Physical activity, fatness, and adiponectin in young males

by

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A thesis submitted to the graduate faculty in
partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

Major: Exercise and Sport Science (Biological Basis of Physical Activity)

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Ames, Iowa
2006
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Signatures have been redacted for privacy
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I would like to extend my sincerest gratitude to my major professor Dr. Joe Eisenmann. My skills as a researcher were cultivated under his tutelage, providing me the tools for professional success. I would also like to thank my POS committee for providing guidance in execution of my thesis. I feel fortunate to have worked with such an intelligent group of individuals. The early contributions of Dr. Paul Flakoll were beneficial to this project and to my growth as a researcher. Even though I had limited contact with Dr. Flakoll it was evident that he was an exceptional scholar.

I would also like to thank my lab mates for making the journey that much more enjoyable. Your willingness to help with data collection, especially on the weekends is very much appreciated. Also, thank you to all of my colleagues for providing a fun work atmosphere.

Finally, I would like to thank my family and especially my wife Kendra. Her constant support and reassurance has kept me grounded throughout the last two years. Who else would read my papers and listen to my presentations even though it is a foreign subject for her. As the old saying goes behind every man is a strong woman, in my case she is right beside me holding my hand along the way.
CHAPTER 1: INTRODUCTION

Obesity is increasing at an alarming proportion in most developed countries and also in countries adopting a Western lifestyle. In fact, obesity is now considered a global epidemic.\(^1\) In the United States alone, approximately 60% of adults are overweight (body mass index $> 25.0$-$29.9$ kg/m\(^2\)) or obese (BMI $> 30$ kg/m\(^2\)).\(^2\) The concern regarding this prevalence is that obesity is associated with several adverse health consequences including cardiovascular, metabolic, mental, and orthopedic diseases.\(^3\)\(^,\)\(^4\)

Obesity and its co-morbidities (e.g., cardiovascular disease [CVD], type 2 diabetes, etc.) are not limited to adults. Recent epidemiological data from the 1999-2000 National Health and Nutrition Examination Survey (NHANES) shows that approximately 15% of 12-19 year old adolescents in the United States are considered obese (body mass index $> 95^{th}$ percentile of age- and sex-specific reference values) which is a 5% increase since NHANES III (1988-1994) and an almost 3-fold increase since the first national survey of 1966-1970.\(^5\)\(^,\)\(^6\) Childhood obesity is also associated with medical consequences as children are experiencing an earlier development of complications related to obesity. Specifically, obese adolescents are at an increased risk for the metabolic syndrome, which is a clustering of dyslipidemia, hypertension, and a disturbance in glucose metabolism\(^7\).

Recent findings in adipocyte biology have shown that the adipocyte not only stores triglycerides but is also a hormonal secretory organ. In the past ten years, many new hormones/cytokines such as leptin, interleuken-6 (IL-6), resistin, tumor necrosis factor-alpha (TNF-\(\alpha\)), and adiponectin have been identified as originating in adipose tissue.\(^8\) Collectively, these secretory products of adipocytes can be referred to as adipocytokines. Of these
adipocytokines, adiponectin is the most abundant of all the adipocyte-released hormones. Adiponectin has been shown to influence insulin sensitivity and anti-inflammatory/anti-atherogenic reactions. Since insulin resistance and atherogenesis are major contributors to CVD, the control of these conditions are crucial in maintaining cardiovascular and metabolic health.

Despite a growing literature on adipocytokines, there has been limited research on adiponectin and adolescents. A recent MEDLINE search revealed only 50 papers using the key terms "adiponectin and adolescents". The majority of these papers focused on the relationship between adiposity and adiponectin, and more specifically, adiponectin in obese adolescents. In general, this research has shown that adiponectin levels are inversely associated with adiposity, and that adiponectin increases following weight loss in obese adolescents. The lower adiponectin concentration associated with an increased fatness may play a role in the pathogenesis of obesity and the metabolic syndrome.

Physical activity has been shown as an important factor regulating the growth and maturation of the fat depot. Research has shown that increasing physical activity and a reduction of caloric intake can result in a decrease of adipose tissue. Increasing physical activity alone can also decrease the fat depot. Although there is research supporting physical activity as a mediator of weight loss and thus a method for preventing the development of obesity, there is a lack of research investigating the independent effects of physical activity on the inflamed state that develops with excess adiposity. Currently, there are no published studies that determine the relationship between physical activity and adiponectin levels in adolescents. Therefore, the purpose of this thesis is to examine the inter-relationships among physical activity, body fatness and adiponectin in adolescent males.
Significance of the study

Current research on adiponectin has focused on the physiological interactions between adiponectin and various metabolic processes within the body. In general, adiponectin has shown adverse effects on CVD risk factors. It can also be inferred from the research that higher circulating concentrations of adiponectin are important for the prevention of the metabolic syndrome and CVD. However, there is a need for research focusing on clinical applications, especially in the adolescent population. The various clinical studies conducted on adolescents focus on weight/adiposity relationships with adiponectin concentrations. Research in the adolescent population has neglected to investigate the possible relationship between physical activity and adiponectin concentrations. Physical activity may benefit adolescents by increasing adiponectin concentrations and thus the identification of a possible relationship between physical activity and adiponectin levels could lead to physical activity recommendations to maintain proper health in adolescents.

Limitations

Since androgens are not being measured in this study, the influence androgens have on adiponectin levels in adolescents may be a potential limitation. To control for androgen involvement, the study will use male participants between the age of 12 and 18 years. In order to control for variation in age, maturity status will be assessed and statistically controlled. Due to the influence of adiposity on adiponectin concentrations, adiposity will also be controlled in the analysis. Another area where a limitation exists is in physical
activity assessment. Currently there is not a “gold standard” measurement for physical activity; every method has its strengths and weaknesses.

**Research Hypotheses**

Young males with higher levels of regular physical activity will have increased plasma adiponectin concentrations independent of age and adiposity.

**Thesis Organization**

This thesis is structured into four key sections. The first of which is a general introduction which briefly identifies background information on the subject and identifies the purpose of the study. Following the introduction is comprehensive literature review that examines the current literature on the subject at hand, building the case for the relevance of the study. Section three is the complete study in manuscript form that is intended for publication. The fourth and last section summarizes the main conclusions. All works cited are in the format required by the Journal of American Medical Association.

**References**


CHAPTER 2: REVIEW OF LITERATURE

Introduction

The epidemic of obesity in children and adults continues to stimulate research into the causes and complications related to the disease. Recent findings on the function of adipose tissue as a secretory cell has shifted research into a new direction. The discovery of hormonal secretions from adipose tissue changes the original and long-standing view of fat being a storage depot. ¹ These adipose secreted hormones, known as adipocytokines, have profound and widespread physiological effects on the body. One such adipocytokine is adiponectin, which has been shown to influence insulin sensitivity and the development of atherosclerosis. The purpose of this review of literature is to address the epidemiology of pediatric obesity, the complications of childhood obesity, and adiponectin.

Epidemiology of Pediatric Obesity: Prevalence and Consequences

In the past few decades, there has been a substantial increase in childhood and adolescent obesity in several nations of the World. In the United States over 15% of the youth are obese.² Along with the increase in obesity, children are developing complications that normally occur in adults, such as type II diabetes and the metabolic syndrome.³ Excess weight in childhood can also lead to greater complications in adulthood. An increased BMI can track from childhood into adulthood.⁴ In order to test whether BMI tracked into adulthood Srinvasan et al.⁴ analyzed the Bogalusa Heart Study data, children in the highest BMI and insulin levels were at greater risk for developing adult complications (odds ratio of 11.7 and 3.6 respectively). Between the two aforementioned predictors, BMI had the strongest relationship to a clustering of metabolic complications later in life.⁴ Similar
research has identified that an increase in adiposity during childhood can be a predictor of cardiovascular risk factors. Freedman et al.\textsuperscript{5} investigated the relationship between overweight participant classification and cardiovascular risk factors in children using the Bogalusa Heart Study data. Freedman’s group found that 20\% of overweight children have one CVD risk factor, with 80\% of that 20\% having three or more risk factors. The most common risk factors in overweight children are high triglycerides and low concentrations of high density lipoprotein cholesterol (HDLC).\textsuperscript{5}

**The Adipocyte: Beyond a Storage Depot**

Traditionally, adipose tissue has been considered to function as a storage depot for triglycerides and insulation for retention of body temperature. However, recent research has found that adipose tissue is not only used for triglyceride storage, but also has hormonal functions. The discovery of lipoprotein lipase, a protein structure that is released from adipose tissue, in the mid 1980’s provided the first evidence that adipose tissue is more than just a storage depot.\textsuperscript{6} In 1994, roughly ten years after the identification of lipoprotein lipase, Zhang et al.\textsuperscript{1} discovered leptin a cytokine released from adipose tissue, thus identifying adipose tissue as a hormonal organ.\textsuperscript{1} The cytokine leptin was later shown to be involved in energy homeostasis.\textsuperscript{7} Shortly after leptin was identified other adipocytokines (cytokines originating from adipose tissue) that have diverse effects on whole body physiology were discovered. To date, more than 10 adipocytokines have been identified. (See Table 1 on next page)\textsuperscript{8} With the advancement of technology new adipose derived biomarkers are continuing to be discovered.\textsuperscript{11} One such adipocytokine is adiponectin, which has been shown to have anti-inflammatory and insulin sensitizing properties.\textsuperscript{9,10}
### Table 1. Listing of common adipocytokines and their function

#### General Biology of Adiponectin

<table>
<thead>
<tr>
<th>Adipocytokine</th>
<th>Major Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leptin</td>
<td>Energy homeostasis</td>
</tr>
<tr>
<td>Tumor Necrosis Factor Alpha (TNF-α)</td>
<td>Inflammatory response, insulin resistance</td>
</tr>
<tr>
<td>Interleukin-6 (IL-6)</td>
<td>Energy homeostasis</td>
</tr>
<tr>
<td>Macrophages and Monocyte Chemoattractant Protein (MCP-1)</td>
<td>Inflammatory response, monocyte accumulation</td>
</tr>
<tr>
<td>Plasminogen Activator Inhibitor (PAI-1)</td>
<td>Inhibits fibrinolysis, angiogenesis, atherogenesis</td>
</tr>
<tr>
<td>Adiponectin</td>
<td>Anti-inflammatory, Anti-atherogenic, Insulin Sensitivity</td>
</tr>
<tr>
<td>Adipsin and Acylation Stimulating Protein (ASP)</td>
<td>Influences lipid and glucose metabolism</td>
</tr>
<tr>
<td>Resistin</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td>Angiotesin Family (AT1,AT2, ACE)</td>
<td>Electrolyte balance, vascular tone</td>
</tr>
<tr>
<td>Visfatin</td>
<td>Insulin Sensitivity</td>
</tr>
</tbody>
</table>

Adiponectin is a 244 amino acid residue that is exclusively produced in white adipose tissue with a similar structure to tumor necrosis factor alpha. The gene for human adiponectin expression is on chromosome 3q27. Adiponectin was originally named APM1 (adipose most abundant gene transcript) because it is the most abundantly transcribed gene in adipose tissue. Adiponectin makes up approximately 0.01% of total plasma content in healthy individuals, which is almost 1,000 times greater than the remaining adipocyte released (adipocytokine) hormones.
Adiponectin differs from other adipocytokines because it decreases as adiposity increases, which is the opposite reaction from the rest of the known adipocytokines. Adiponectin has been shown to be inversely correlated to FFA concentrations and triglycerides; and positively related to HDL cholesterol, thus it has been related to obesity and the metabolic syndrome.\textsuperscript{16}

**Adiponectin and the Metabolic Syndrome**

Adiponectin is linked to influencing contributors of the metabolic syndrome. The metabolic syndrome consists of the co-occurrence of visceral obesity, dyslipidemia, insulin resistance, and hypertension.\textsuperscript{17} Increased adiposity and physical inactivity are also related to the metabolic syndrome. As a result of increased adiposity and physical inactivity, the metabolic syndrome is more common in people that are considered to be overweight or obese. Effects of the metabolic syndrome can lead to a greater risk of developing cardiovascular complications such as atherosclerosis.\textsuperscript{18} A main contributor to the complications associated with the metabolic syndrome is insulin resistance.

Insulin resistance is when the body becomes desensitized to insulin causing less glucose to enter the cells. When glucose cannot enter the cells for metabolism, alternate fuel sources are needed. The main fuel source that is relied upon when glucose metabolism cannot be used is fat. However, the problem with relying on fat for energy is that there is a greater amount of free fatty acids (FFA) in the blood. In turn these free fatty acids can attach to damaged areas in the endothelium and cause atherosclerosis.

Adiponectin has been found to decrease the level of insulin resistance.\textsuperscript{19}
In obese mice the administration of adiponectin lowers plasma glucose concentrations and prevents plasma triglyceride increase while lowering liver and muscle triglyceride content.\textsuperscript{20} Yamauchi et al.\textsuperscript{21} uncovered similar findings in mice with adiponectin injection, their data supports the findings that adiponectin increases FFA utilization (adiponectin increases Beta-oxidative enzymes) thus reducing stored triglyceride content in the muscle and liver. It is believed that excess triglycerides in tissue can hinder glucose transport and subsequent uptake. Yamauchi and colleagues concluded that insulin sensitivity is increased via a lowering of triglycerides.\textsuperscript{21}

Another area related to insulin sensitivity is glucose production. Endogenous glucose production has been negatively correlated to adiponectin. A decrease in endogenous glucose production in turn lowers the need for increased insulin secretion. Lowered glucose production via increased adiponectin concentrations may have a hindering effect on the development of type II diabetes or the metabolic syndrome.\textsuperscript{22, 23}

**Adiponectin and Atherosclerosis**

Along with the insulin sensitizing properties of adiponectin, it also has anti-atherogenic effects on vascular tissue. Atherosclerosis is the main cardiovascular complication within cardiovascular disease, which is the leading causes of death in several developed countries.\textsuperscript{18} Each year approximately $38\%$ of all deaths in the United States per year are caused by cardiovascular disease.\textsuperscript{24} Atherosclerosis is the deposition of body materials (mostly lipids and monocytes) in the vascular tissue where an injury has occurred. The main cause of atherogenesis is the development of crystallized plaque on the endothelium.\textsuperscript{25} This plaque is the result of increased monocyte binding with endothelial
tissue. Monocyte binding influences the uptake of low density lipoproteins. Low density lipoproteins are taken up to form foam cells which turn into atherosclerotic plaque. The uptake of low density lipoproteins are modulated through scavenger A macrophage receptors.26,27 The previously mentioned Atherosclerotic processes have been identified as starting in children.5

Adiponectin has been shown to decrease the formation of atherosclerotic plaques by 30% in mice.28 A decrease in atherosclerotic formation with adiponectin may be related to adiponectin's inhibitory effect on foam cell formation through hindering class A scavengers.29 Adiponectin has been found in areas of injured endothelium where populations of macrophages are present.29 Adiponectin is not detected in areas where endothelium remains whole, suggesting adiponectin presence at injured endothelial tissue is part of an anti-inflammatory response. Ouchi et al.29 established that the treatment of adiponectin administered over 3 days decreases cholesterol ester in macrophages by 50%.

Adiponectin is not only effective in slowing down the process of atherogenesis but it may also have an inhibitory role in the early phases of atherosclerotic development. When an injury first occurs to the endothelium an inflammatory response is initiated. This inflammatory response leads to an increased adhesion of monocytes to the endothelial tissue. One inflammatory marker that is present during the initial phase of injury is tumor necrosis factor alpha (TNF-α). TNF-α is directly associated with an increase in monocyte adhesion. Once TNF-α binds to its prospective site it initiates a cascade of reactions that result in monocyte adhesion.30 Research has shown that adiponectin interferes with atherosclerosis by preventing monocyte binding to endothelial tissue. However, adiponectin’s inhibition of monocyte binding does not occur via the hindering of TNF-α binding, rather it acts through
the disruption of TNF-α signaling after it has bound to the cell. This disruption in TNF-α signaling prevents activation of NF-κB which is a controller of monocyte adhesion and inflammatory response. Decreased monocyte binding leads to a smaller uptake of low density lipoprotein, causing smaller development of atherosclerotic plaque.10

If an atherosclerotic situation is not interrupted by adiponectin and has damaged the vascular structure substantially enough to cause ischemic conditions, adiponectin can still intervene. Shibata et al31 concluded that adiponectin has angiogenic properties in vivo in mice. After an ischemic condition was indicated in the mice an 80% recovery to normal blood flow levels occurred in the adiponectin producing mice compared to adiponectin deficient mice.31 Angiogenesis is an important mediator in keeping normal blood flow, preventing cardiac episodes.

**Sex-associated Variation in Adiponectin**

Adiponectin levels differ between males and females even after BMI and/or body fat is statistically controlled.19 With women having greater concentrations of adiponectin compared to their male counterparts. Research comparing men and women with the same BMI shows women having larger concentrations of adiponectin even with greater amounts of adipose tissue.19,32,33

Gender differences in adiponectin have been investigated in a mouse model using castrated mice that received androgen replacement.32 Androgens such as testosterone were found to decrease adiponectin concentrations in the mouse model. From animal research it can be inferred that gender differences in humans may be related to the higher androgen levels in males.32 The gender paradigm seen in adults is also present in the youth; boys have
lower adiponectin concentrations compared to girls. Research has shown that the gender differences are not present in pre-pubescent. Prior to the initiation of puberty, boys and girls have similar levels of adiponectin; children also have higher adiponectin concentrations compared to the adult population. Research in adiponectin during puberty has shown that adiponectin concentrations are inversely related to development. (See Graph 1) At the beginning of puberty, boys experience a decline in adiponectin levels followed with an inverse relationship of adiponectin and stage of puberty. The age-pubertal changes seen in boys have not been shown to be present in girls. Thus, gender differences in adolescents may also be related to androgen release, which is similar to the adult population.

Figure 1. Adiponectin concentrations with increasing age
Adiponectin in obese and non-obese adolescents

The majority of adiponectin research involving adolescents has investigated the differences between obese and non-obese individuals. In addition, studies have also addressed the affects of weight loss. In general, results in adolescents are similar to what is seen in the adult population. Adiponectin concentrations in adolescents are negatively correlated to adiposity. More specifically, the amount of visceral adiposity influences adiponectin levels. The higher visceral fat (non-obese: 39 cm$^2$, obese 71 cm$^2$), the lower the adiponectin concentrations (14 μg/ml and 9.2 μg/ml).\cite{35} Accompanying the lower adiponectin levels in obese adolescents, there is an increase in insulin concentrations due to the lowering of insulin sensitivity.\cite{35,36} Adiponectin is positively correlated with insulin sensitivity in adolescents even after accounting for BMI and sex differences.\cite{37,38} With increased insulin concentrations, there are more triglycerides and free fatty acids present in overweight adolescents.\cite{35,39}

One aspect of adiponectin research in adolescents which helps shed light on the relationship between adiposity and adiponectin level is the area of weight loss. Research in adiponectin and weight loss has uncovered that a decrease in weight significantly increases adiponectin concentrations in adolescents.\cite{34,39} Similar findings have been seen with adult weight loss.\cite{40}

Physical activity and adiponectin (adults)

Few studies have examined the relationship between physical activity and adiponectin in adults and no studies have investigated this topic in adolescents. Monzillo et al.\cite{41} used physical activity in the form of an exercise program incorporated into a lifestyle
adjustment and found an increase in adiponectin levels after the 6 month intervention. However the increase in adiponectin more than likely came from a decrease in adipose tissue. A second group investigated the effects of intense intermittent exercise on adiponectin levels, there were no significant differences identified between control and exercise groups. More research is needed to determine if physical activities plays a role in the control of plasma adiponectin concentrations.

Summary and Conclusions

Obesity and its link to the metabolic syndrome and atherosclerotic complications currently affect developed countries around the world. The metabolic syndrome and atherosclerosis are serious conditions that may lead to death if left untreated. In order to address these problems more information is needed to formulate preventative measures. One avenue of investigation that may reveal more information about the control of obesity is the secretory role of adipose tissue. Adiponectin is one of the primary adipocytokines of interest due to its anti-atherogenic, anti-inflammatory, and insulin sensitizing effects. Numerous questions have been answered regarding adiponectin including the relationships with adiposity, gender, age, and metabolic/atherogenic interactions. Research has thus far neglected to address the area of physical activity and adiponectin in an adolescent population. Physical activity could play a strong role in the concentrations of adiponectin released in the body. The discovery of a connection between adiponectin and physical activity would lead to a greater understanding of how to address the negative consequences associated with adolescent obesity.
References


CHAPTER 3: PHYSICAL ACTIVITY, FATNESS, AND ADIPONECTIN IN YOUNG MALES (MANUSCRIPT)

Introduction

Obesity is increasing by alarming proportions in developed countries and is now considered a global epidemic.\(^1\) To better understand the etiology and consequences of obesity and to develop effective treatment strategies, an emerging research area involves the secretory role of the adipocyte. Traditionally considered a storage depot for triglycerides, the hormonal function of adipose tissue appears to play a significant role in inflammatory homeostasis through the release of cytokines (e.g., adipokines or adipocytokines).\(^2\)

Adiponectin is an adipocyte-released cytokine identified as having a mediating role in obesity and its co-morbidities. Adiponectin has anti-inflammatory and anti-atherogenic properties and has been linked to insulin resistance.\(^3\)-\(^5\) Recent research indicates that the administration of adiponectin to insulin resistant mice increases free fatty acid utilization, lowers plasma glucose levels, and hinders the development of atherosclerotic plaque.\(^6\)-\(^8\)

Several studies have shown an inverse association between measures of adiposity (e.g., body mass index (BMI), fat mass, etc.) and adiponectin.\(^9\)-\(^13\) Hence, given the association between obesity, inflammation, atherosclerosis, and insulin resistance, other research has examined the effects of weight loss on adiponectin in obese subjects. The findings from these studies indicate that adiponectin concentrations increase following weight loss in conjunction with diet and exercise intervention.\(^14\)-\(^16\) For example Reinehr et al.\(^14\) showed a 22% increase in adiponectin following a 3.1 kg decrease in body weight and 5% decrease in %body fat among 6-14 year old obese children involved in a weight loss intervention. However, it is yet to be determined if exercise plays an independent role from
adiposity in circulating serum adiponectin levels. The majority of exercise-related research, whether acute or training interventions, has failed to identify an increase in adiponectin concentrations.\textsuperscript{17-21} To date, only one study has reported an increase in adiponectin following multiple bouts of low-to-moderate intensity exercise.\textsuperscript{22} Although previous research has examined the effects of exercise training on adiponectin, no study has examined free-living daily physical activity. Training sessions are usually high intensity, short duration, and do not account for physical activity outside the training bout. On the other hand, measurement of free-living daily physical activity provides a representation of total accumulated physical activity, rather than a specific training bout. Therefore, the purpose of this study was to identify an independent relationship between physical activity and adiponectin in young men. The approach used in this study was to examine differences in adiponectin between three distinct groups—distance runners, normal weight and overweight subjects, and also to identify correlations between objectively-measured, free-living physical activity and adiponectin.

\textbf{Methods}

\textit{Participants:} Thirty-eight young males, 12-21 years of age, participated in the study. Subjects were recruited by advertisement and word-of-mouth. Five participants were excluded due to incomplete physical activity and/or maximal treadmill data. Participants were divided into three groups: distance runners, normal weight, and overweight. The latter two groups were based on the BMI. Overweight participants possessed a BMI equal to or greater than the age appropriate reference value according to Cole et al.\textsuperscript{23} This study was approved by the university human subjects review board. Informed consent and assent forms
(when applicable) were signed by parents and child, respectively.

**Anthropometry:** Standing height was measured to the nearest 0.1cm with a wall mounted stadiometer (Harpenden, London, UK). During the standing height measurement participants removed shoes, stood with feet together, and had arms relaxed at their sides. For standing height measurements the head was in the Frankfort plane, participants were instructed to inhale while the measurement was taken. Body mass was measured with participants in a t-shirt and shorts on an electronic scale (Seca 770) to the nearest 0.1 kg. The BMI was calculated as weight (kg)/height (m²). To provide an indicator of visceral or abdominal adiposity, waist circumference (WC) was measured to the nearest 0.1 cm with a Gullick tape at the superior border of the iliac crest. A bio-electrical impedance analyzer (RJL 101, Clinton, MI) was used to assess body composition according to manufactures procedures. Fat free mass was calculated using the equations of Goran et al. Fat mass and percent fat were obtained through calculations (fat Mass = body mass-fat free mass, %fat= (fat mass/body mass) *10).

**Assessment of Peak Oxygen Consumption (Peak Vo2):** Peak Vo₂ was determined during a graded maximal exercise test to exhaustion. The treadmill protocol consisted of 3-minute stages of increasing speed and grade until volitional exhaustion or test termination. Expired respiratory gases were collected and continually sampled via indirect calriometry (Cosmed Quark b2, Rome, Italy) for the measurement of oxygen consumption (Vo₂), carbon dioxide production (VCo₂), and minute ventilation. Peak Vo₂ was expressed relative to body mass (ml/kg/min).

**Habitual Physical Activity:** Habitual free-living physical activity was assessed with the Manufacturing Technology Inc. (MTI) uniaxial accelerometer (Shalimar, FL). The MTI is a
small (5x4x1.5 cm), lightweight (43 g) unit that produces values that are represented as total activity counts. The activity monitor was worn on the right hip for four days with at least one weekend day. Days were excluded if the unit was worn less than 8 hours and/or multiple undocumented large gaps of zero counts were present in the data. Summing the 24, 60-minute time blocks comprising each day generated daily total activity counts which were converted to counts/min based on the total daily time the unit was worn. Time spent in moderate physical activity (3-5.9 METS) (MPA) and vigorous physical activity (≥6 METS) (VPA) were determined based on age-specific cut-points.  

Blood Measurements: Participants arrived at the laboratory following a 12 hour over-night fast. Immediately following bio-electrical impedance a blood draw occurred via an antecubital venipuncture performed by a trained phlebotomist. Immediately following phlebotomy, blood samples were centrifuged at 4,000 rpm at 4° C and stored at -80° C until assayed. Adiponectin was measured using an enzyme-linked immunosorbent assay (ELISA) (R&D Systems, Minneapolis Minnesota) following manufactures instructions. Duplicate sampling was used to determine intra-assay variability. Intra-assay coefficient of variation was 9.04%.

Statistical Analysis: Descriptive statistics and the differences between the three groups were initially examined by one-way ANOVA. The inter-relationships among physical activity, peak Vo2, adiposity measures and adiponectin were initially examined by bivariate correlations. To examine the independent aspects of physical activity on adiponectin, subsequent analyses were covaried for age and fat mass. Analysis of covariance was used to further examine differences in adiponectin between the overweight, normal weight, and runners, and partial correlations, controlling for both age and fat mass, were used to further
examine the association between physical activity, peak Vo₂ and adiponectin. An alpha level of p<0.05 was used in all analyses which were calculated with the SPSS package (SPSS, Chicago, Illinois).

Results

Descriptive characteristics of the total sample and for the subjects grouped by runners, normal weight, and overweight are shown in Table 1. The overweight group had significantly higher BMI, WC, fat free mass, fat mass, and lower peak Vo₂ compared to the runners and normal weight. Age, vigorous physical activity, total physical activity (expressed as counts per minute), and peak Vo₂ were significantly higher in the runners compared to the other two groups. There were similar values for BMI and body fat measures between the runners and the normal weight. Results for ANOVA indicated that adiponectin was significantly greater in the runners compared to the overweight and normal groups. The large variation within and between the groups should be noted (i.e., range of values).

Bivariate correlations among the variables are shown in Table 2. Fat mass, WC and BMI were all highly correlated (r = 0.953 to r = 0.961). There was also a strong correlation between vigorous physical activity (VPA) and peak Vo₂ and (r = 0.709). There was a significant correlation between peak Vo₂ and adiponectin (r = 0.33). Likewise, fat mass was shown to be moderately inversely related to adiponectin (r = -0.24). There was also a moderately strong correlation between peak Vo₂ and fat mass (r = -0.71).

Given the association between age and fat mass with adiponectin, these variables were controlled using ANCOVA to examine the independent contribution of physical activity and possibly peak Vo₂ on adiponectin. Using this approach, there was no significant
difference in adiponectin between groups (p = 0.22) (Figure 1). However, the difference between runners and the other two groups was about 66% (7.43µg v. 4.93µg v. 4.81µg). The correlations between VPA and adiponectin was r = 0.252. However, when partial correlation was utilized the association between VPA and adiponectin decreased (r = 0.083).

Based on the inter-relationships between vigorous physical activity, peak Vo2, fat mass, and adiponectin (Figure 2), partial correlations were used to further investigate independent relationships between adiponectin and 1) peak Vo2 controlling for age and fat mass, 2) fat mass controlling for Vo2 peak and age. When age and fat mass were controlled, the significant relationship between adiponectin and Vo2 peak (r = 0.11, p = 0.509) was no longer significant. Controlling for Vo2 peak and age, the correlation between fat mass and adiponectin was also lowered (r = -0.08, p = 0.63).

Discussion

In the past 5-10 years, the prevalence of obesity has continued to increase and the view of adipocyte physiology has also changed. Adipose tissue has traditionally been thought of as just a storage depot for triglycerides. However, it is now known that adipose tissue secretes hormonally active substrates (e.g., adipocytokines) that appear to mediate the relationship between obesity and features of the metabolic syndrome (e.g. insulin resistance, hypertension, atherogenesis). 2 One such adipocytokine - adiponectin – was examined in the present study. The findings indicate that adiponectin differs between highly physically active/lean distance runners and normal weight and overweight young males. The observed differences in adiponectin between groups may suggest that several factors including
oxidative capacity, muscle-fat bi-directional communication, and vigorous physical activity may contribute to an up-regulation of adiponectin production.

The inverse correlations between measures of adiposity and adiponectin found here are consistent with previous research. In general, correlations between measures of adiposity (% body fat, BMI, FM) and adiponectin range between -0.22 to -0.43. In the present study, correlations were at the lower end of this spectrum (r = -0.24 to -0.29). The lower correlations in this study compared to previous research may be due to a relatively lean population as previous research has focused mainly on obese individuals. Given that the level of adiposity is a correlate of adiponectin concentrations, recent investigations have focused on the effects of weight loss through exercise, diet, or surgical interventions on adiponectin. The results of these studies demonstrate an increase in adiponectin concentrations with weight reduction. However, it remains to be determined if there is an independent effect of exercise on adiponectin. To date, the limited research has focused on the effects of acute exercise, specifically high-intensity intermittent exercise sessions. Kramer et al. failed to show an increase in adiponectin concentration with a 30 minute bout of high intensity running. The effects of long-term exercise training on adiponectin have also been investigated, and in general, indicate no change in plasma adiponectin levels. Kriketos et al. is the only study to show an increase (260%) in adiponectin levels following ~ 1 week, of 40 minutes of moderate intensity aerobic exercise performed on at least 2 days. In the present study, adiponectin was compared in three distinct groups of males. Highly-trained long distance runners, a normal weight group and an overweight group with the long distance runners serving as a special exposure group since they accumulate a large amount of total and vigorous intensity physical activity that is rarely seen in the general
population. When adiponectin concentration was compared between groups, the runners had significantly higher adiponectin levels \((p = 0.027)\). After covary for fat mass the runners retained a higher level of adiponectin \((-66\%)\) compared to the other groups, although the effect did not meet statistical significance. It is important to note that the normal weight and runners had similar body compositions but differing adiponectin concentrations, indicating fat mass does not explain much of the variance between these two groups. Previous research has only examined exercise training protocols and thus has failed to recognize the importance of habitual free-living physical activity on adiponectin. In the present study, habitual free-living physical activity was measured with an objective measurement tool (MTI accelerometer). Although the results failed to identify a significant correlation between physical activity and adiponectin, it remains possible that vigorous physical activity (as opposed to total physical activity) may act indirectly through its influence on peak \(\text{Vo}_2\) and/or fat mass (see Figure 2).

Given the inter-relationships between several key variables, a subsequent analysis was undertaken to further explore the complex relationships between peak \(\text{Vo}_2\), fat mass and adiponectin. Peak \(\text{Vo}_2\) is accepted as an indicator of the oxidative capacity of skeletal muscle. Although research has not examined the relationship between oxidative capacity of muscle and cytokine release from this tissue, it is possible a relationship exists due to the research indicating an altered IL-6 concentration in special populations. Therefore, it was of interest to further examine the potential role of peak \(\text{Vo}_2\) and adiponectin. Although the relationship between peak \(\text{Vo}_2\) and adiponectin was significant \((r = 0.33)\) (Figure 2) the statistical significance was not retained when fat mass was controlled in partial correlation. Likewise, statistical significance was not attained when the relationship between fat mass and
adiponectin was investigated controlling for \( \text{Vo}_2 \). Overall, the results indicate that both fat mass and peak \( \text{Vo}_2 \) are equally important in influencing adiponectin concentrations.

Even though the oxidative capacity of muscle may not have a direct role in the regulation of cytokines, muscle tissue does have an active role in inflammatory homeostasis. \(^{31,32}\) Furthermore, several authors have suggested the importance of a muscle-fat cross-talk relationship with adiponectin. Bi-directional communication between muscle and fat suggests that muscle derived cytokines mediate effects on adipose mass and adipokine production. \(^{31-33}\) It is possible that cytokines derived from muscle may regulate adiponectin and the inflammatory response of adipose tissue, thereby playing a key role in the metabolic syndrome and obesity. Further examination into adipose and muscle cytokine signaling may reveal a possible treatment to target cytokine induced metabolic dysregulation.

The mild inflammatory state seen in obesity has been implicated as a mediator of metabolic disruption (i.e. insulin resistance). \(^{34}\) Research demonstrates that substrate utilization and metabolic function are down-regulated by interactions with inflammatory cytokines. Two of the main cytokines that can influence insulin resistance and fuel utilization are TNF-\( \alpha \) and IL-6. \(^{34,35}\) Acute exercise has been shown to result in an increase in IL-6. It is unknown if IL-6 released during exercise affects fuel sparing or aids in releasing available fuel sources for use in working tissues. Bi-directional communication between muscle and fat that occurs during and after exercise may influence fuel utilization and potentially result in an anti-inflammatory response, which would ultimately affect obesity. Cytokines thought to be involved in bi-directional communication include IL-6, IL-15, and adiponectin.

Research indicates that muscle tissue can secrete IL-6, which is an important cytokine related to inflammation. \(^{36}\) There are currently two view points regarding the role of IL-6,
one considers IL-6 to be anti-inflammatory while the other attributes inflammatory properties to the cytokine. In vitro research has identified an inhibition of adiponectin in the presence of IL-6.\textsuperscript{37} In vitro down regulation of adiponectin identifies IL-6 as an inflammatory cytokine. However, the effects of IL-6 on adiponectin in vivo are inconclusive.\textsuperscript{38} As an anti-inflammatory cytokine IL-6 has been identified as inhibiting the release of one inflammatory cytokine, TNF-alpha.\textsuperscript{39-44} It is speculated that TNF-alpha plays a role in the inhibition of adiponectin production and release.\textsuperscript{38,45} Therefore, it may be hypothesized that a brief increase in IL-6 may initiate an anti-inflammatory response. Research suggests IL-6 can stimulate production of the two anti-inflammatory cytokines IL-10 and IL-1ra.\textsuperscript{46} A brief induction of anti-inflammatory processes whether by IL-6 directly or through down stream signaling may suppress the effects of the mild inflammatory state associated with obesity. In respect to the current study, it may be possible that a short term increase in IL-6 during physical activity is restricting TNF-α production, thus alleviating the inhibition of adiponectin.

Due to the large production of IL-6 by muscle tissue, research has focused on the role exercise plays on IL-6 concentration. IL-6 concentrations have been shown to increase following acute bouts of exercise and the exercise intensity is positively related to IL-6 concentrations.\textsuperscript{47,48} Given that runners exercise at high intensities for longer duration, it is expected that the total amount of IL-6 released by muscle during the exercise session would be greater than in the normal population (although at rest serum levels of IL-6 are lower in runners). Current research suggests the main functions of IL-6 during exercise are to aid in fuel mobilization through lipolysis of adipose tissue and improvement of glucose uptake.\textsuperscript{49}
The combined metabolic effects of increased glucose uptake and lipolysis seen with increased IL-6 are advantages to working tissue during exercise.

Contrary to acute exercise, the concentration of IL-6 either decreases or remains stable with chronic training. \(^{50,51,52}\) Research has shown that 12 weeks of aerobic training in young adults failed to elicit a change in IL-6. \(^{50,51}\) While participation in aerobic training was shown to lower IL-6 in elderly individuals that commonly experience exaggerated baseline inflammatory levels. \(^{52}\) The current research in aerobic training and IL-6 is supportive of the long standing belief that exercise can decrease the risk of cardiovascular disease.

The second cytokine involved in the muscle-fat cross-talk model is IL-15. IL-15 is a relatively new cytokine to be considered in the metabolic syndrome milieu. Research indicates that IL-15 may increase adiponectin concentrations and have greater lipolytic activity than IL-6. \(^{32,53}\) IL-15 is secreted from muscle fibers and adipose tissue. \(^{54}\) The factor responsible for triggering IL-15 release from skeletal muscle is still unknown. However, it can be speculated that IL-15 concentration may be up-regulated as a result of physical activity/muscle contraction. The high lipolytic effects attributed to IL-15 would be beneficial in maintaining energy release for use in working tissue. However, research has not identified a pathway in which muscle contraction would result in IL-15 release; thus it is unclear if physical activity results in greater IL-15 concentrations. Regardless, greater IL-15 concentrations could theoretically explain the higher adiponectin concentration in runners compared to the normal weight group, despite similar body composition.

The role of physical activity on the regulation of immune function is a complicated issue. As mentioned previously, tissue specific inflammation results in a down regulation of metabolic function. Metabolic dysregulation may lead to lowering of anti-inflammatory
cytokine production. Recall that the runners had greater peak $V_o_2$ than the normal weight or overweight groups. It can be inferred from peak $V_o_2$ that the oxidative capacity of the runner's muscle is greater. When oxidative capacity increases the metabolic machinery in that individual becomes more energy efficient. Specifically, there is a shift to a greater reliance on FFA for fuel. Since the metabolic machinery in the muscle shift to a reliance on more FFA there would need to be an increase in lipolysis to provide adequate FFA for fuel. The increase in lipolysis may occur through communication from lipolytic cytokines originating from muscle (IL-6 and IL-15). If IL-6 and IL-15 are increasing to aid in lipolysis, their presence may initiate anti-inflammatory processes. The peak $V_o_2$, adiponectin, muscle-fat cross-talk research reiterates the fact that multiple factors are involved in the regulation of adiponectin.

When peak $V_o_2$, fat mass and vigorous physical activity were used in multiple linear regression, they combined to explain 11% of the variance of serum adiponectin concentrations (data not shown). Taking this into account it appears the combination of multiple variables may be responsible for the higher adiponectin in the runners. One variable not examined here that may explain a large percent of the unexplained variance is genetics. A limited number of studies suggest a strong influence of genetics on adiponectin. In a recent study of 805 Hispanic children, Butte et al. identified that adiponectin is 93% heritable in this population. Among 1100 adults with northern Europe ancestry, Comuzzie et al. found an estimated heritability of 46%. Taken together, serum adiponectin is a complex, multifactorial phenotype influenced by genes, the environment, and possibly gene-environment interactions.
One limitation to the present study was the use of BMI to separate the normal and overweight groups. It is widely known that BMI fails to account for FFM. Three subjects in the overweight group had a %body fat less than 10%, which indicates greater lean mass for height. Since BMI is widely used in clinical medicine, it was chosen to separate the normal weight and overweight groups. Another limitation that possibly explains the reason why adiposity and adiponectin were weakly correlated in this study may be the use of bioelectrical impedance. Bioelectrical impedance is dependent on hydration, and if participants were not at optimal hydration room for error would increase. Several studies have bypassed bioelectrical impedance by utilizing dual x-ray absorbtionmetry to determine adiposity.

In summary, the results of this study show an increased fasting plasma adiponectin in individuals that accumulate large amounts of vigorous physical activity accompanied by high peak Vo\(_2\) and low fat mass. These findings highlight the complex relationship between vigorous physical activity, fat mass, Vo\(_2\) peak and adiponectin. Further research is warranted to identify the specific roles these variables play in the elevation of adiponectin concentrations.

Acknowledgements

This work was supported by an Iowa State University Sponsored Programs Initiative Grant. The authors wish to thank Dr. Paul Flakoll (deceased) for his input during the initial stages of this project and his inspirations for work in the area of obesity.
References


### Table 1. Descriptive characteristics of the sample. Values represent mean (SE) and range.

<table>
<thead>
<tr>
<th></th>
<th>Runners (n=12)</th>
<th>Normal weight (n=10)</th>
<th>Overweight (n=11)</th>
<th>Total (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td>19.9 (0.3)</td>
<td>16.8 (1.1)</td>
<td>16.2 (0.7)</td>
<td>17.5 (0.5)</td>
</tr>
<tr>
<td></td>
<td>18.5-21.7</td>
<td>12.6-22.6</td>
<td>12.1-19</td>
<td>12.1-22.6</td>
</tr>
<tr>
<td><strong>Ht (cm)</strong></td>
<td>177.8 (1.8)</td>
<td>175.9 (3.0)</td>
<td>170.5 (2.6)</td>
<td>175.1(1.4)</td>
</tr>
<tr>
<td></td>
<td>163.7-186.6</td>
<td>161.1-188.5</td>
<td>155.4-183.0</td>
<td>155.4-188.5</td>
</tr>
<tr>
<td><strong>Wt (kg)</strong></td>
<td>63.9 (1.9)</td>
<td>64.9 (3.9)</td>
<td>91.0 (7.8)</td>
<td>74.2 (3.6)</td>
</tr>
<tr>
<td></td>
<td>55.3-79.6</td>
<td>42.5-80.5</td>
<td>53.9-137.3</td>
<td>42.5-137.5</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>20.2 (0.4)</td>
<td>21.0 (1.1)</td>
<td>31.1 (2.5)</td>
<td>24.3 (1.2)</td>
</tr>
<tr>
<td></td>
<td>18.7-22.9</td>
<td>15.9-27.1</td>
<td>22.3-47.1</td>
<td>15.9-47.1</td>
</tr>
<tr>
<td><strong>WC (cm)</strong></td>
<td>73.9 (1.0)</td>
<td>76.2 (2.7)</td>
<td>100.5 (6.6)</td>
<td>84.4 (3.2)</td>
</tr>
<tr>
<td></td>
<td>69.8-82.0</td>
<td>62.5-87.3</td>
<td>72.3-144.3</td>
<td>62.3-144.3</td>
</tr>
<tr>
<td><strong>FFM (kg)</strong></td>
<td>55.4 (1.5)</td>
<td>57.2 (3.2)</td>
<td>64.5 (3.3)</td>
<td>59.2 (1.7)</td>
</tr>
<tr>
<td></td>
<td>48.7-68.7</td>
<td>40.7-74.5</td>
<td>44.0-82.9</td>
<td>40.7-82.9</td>
</tr>
<tr>
<td><strong>FM (kg)</strong></td>
<td>8.5 (0.7)</td>
<td>7.7 (1.6)</td>
<td>26.6 (5.1)</td>
<td>14.7 (2.3)</td>
</tr>
<tr>
<td></td>
<td>4.2-10.9</td>
<td>1.7-15.5</td>
<td>8.8-60.1</td>
<td>1.7-60.1</td>
</tr>
<tr>
<td><strong>BF%</strong></td>
<td>13.2 (1.0)</td>
<td>11.4 (2.2)</td>
<td>26.9 (2.9)</td>
<td>17.6 (1.7)</td>
</tr>
<tr>
<td></td>
<td>7.3-17.2</td>
<td>3.1-21.1</td>
<td>14.3-46.0</td>
<td>3.1-46.0</td>
</tr>
<tr>
<td><strong>Vigorous PA (min/d)</strong></td>
<td>51.1 (5.2)</td>
<td>16.2 (6.2)</td>
<td>11.2 (4.7)</td>
<td>25.7 (4.4)</td>
</tr>
<tr>
<td></td>
<td>24.0-86.0</td>
<td>0-62.0</td>
<td>0-47.0</td>
<td>0-86.0</td>
</tr>
<tr>
<td><strong>PA (cnts/min)</strong></td>
<td>1074 (119.4)</td>
<td>664.5 (139.1)</td>
<td>514.4 (69.1)</td>
<td>746.6 (75.5)</td>
</tr>
<tr>
<td></td>
<td>700.6-2169.2</td>
<td>325.8-1837.1</td>
<td>254.7-863.2</td>
<td>208.7-2169.2</td>
</tr>
<tr>
<td><strong>Vo₂ Peak (ml/kg/min)</strong></td>
<td>71.9 (1.2)</td>
<td>53.5 (2.7)</td>
<td>39.5 (3.8)</td>
<td>54.8 (2.8)</td>
</tr>
<tr>
<td></td>
<td>66.9-80.6</td>
<td>35.5-67.9</td>
<td>21.7-62.7</td>
<td>21.7-80.6</td>
</tr>
<tr>
<td><strong>Adiponectin (µg)</strong></td>
<td>7.6 (1.0)</td>
<td>5.0 (0.8)</td>
<td>4.4 (0.5)</td>
<td>5.8 (0.5)</td>
</tr>
<tr>
<td></td>
<td>2.6-14.8</td>
<td>2.5-10.5</td>
<td>1.7-8.0</td>
<td>2.7-14.8</td>
</tr>
</tbody>
</table>

*a significant difference between runners and normal weight, b runners and overweight, c normal weight and overweight; Ht, height; Wt, weight; BMI, body mass index; WC, waist circumference; FFM, fat free mass; FM, fat mass; BF%, %body fat; PA, physical activity
Table 2. Inter-relationships among age, adiposity, physical activity, peak Vo₂ and adiponectin.

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>WC</th>
<th>BMI</th>
<th>FM</th>
<th>Peak Vo₂</th>
<th>VPA</th>
<th>PA cts/min</th>
<th>Adiponectin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-</td>
<td>-0.079</td>
<td>-0.088</td>
<td>-0.015</td>
<td>0.475*</td>
<td>0.486*</td>
<td>0.504*</td>
<td>0.247</td>
</tr>
<tr>
<td>WC</td>
<td>-</td>
<td>0.953*</td>
<td>0.961*</td>
<td>0.743*</td>
<td>-0.427*</td>
<td>-0.36*</td>
<td>-0.290</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>-</td>
<td>0.955*</td>
<td>0.696*</td>
<td>-0.413*</td>
<td>0.365*</td>
<td>-0.289</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FM</td>
<td>-</td>
<td>0.707*</td>
<td>-0.364*</td>
<td>-0.35*</td>
<td>-0.244</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak Vo₂</td>
<td>-</td>
<td>-0.083</td>
<td>-0.166</td>
<td>0.108</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VPA</td>
<td>-</td>
<td>-0.709*</td>
<td>0.583*</td>
<td>0.332*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA cts/min</td>
<td>-</td>
<td>0.823*</td>
<td>0.252</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adiponectin</td>
<td>-</td>
<td>-0.062</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values represent bivariate Pearson correlation coefficients.
*p<0.05

Table 3. Partial correlations, controlling for age and fat mass, between physical activity, peak Vo₂ and adiponectin.

<table>
<thead>
<tr>
<th></th>
<th>Adiponectin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vigorous PA</td>
<td>0.083</td>
</tr>
<tr>
<td>PA cts/min</td>
<td>-0.166</td>
</tr>
<tr>
<td>Peak Vo₂</td>
<td>0.108</td>
</tr>
</tbody>
</table>

Figure 1. Differences in adiponectin between runners, normal weight and overweight males. Values are age and fat mass adjusted mean (SE)

![Graph showing differences in adiponectin between groups](image-url)
Figure 2. Inter-relationships among vigorous physical activity, peak Vo₂, and fat mass, and adiponectin among young males, 12-21 yrs.
CHAPTER 4: GENERAL CONCLUSIONS

The metabolic syndrome and atherosclerotic complications are frequently seen in obese individuals in developed countries around the world. It is now known that the secretory function of adipose tissue plays a role in inflammatory homeostasis. Adiponectin is responsible for anti-atherogenic, anti-inflammatory, and insulin sensitizing effects. The relationships adiponectin has with adiposity, gender, age, and metabolic/atherogenic interactions have been previously investigated. Physical activity has received little attention with regards to adiponectin. The results from this thesis identify an increase in fasting plasma adiponectin in young males that accumulate large amounts of vigorous physical activity and exhibit a high peak $V_o_2$ and low fat mass. This thesis highlighted the various factors that effect adiponectin concentration. It is evident that the relationships between vigorous physical activity, fat mass, $V_o_2$ peak, muscle-fat bi-directional communication and adiponectin are complex, and justify further research.

References
