further helped me analyze the data for my thesis. He was my main source of knowledge and expertise throughout this project.

CHAPTER VIII

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CHAPTER VIII

Appendices

APPENDIX A

Table 1. Selected key proteins secreted from adipose tissue into bloodstream

| Molecule | Function | Reference(s) |
|---|---|---|
| Adipsin | Serine protease secreted by AT cells Downregulated in rodent obesity May possess the same function as complement D (complementary pathway) | (Fruhbeck et al. 2001) (Fruhbeck et al. 2001) (Fruhbeck et al. 2001) |
| Acyclation-stimulating Protein (ASP) | | (Fruhbeck et al. 2001) |
| Interleukin-6 (IL-6) | Involved in the host defence & in glucose & lipid metabolism ↓ related with adiponectin, <i>in vitro</i> & <i>in vivo</i> ↑ in obese individuals May act in paracrine or autocrine manner | (Fruhbeck et al. 2001) (Bruun et al. 2003) |
| Interleukin-8 (IL-8) | No direct effect on adiponectin production | (Bruun et al. 2003) |
| Insulin | Inhibits lipolysis & activates lipogenesis Stimulation of glucose uptake & oxidation ↓ related to adiponectin Stimulates leptin expression | (Fruhbeck et al. 2001) (Fruhbeck et al. 2001) (Fruhbeck et al. 2001) |
| Leptin | Signals brain about body fat stores Regulates appetite & EE ↓ related to adiponectin Key role in fuel utilization Inhibits lipogenesis & stimulates Lipolysis | (Fruhbeck et al. 2001) (Bruun et al. 2003) (Fruhbeck et al. 2001) (Fruhbeck et al. 2001) |
| Peroxisome proliferators-activated receptor (PPAR) γ | (Nuclear receptor)→adipocyte differentiation & influences SI | (Fruhbeck et al. 2001) |
| Tumor-necrosis factor (TNF)- α | Stimulates lipolysis Involved in insulin resistance ↑ in obese individuals (+ correlated with adiposity) ↓ after weight loss Not correlated to adiponectin after weight loss <i>in vivo</i> , the opposite occurs <i>in vitro</i> ; thus, combination of TNF- α & IL-6 may inhibit adiponectin Acts in an autocrine or paracrine manner Adiponectin improves insulin resistance by inhibiting gluconeogenesis by interfering with TNF-alpha production & increasing fatty acid oxidation | (Fruhbeck et al. 2001) (Fruhbeck et al. 2001) (Fruhbeck et al. 2001) (Fruhbeck et al. 2001) (Holdstock et al. 2003) (Bruun et al. 2003) (Holdstock et al. 2003) |

SI=insulin sensitivity

APPENDIX B:**B1: Advertisement flyer****B2: Phone screening****B3: Informed consent form****B4: Medical history questionnaire****B5: Payment form**

APPENDIX B2:

Phone screening

Instructions au sujet qui appelle pour s'informer à propos de l'étude

✓ 4 Sessions

-Pré-test

- Formulaires, questionnaires, Mesures anthropométriques, Bioimpédance électrique, VO₂ max.
- Renseignement sur le déroulement de l'étude.
- doit être fait de 8h30 à 10h30 ou 13h à 15h

-Phase 1-2-3

- doivent être disponible de 8h à 12h30, puis de 17h15 à 18h.
- pendant la phase folliculaire du cycle menstruel (jour 1 à 5 des pertes)
donc 1 mois entre chaque phase
- pendant ces jours, tous les repas et collations sont fournis.
- seule chose qui change entre les séances : intensité de l'exercice (repos, faible, haute).
- Échantillons sanguins (cathéter installé par un infirmier) de 8h à 12h
- Repas, questionnaires, métabolisme de repos, échantillons sanguin, température tympanique, exercice, douche

Avant phase 1-2-3

- Suivre guide de recommandations alimentaires pendant 3 jours.

Après phase 1-2-3

- Faire un journal alimentaire pendant 3 jours
- Porter un pedomètre pendant 3 jours

- ✓ Compensation financière de 75\$ à la fin de l'étude.

✓ **si le sujet semble intéressée....**

- questionnaire de screening
- critères d'inclusion
- date possible des prochaines menstruations?
- céduler date pour le pré-test
- Dire d'apporter linge de sport + espadrilles, bien s'hydrater les jours avant.

APPENDIX B3:**Informed consent form****THE EFFECTS OF DIFFERENT EXERCISE INTENSITIES ON APPETITE IN FEMALE
PRE-MENOPAUSAL WOMEN****Graduate Students:****Marjorie Pomerleau (B.Sc.) and Torrey Parker (B.Sc.)****Advisors:****Dr. Eric Doucet (Ph.D.) and Dr. Pascal Imbeault (Ph.D.)****University of Ottawa, Faculty of Health Sciences,
School of Human Kinetics**

I, _____, am interested in participating in this study conducted by Marjorie Pomerleau and Torrey Parker (graduate students) and Dr. Eric Doucet and Dr. Pascal Imbeault of the School of Human Kinetics at the University of Ottawa.

GOAL OF THE STUDY

The main objective of this study is to determine if practical exercise with varying intensities will have an impact on appetite. Secondly, we are interested in examining if there is an association between specific components of appetite and changes in certain hormones. This document will detail and provide all the necessary information pertaining to this project. Therefore, it is absolutely essential that you read very carefully this document before signing it. Please do not hesitate to ask any questions, as we are more than happy to address any issues or concerns. This research project is subsidized by the Research fund of the Health Sciences Faculty.

PROCEDURES OF THIS STUDY

My participation in this study requires that I participate in a baseline measure (pre-selection: ~2.5 hours) and 3 experimental sessions (each one day long) during which various measures will be taken. The experimental sessions will take place once a month in the follicular phase of your menstrual cycle. Details of the experimental protocol are described below.

Pre-selection of participants

The pre-selection meeting is necessary in order to evaluate whether individuals that have been recruited and phone screened for this study are in fact eligible according to the inclusion criteria. During this session participants will be informed of the experimental procedures involved in this study and will fill out questionnaires concerning medical history and their aptitude for physical activity (Q-AAP). Proceeding, participants will undergo anthropometric measurements such as skin folds, and waist circumference. Body composition will be measured by using hydrostatic weighing, which is considered gold standard for calculating percent body fat. Maximal aerobic capacity (VO₂max) will be tested using a treadmill protocol to perceived maximal exertion.

The intervention

If I meet the inclusion criteria necessary for this study and choose to continue as a participant I am aware that I will be participating in 3 different experimental days of testing, in which I will be

participating in physical activity at varying intensities in addition to receiving three meals a day.

DESCRIPTION OF MEASUREMENTS

I will be equally likely to undergo certain experimental measures that will take place during the 3 designated experimental days. One month will separate each experimental session. I am aware that I am being asked to be available at least for one whole day (8am to 6:30pm), although I am allowed to leave for the afternoon from 12:30pm to 5:15pm. The same procedures will take place at each of the three experimental sessions during this study, with the exception that there will be varying levels of intensity of physical activity. More details are provided below.

Pre-test session

9:30am to 10:30am Explanation of the experimental protocol and filling-out of documentation.

At this time participants will be explained all of the procedures that are involved in the study and will have the opportunity to ask any questions or address any concerns. After all issues and concerns are dealt with participants will be asked to sign the free and informed consent form before proceeding. After consent has been given, participants will be asked various medical questions concerning different pathologies or allergies that may interfere with the protocol of this study. This is important because participants will be given 3 meals a day and we want to be aware of any food allergies and/or medical concerns as a precaution. Participants will then disclose when their next menstrual cycle begins; thus, the research assistant can book experimental sessions. Participants must be tested during the first 8 days of their menstrual cycle, the follicular phase, which is when women's sexual hormones are at their lowest value. This is important because variations are visible in estrogens and progesterone, which ultimately affects energy expenditure and the oxidation of certain substrates. Participants will be explained how to use the dietary journals and pedometers, in which they will be required to complete data entries 3 days after their experimental session. Participants will also be shown how to work the pedometers, which objectively measures physical activity. Also, participants will be taught what is considered a standardized diet for three days before each experimental session.

10:35am Anthropometric measurements

This part of the protocol will include weighing the participants using a standard balance beam, measuring waist circumference with a standard measuring tape, and body composition testing by underwater weighing.

10:45am Bioimpedance

There are many methods that can be used to calculate percent body fat. For the purpose of this study, we will be using bioelectrical impedance. The value obtained is a direct measurement of the electrical current that runs from foot-to-foot. The results are based on the fact that an electrical current runs faster through lean body mass and slower through fat mass.

11:00am Test of maximal aerobic capacity

Participants will be asked to complete a VO_2 max test during the pre-test in order to establish their specific intensities for the proceeding experimental sessions, for the physical activity component. The VO_2 max protocol used for this study will be the Jean Jobin, which is a progressive protocol on a treadmill. Cardiac frequency of the participants will be measured every minute and blood pressure at the end of each stage of exercise. Perceived exertion will be checked at the beginning of each exercise stage using a standard Borg scale. The instrument used to measure other physiological variables will

be the CPX. The participants will be required to wear a mouthpiece while they breathe throughout the exercise protocol, which is similar to a device worn underwater for scuba diving. Participants will also wear a nosepiece during the test, which is similar to a nosepiece worn by swimmers. After the test is complete the participants will be invited to take a shower and clean up.

Experimental sessions 1, 2, and 3

At each experimental session participants will arrive early in the morning (8:00am), after a 12-hour fast and without having participated in moderate-to-vigorous physical activity in the last 48 hours. The following protocol will be used:

8h00 Anthropometric measurements

Body weight and waist circumference will be taken.

8:05am Insertion of catheter

The beginning of the session will consist of having a catheter inserted into the forearm of participants following a 12 hour fast. A blood sample will be taken before exercise on the treadmill (9:45am), at mid-time of the exercise sessions, after exercise (at 11:00am), and just prior to dinner. Approximately one tube of blood will be taken each time for a total of 4 tubes (60mL) per session.

8h10 Resting metabolic rate measurement

Resting metabolic rate (RMR) is established by measuring the amount of oxygen consumed and carbon dioxide produced. This measurement will be taken as I sleep on a bed while wearing a mouth and nosepiece for a period of 15 minutes.

Before 8:30am Visual analogue scale

Measurements by visual scale analogue will be done at this time. This measure evaluates the appetite of participants using a specific scale. Participants will be asked to rate their appetite according to the given scale at different times during the experimental protocol. This measurement will be taken before breakfast and every 15 minutes for the hour following this breakfast (rest period). This procedure will be repeated at lunch, every hours following the end of the lunch until dinner and a three final measurements will take place at home in the evening.

8:30am Breakfast

Breakfast will consist of 2 pieces of whole-wheat toast, 20 grams of peanut butter, 20 grams of raspberry jam, a slice of cheese, and 250 ml of orange juice. Participants will be given 15 to 20 minutes to ingest their food.

Before 9h45am Body temperature measurement

Body temperature will be taken with disposable eardrum thermometers at different moments during the experimental session. Specifically, this measurement will be taken before exercise (9:45am), after exercise (11:00am), before lunch (12:00pm), and before dinner (5:30pm).

9:45am Exercise session

The exercise session intensities and speed on the treadmill are based on the pre-test values from the VO₂max test (maximal aerobic capacity as described on pg.3). There will be a rest period preceded by

exercise at low-intensity (40% VO_2 max) and followed by a higher exercise intensity (70% VO_2 max). Participants' will required to wear a mouth and nosepiece, as has been previously described above.

12:00pm and 5:30pm Spontaneous dietary recall

A buffet will be served at both lunch and dinner to the participants during the experimental session; lunch at 12:00pm and dinner at 5:30pm. All the food will be prepared and presented to the participants, who will be invited to eat until satiety. They will be allowed to digest for 30 minutes after their meal.

Afternoon and evening snack

An afternoon and evening snack will be given to each participant. The snack will include a diverse dietary selection with a wide variety of energy rich foods. Specifically the snack will include: cookies, fruits, juice, a soft drink (coke), a bottle of water and a package of peanuts. Participants will choose what they want to eat; and, what is not eaten, if anything, will be recorded.

FORSEEABLE RISKS

The methodology used in this study does not pose any health risks to those that participate. The anthropometric measurements also do not pose any known health risks. The maximal aerobic capacity test (completed at pre-test) may cause fatigue and muscles soreness due to the intensive nature of the exercise in the hours after the test. However, the testing protocol used is a standard protocol and will be administered by a trained research assistant. The food provided in this study should not cause any health problems, as long as all allergies are properly reported in the opening questionnaire, in which participants are asked specifically about any food allergies. Blood sampling may cause slight bruising in the area in which the needle was inserted and tenderness may be evident for several days after. Even though the risks of blood sampling are extremely low it is important that participants be aware in any event. It is also possible that certain participants may feel faint when the needle is inserted or when blood is being withdrawn. It is important to note that an experienced registered nurse (RN) will be withdrawing the blood.

ADVANTAGES

This study will provide participants with interesting information with regard to body composition and maximal aerobic capacity. Participants will be given some nutritional counseling as well as learning about the benefits of physical activity. In addition, participants will be advised about how to decrease body weight, if they so desire.

FINANCIAL COMPENSATION

Each participant will be offered \$75 for their participation in this study by the researchers involved. The participant, at any time, can withdraw from the program without penalty.

CONFIDENTIALITY AND ANONYMETITY

- ✓ Participants should be assured that their participation will be kept strictly confidential and all necessary precautions will be taken to ensure that this takes place.
- ✓ Names of participants will not appear on any report. A code is used for all identification purposes for the research.
- ✓ If the data is given to an external source the identification in the event that a secondary data analysis would be required, code will be used, not names.
- ✓ All material (including personal information) collected in this study will be guarded under lock and

WEALTH projet

| Phase | Visite | Date (j/m/a) | | | Initiales du sujet | | | Code du sujet | | |
|-----------|----------|--------------|--|--|--------------------|--|--|---------------|--|--|
| PT | 1 | | | | | | | | | |

Initiales de l'évaluateur : _____

HISTOIRE MÉDICALE ET NUTRITIONNELLE
SUITE...

| ANTÉCÉDENTS MÉDICAUX/CHIRURGICAUX : (Si cette condition persiste, veuillez la décrire ci-dessous) | | AUCUN <input type="radio"/> |
|---|--|------------------------------------|
| CONDITION | | ANNÉE |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

HISTOIRE DU CYCLE PONDÉRAL :Avez-vous déjà fait une diète (perte de poids (4 kg ou 10 livres)? oui non Si **oui**, quel était votre poids avant la diète? _____ kg

Votre âge à cette période? _____ ans

Si **oui**, spécifiez combien de fois avez-vous suivi une diète? _____ fois

Initiales de l'évaluateur : _____

WEALTH projet

| Phase | Visite | Date (j/m/a) | | | Initiales du sujet | | Code du sujet | | |
|-----------|----------|--------------|--|--|--------------------|--|---------------|--|--|
| PT | 1 | | | | | | | | |

Physical Activity Readiness
Questionnaire (PAR-Q)
Revised 1994

PAR - Q & YOU

(A Questionnaire for People Aged 15 to 69)

Regular physical activity is fun and healthy, and increasingly more people are starting to become more active every day. Being more active is very safe for most people. However, some people should check with their doctor before they start becoming much more physically active.

If you are planning to become much more physically active than you are now, start by answering the seven questions in the box below. If you are between the ages of 15 and 69, the PAR-Q will tell you if you should check with your doctor before you start. If you are over 69 years of age, and you are not used to being very active, check with your doctor.

Common sense is your best guide when you answer these questions. Please read the questions carefully and answer each one honestly. Check YES or NO.

| YES | NO | |
|--------------------------|--------------------------|---|
| <input type="checkbox"/> | <input type="checkbox"/> | 1. Has your doctor ever said that you have a heart condition and that you should only do physical activity recommended by a doctor? |
| <input type="checkbox"/> | <input type="checkbox"/> | 2. Do you feel pain in your chest when you do physical activity? |
| <input type="checkbox"/> | <input type="checkbox"/> | 3. In the past month, have you had chest pain when you were not doing physical activity? |
| <input type="checkbox"/> | <input type="checkbox"/> | 4. Do you lose your balance because of dizziness or do you ever lose consciousness? |
| <input type="checkbox"/> | <input type="checkbox"/> | 5. Do you have a bone or joint problem that could be made worse by a change in your physical activity? |
| <input type="checkbox"/> | <input type="checkbox"/> | 6. Is your doctor currently prescribing drugs (for example, water pills) for your blood pressure or heart condition? |
| <input type="checkbox"/> | <input type="checkbox"/> | 7. Do you know of any other reason why you should not do physical activity? |

YES to one or more questions

If you answered

Talk with your doctor by phone or in person **BEFORE** you start becoming much more physically active or **BEFORE** you have a fitness appraisal. Tell your doctor about the PAR-Q and which questions you answered YES.

- You may be able to do any activity you want—as long as you start slowly and build up gradually. Or, you may need to restrict your activities to those which are safe for you. Talk with your doctor about the kinds of activities you wish to participate in and follow health advice.
- Find out which community programs are safe and helpful for you.

NO to all questions

If you answered NO honestly to all PAR-Q questions, you can be reasonably sure that you can:

- start becoming much more physically active—begin slowly and build up gradually. This is the safest and easiest way to go.
- take part in a fitness appraisal. This is an excellent way to determine your basic fitness so that you can plan the best way for you to live actively.

DELAY BECOMING MUCH MORE ACTIVE.

- if you are not feeling well because of a temporary illness such as a cold or a fever—wait until you feel better; or
- if you are or may be pregnant—talk to your doctor before you start becoming more active.

Please note: If your health changes so that you then answer YES to any of the above questions, tell your fitness or health professional. Ask whether you should change your physical activity plan.

Informed Use of the PAR-Q: The Canadian Society for Exercise Physiology, Health Canada, and their agents assume no liability for persons who undertake physical activity, and if in doubt after completing this questionnaire, consult your doctor prior to physical activity.

You are encouraged to copy the PAR-Q but only if you use the entire form

NOTE: If the PAR-Q is being given to a person who is not the person who is actually doing the activity, the person doing the activity must be asked for explicit administrative permission.

I have read, understood and completed this questionnaire. Any questions I had were answered to my full satisfaction.

NAME _____

SIGNATURE _____ DATE _____

SIGNATURE OF PARENT _____ WITNESS _____
or GUARDIAN (for persons under the age of majority)


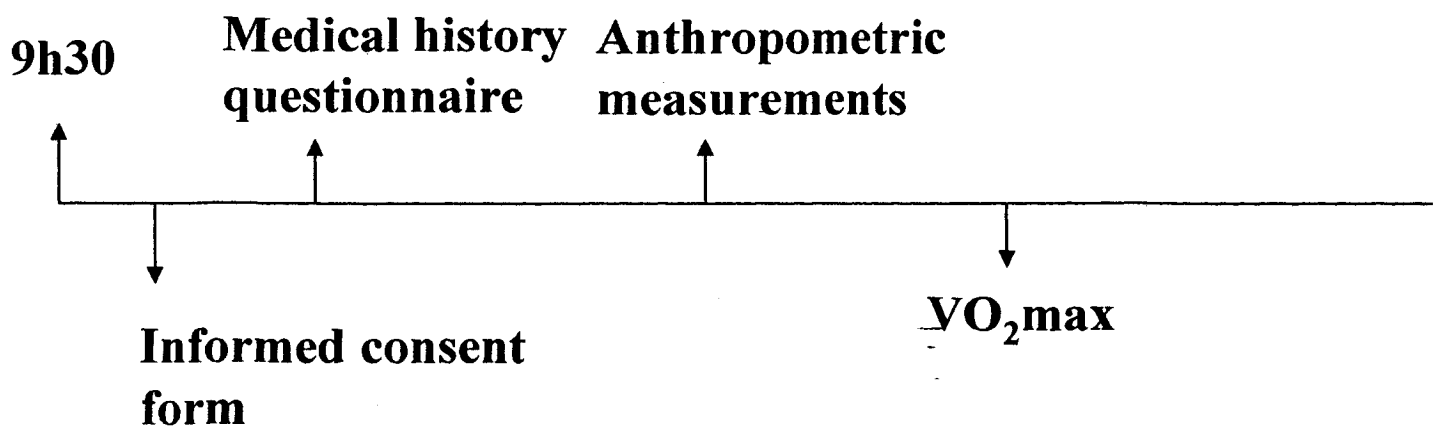
© Canadian Society for Exercise Physiology / Société canadienne de physiologie de l'exercice Supported by  Health Canada / Santé Canada

FIGURE 2-1. PAR-Q form. (Reprinted with permission from the Canadian Society for Exercise Physiology, Inc., 1994.)

Pre-test session protocol

Arrival



Legend:

- Blood sample
- Exercise (LI or HI) or rest

