EFFECTS OF RESISTANCE TRAINING ON INSULIN SENSITIVITY AND MARKERS OF INFLAMMATION IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH REMICADE

by

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A Dissertation Submitted to the Faculty of the

GRADUATE INTERDISCIPLINARY PROGRAM IN PHYSIOLOGICAL SCIENCES

In Partial Fulfillment of the Requirements
For the Degree of

DOCTOR OF PHILOSOPHY

In the Graduate College

THE UNIVERSITY OF ARIZONA

2009

THE UNIVERSITY OF ARIZONA
GRADUATE COLLEGE

As members of the Dissertation Committee, we certify that we have read the dissertation

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entitled Effects of Resistance Training on Insulin Sensitivity and Markers of Inflammation in Rheumatoid Arthritis Patients Treated with Remicade

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This dissertation has been submitted in partial fulfillment of requirements for an advanced degree at the University of Arizona and is deposited in the University Library to be made available to borrowers under rules of the Library.

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ACKNOWLEDGEMENTS

Science has always been an interest of mine, if not a passion. I recall considering a Career Day project in the 4th grade where I presented myself as an oceanographer. A year later I made a filmstrip, diorama and poster about my interest in being an astronomer. My prized poster wasn't of a pop icon, movie star or model, but of the Solar System, complete with to-scale representations of the planets and important facts ranging from surface temperatures to orbital periods. Star Trek and Star Wars, both staples of my formative years were inspiring in their geekdom, painting stories of adventure and discovery wrapped in science and technology, always encouraging us to wonder what was just out of sight. Life sciences eventually became more appealing, and in particular, the workings of the human body. Such a wonderful, intricate and compelling subject is human physiology. It screams as much of art as science, and the beauty I once saw in telescope images is matched and complimented by that in microscopy.

I would like to acknowledge the many people who have helped me along the road that has led to the work you hold in your hands. Teachers throughout my schooling have shaped me. From elementary school in Hastings to graduation from Faribault Senior High School there were teachers who inspired effort and interest in science. I'd like to specifically mention Bill Hohenthaner, for making it clear that scientists aren't just geeks, and Harvey Schuldt, for showing that passion and logic both have places in math. Instructors and professors far too numerous to mention honed that interest here at the University of Arizona. The members of my Exam and Dissertation committees stand in excellent stead for all those unnamed others. Scott Going, with one foot planted in academic science and other rooted in life outside the institution, represents the balance that has to be struck so that science is applicable. Andrew Fuglevand, always a wonderful teacher, inspires those around him to instruct as well as learn, and that information is best understood when it has been shared. Timothy Lohman, a patriarch of research, underscores the need for scientists to be a multidisciplinary community, not just a collection of isolated experts. Cindy Rankin, generous with her time and attention, made it clear that knowing the scientist is as important as knowing the science and that development of each successive group of aspirants is an important duty of today's scientists. Doug Stuart, an amazing story teller, reminded us all that membership in this elite community brings us in contact with many wonderful people, each with their own stories to tell.

The encouragement and acceptance of my interests by those around me as I grew up has always been important. Family trips to the Science Museum, the iMax theater and the "new" zoo were made every bit as enjoyable as an amusement park could ever be and were never in short supply. At long last, when someone asks what I'm doing, they can answer "He's a scientist."

Most importantly, without the love, patience and support of my family – Julia, Emily and Daniel – I doubt that I could have finished this work and even if I did it wouldn't have meant so much as it does now. The book report's all finished!

DEDICATION

To Julia, Emily and Daniel.

Thank you for your love, patience and support. Because of you I get to share in the excitement of poking around in tide pools, the fun of trips to Disneyland, the treat of eating “the #5” and the joy of being with the people that I love.

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ABSTRACT

INTRODUCTION

Rheumatoid arthritis (RA) is a disease of chronic inflammation in the joints and organs. RA patients exhibit 4-fold increased incidence of CVD, increased prevalence of insulin resistance (IR) and increased mortality. Aerobic and resistance training (RT) programs have been suggested for the management of RA symptoms and reduction of comorbidities, including insulin resistance. Exercise has been shown by recent evidence to be safe and beneficial in RA patients. RT has been documented to improve inflammation and insulin sensitivity. The present study was undertaken to examine the impact of a sixteen week intensive training regimen on disease status, body composition, markers of inflammation and indicators of insulin resistance in RA patients undergoing infliximab therapy, a potent RA treatment.

METHODS

30 RA patients were randomized into exercise (EX) or control (C) groups. EX patients underwent a 16-week supervised, intensive, progressive and individualized resistance training regimen. Participants were monitored by professional fitness trainers during all exercise sessions. Subjects were assessed prior to and after intervention. Assessments included disease status, strength and functional testing, anthropometrical and body composition analysis, analysis of markers of inflammation and assessment of insulin sensitivity.

RESULTS

EX subjects significantly increased in strength and functional ability without worsening of disease state, and increased lean mass from baseline. Fat mass was significantly reduced in EX. Glucose and resistin levels increased significantly following EX intervention. Mean IR was unchanged, but EX subjects with elevated IR did show improvement following training. Regression analysis indicates duration of infliximab therapy to be correlated with improved insulin sensitivity.

CONCLUSIONS

RA patients taking infliximab tolerated an intensive resistance training program. Participants increased strength and lean mass while decreasing fat mass and displayed improved functional capacity. Disease status was not worsened by the regimen. Though the mean measure of IR did not improve, those patients with the most adverse scores did show improvement following the intervention. Furthermore, regression analysis indicates that infliximab treatment duration was linked to reduced IR. In conclusion, resistance training improved strength and functional ability in RA patients taking infliximab without disease degradation, and may help reduce IR in those patients with elevated resistance.

CHAPTER I: INTRODUCTION

The primary function of insulin, a polypeptide hormone secreted by the β-cells of the pancreas, is to expedite the uptake of glucose into both muscle and adipose cells. A secondary function is the reduction of hepatic glucose production via glycogenolysis or gluconeogenesis in the liver. Insulin secretion is stimulated by elevated blood glucose, as seen following meals or other ingestion of food. Once released, insulin travels through the bloodstream and binds to specific receptors on muscle and adipose cells, initiating an intracellular cascade that results in the translocation of glucose transporter proteins (most notably the GLUT4 transporter) to the cell membrane, allowing glucose to enter the cell.(Trout 07) Glucose is the primary molecule in carbohydrate metabolism and is vital for meeting the body's energy demands. Glucose also serves as the brain and central nervous system's sole energy source. Most ingested glucose is stored in the body as glycogen in the liver, muscle and adipose tissue. From these locations it can be used for energy or mobilized for use as fuel in other parts of the body. Glucose levels below 60 mg/dL are considered dangerous and may lead to progressive central nervous system impairment, possibly culminating in coma or death. Excessively high levels of blood glucose, if sustained, can result in a variety of tissue damage (as seen in advanced diabetes) including neuropathy, vision defects including blindness, and renal damage. It is because of this risk that efficient and appropriate insulin signaling and action is so vital.(Berne 00)

Insulin resistance (IR) is best defined as the inability of a given amount of insulin (either native or exogenous) in a given individual to stimulate glucose uptake to the same

extent as in a healthy member of the same population.(Oncul 02) IR is considered a strong marker of pre-diabetes, a condition of impaired glucose tolerance that is a strong risk factor for the development of Type II diabetes. Patients with Type II diabetes are (or were) able to produce insulin at normal levels, but the cells of the body exhibit reduced responsiveness to the secreted insulin as compared to a healthy subject. In time, the pancreas may reduce or cease insulin production altogether, further exacerbating the disease. The impact of insulin resistance and diabetes is significant, effecting 7% of the United States population. 20.8 million people, have some form of diabetes, and nearly 54 million more are considered pre-diabetic, each of whom may develop serious complications including stroke, heart or kidney disease, and blindness. With such an array of comorbid conditions it is no surprise that diabetes is among the deadliest diseases in the United States.(ADA 07)

There are several methods available for the assessment and quantification of insulin resistance or overt diabetes. These methods vary in invasiveness and expense and are seldom employed in a clinical setting without significant cause. The euglycemic hyperinsulinemic clamp is considered the gold standard for assessment of glucose and insulin metabolism, but requires a significant time investment on the part of the patient and multiple intravenous lines. The Oral Glucose Tolerance Test (OGTT) is a simple, expedient and more cost-effective method of estimating insulin response frequently given to pregnant women to assess gestational diabetes. Patients ingest a known volume of glucose, and two hours later blood is drawn for glucose analysis. This basic assessment is popular among clinicians because of the ease of administration and the relatively low

patient discomfort. (Bloomgarden 06, Trout 07) Two common methods in use assess insulin action from a single blood draw, thus minimizing patient discomfort and time expenditure. Both QUICKI and HOMA-IR use plasma insulin and plasma glucose values from a single fasted patient blood draw and rely on the ratio of insulin to glucose to provide insight.(Bloomgarden 06, Matthews 85, Trout 07)

Treatment of insulin resistance can include lifestyle modification, weight reduction, stress control and pharmacological intervention. Weight reduction via diet and increased physical activity are frequently touted as the primary treatments. Reduction of dietary fat, cholesterol and total caloric intake are part of many treatment plans, and there is some indication that reducing both carbohydrate intake and glycemic index can be beneficial in improving the health of insulin resistant patients. Pharmacological treatments are aimed at reducing stress effects or improving glycemic control. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin II blockers are the usual first choices in controlling stress effects. A broad host of drugs are used to improve glycemic control. These include Metformin (reduces hepatic glucose production and increases muscle glucose uptake), sulphonylureas (stimulate insulin release), alpha-glucosidase inhibitors (reduce postparandial hyperglycemia by delaying absorption of carbohydrate from the digestive system) and thiazolidinediones (similar to Metformin but with greater and more wide-ranging impacts). Exogenous insulin is used in certain cases of advanced or severe insulin resistance, often in an acute regimen.(Rosenberg 05)

Insulin resistance is a significant component of Syndrome X, also called Metabolic Syndrome. This conglomeration of disorders is typified by central obesity,

hyperinsulinemia, hypertriglyceridemia, disadvantageous cholesterol profile and hyperglycemia. This condition poses a significant public health risk to the population as it has been implicated in the development of Type II Diabetes (NIDDM), hypertension and coronary heart disease (CHD), all very expensive and potentially fatal conditions. (Bloomgarden 06, Fam 02, Hjemdahl 02) The etiology of IR does not appear to be uniform across all individuals, or if there is a common cause, it has yet to be elucidated.

What is clear is that a poor diet, particularly one high in fat and total energy intake with a sedentary lifestyle easily leads to obesity and each of these three factors has been linked to diabetes. Sedentary subjects, regardless of weight, have been shown to have greater levels of glucose, insulin and insulin resistance than active subjects of similar weight status, while active overweight subjects in the same study displayed similar levels of glucose with reduced levels of insulin when compared to sedentary lean subjects, underscoring the importance of physical activity in combating insulin resistance.(Kavouras 07) Obesity in particular stands out as a common risk factor for insulin resistance, diabetes, cardiovascular disease and osteoarthritis.(Bloomgarden 06, Goralski 07, Sowers 03) Chronic or recurring inflammation has also been implicated in the generation of insulin resistance. Excessive consumption of sugars a transitory state of inflammation for up to 3 hours following ingestion and a traditional fast-food meal, high in fat and calories, leads to an inflammatory state of up to 4 hours.(Dandona 04) JS Rana et al.(Rana 07) discussed the interplay between obesity, inflammation, cardiovascular disease and diabetes in a recent review, noting that 1.2 billion people in the world are overweight and at least 300 million are overtly obese and Evidence indicates that many of these people

are likely to have insulin resistance or Type II diabetes. Furthermore the authors indicate that the chronic state of inflammation accompanying obesity is likely to interfere with insulin signaling, further exacerbating this condition.

A number of independent inflammatory factors are known to interfere with insulin signaling at the tissue level. Cytokines such as interleukin-2 (IL-2), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) display anti-insulinemic effects in humans.(Biarnes 05, Oncul 02, Ruan 03) It has been indicated that increases in these markers of inflammation may predict the future development of obesity and diabetes. Furthermore, adipose tissue releases TNF-α constitutively, leading to the obese secreting more TNF-α than the non-obese. This TNF-α can interfere with insulin action by suppressing signal transduction, increasing insulin resistance and fostering adipose tissue expansion. Completing the cycle, it seems that insulin has an anti-inflammatory impact at the cellular level, and thus insulin resistance may reduce this impact and be, in effect, pro-inflammatory.(Csehi 05, Dandona 04, Plomgaard 05) Resistin, a small protein produced in adipose tissue and during inflammatory responses in the body, has been strongly associated with obesity and insulin resistance in mice. Research in human patients has been less conclusive, but resistin has been strongly correlated with inflammation and there are indications that resistin levels may be correlated with insulin resistance as well.(Azuma 03, Bokarewa 05, Silswal 05) All of this taken together suggests that disorders which feature dysregulation of these inflammatory factors may express or contribute to insulin resistance in those same patients. One such disorder is rheumatoid arthritis, a form of arthritis is typified by altered immune system function and a broad array of metabolic

complications.

Rheumatoid arthritis (RA) is a disease of chronic inflammation in the lining of the joints and internal organs. Symptoms besides pain include frequent fever, lack of appetite, difficulty moving, anemia, and of course swelling of the affected joints. A wealth of information on RA can be found at the Arthritis Foundation website (http://www.arthritis.org/). According to the foundation's online information:

- Rheumatoid arthritis affects 2.1 million Americans;
- Onset is usually in middle-age, appears more frequently in older people, but also affects children and young adults;
- Women represent more than two-thirds of the US cases (1.5 million patients), twice the incidence seen in men (600,000 patients).

Furthermore, Arthritis Foundation literature indicates that conditions such as RA cost the US economy over $125 billion in medical expenses and lost wages/productivity.

The primary symptom of rheumatoid arthritis in the early stages of the disease is pain. It is often accompanied by fatigue and stiffness (particularly in the morning or after prolonged rest), though all generally improve with activity and motion. As the disease advances it can cause swelling, stiffness and joint deformities, usually in the hands and feet. If left untreated or poorly controlled, RA can lead to damage to the bones surrounding affected joints, visible on radiographs which are used to assess the degree of disease progression and damage.(Gaffo 06)

Treatment of RA symptoms generally begins with non-steroidal anti-

inflammatory drugs (NSAIDs) including over-the-counter drugs such as aspirin and ibuprofen. This offers inexpensive, rapid, though often incomplete, relief of pain and inflammation. Following diagnosis glucocorticoids such as prednisone are frequently used to limit pain and swelling and as a bridge to other therapies. These drugs exhibit frequent, often severe adverse effects and are best used in low dosages along with other therapies or not at all. Disease-modifying antirhuematic drugs (DMARDs) such as methotrexate and leflunomide, are the primary initial therapy prescribed to RA patients, and while slow-acting bthey address both symptom relief and slow clinical disease progression. The newest and arguably most potent pharmaceutical treatment are the biological response modifiers. These drugs, such as infliximab (Remicade) and etanercept, are designed to target and block the mediators of disease symptoms and progression, limiting the activity of the disease. These therapies are expensive, however, and require regular clinic visits for administration via intravenous infusion. Both of the most common examples are intended to inhibit the activity of TNF-α, a potent and active cytokine.(Emery 06, Gaffo 06)

It was once feared that any form of strenuous exercise could exacerbate disease symptoms and hasten tissue degradation in RA patients, but evidence now exists that indicates that various forms of exercise are not only safe but beneficial.(Baillet, 09, de Jong 05, de Jong 09, Stenstrom 03) A number of studies indicate that aerobic and resistance training programs offer significant therapeutic benefit to RA patients including enhanced endurance, strength, joint stability and improved quality of life. Furthermore, reductions in disease symptoms and comorbidities have been indicated following exercise therapies.

For maximal effectiveness it is recommended that the training programs be sustained over time, performed with social support and feature individualization for safety.(Hakkinen 04, de Jong 05, Kettunen 04, Metsios 08, Stenstrom 03)

Rheumatoid arthritis has been linked to excessive cardiovascular disease, morbidity and mortality risk.(Dessein 03, 02, 02) Investigators have found as much as a 4-fold increased incidence rate for cardiovascular events in patients with fully developed RA.(Dessein 03) RA patients have been shown to have a higher prevalence of metabolic syndrome, a frequent precursor to type II diabetes and a potential contributor to cardiovascular disease.(Chung 07) Obesity and overweight incidence among RA patients is a topic of debate, though it is considered a risk factor by some experts.(Symmons 05, Voight 94) There are indications that rheumatoid arthritis patients have a lower level of physical activity, particularly recreational physical activity, than healthy age-matched controls. Though this relationship is less definitive in younger patients and health professionals, it remains a serious concern.(Eurenius 05, Hootman 03, Turesson 07) Lemmey et al.(Lemmey 01) found a significantly lower self-reported exercise level for rheumatic disorder patients as compared to healthy controls and reported a significantly higher percentage of body fat in the rheumatic patients than the controls. It stands to reason that patients of a disease typified by chronic inflammation, decreased physical activity and elevated body fat would be at increased risk for the development of insulin resistance.

Several investigators have noted the confluence of factors in RA and IR and have examined them in some detail. Dessein et al.(Dessein 03, 02, 02), for example, have addressed the link between RA and IR in a number of recent papers (2002-2003). In their review in

the *Journal of Rheumatology* they write that there is ample evidence pointing to systemic inflammation as a predictor of cardiovascular (CV) events and that potent anti-inflammatory drugs are associated with a substantial reduction in CV disease related deaths. They also report that insulin concentrations in RA patients were 57% higher than non-arthritic controls and 41% higher than in patients with less severe forms of inflammatory arthritis (such as osteoarthritis). High C-reactive protein (a blood-borne marker of inflammation tightly correlated with TNF-α and IL-2/IL-6 levels) was also associated with IR. The authors present a table listing atherogenic features shared by both active RA and IR, which can lead to CV disease, including:

- Increased cytokine production;
- Increased adhesion molecule production;
- Reduced fibrinolysis;
- Reduced HDL cholesterol.

They close with a strong suggestion that CV risk is increased in RA patients due in large part to dysregulation of immune system factors and its effect on insulin sensitivity.(Dessein 03)

In a report of primary research the same investigative group examined the differences in insulin sensitivity and CV risk between RA patients and osteoarthritis (OA) patients. They evaluated 79 RA patients and 39 age- and gender-matched OA patients. The primary variables of interest were insulin sensitivity via QUICKI, C-reactive protein and fasting lipids. Diabetic patients or those who were taking drugs known to alter insulin activity were excluded from analysis. Insulin sensitivity was significantly

decreased in the RA group, but this difference was eliminated when C-reactive protein levels were controlled in the analysis. This strongly suggests that the increased level of inflammatory factors in RA contributes to the adverse impact of RA on insulin metabolism.(Dessein/Stanwix 02)

In their third article on the topic, Dessein et al(Dessein/Joffe 02) examine the differences in HOMA, body mass index (BMI - a measure of fatness/distribution) and blood lipids in 38 RA patients and 49 with non-RA, non-OA arthritis diseases. They again found that RA patients had the most deleterious results when it came to insulin resistance and blood lipids. Additionally, the RA patients had a significantly higher BMI, suggesting increased fatness (though BMI is far from the best method of assessing obesity or body fat distribution), a finding typical with insulin resistance. The most novel finding from this study however was the strong positive correlation between erythrocyte sedimentation rate (ESR - an indicator of arthritic disease severity or lack of control) and insulin resistance. This study did not examine individual inflammatory factors, so examining ESR provides the only reflection (albeit an indirect reflection) of those cytokine levels. It is reasonable to assume that increased disease severity and lack of control would be associated with elevated levels of cytokines associated with RA. This finding then further supports the previous work linking high levels of inflammatory factors with insulin resistance. It also suggests that very poorly controlled or advanced non-rheumatoid arthritis can lead to insulin resistance syndrome just as RA can.

There is some discussion that Type II Diabetes (NIDDM) might be autoimmune in origin - not unlike Type I IDDM and RA - and that the TH-1 derived cytokine IL-2

might be involved in the pathogenesis of both NIDDM and RA. Oncul et al[Oncul 02] examined 36 RA patients and 20 healthy controls in a 2002 paper published in *The Journal of International Medical Research*. The investigators examined IL-2, insulin and glucose (for HOMA analysis). As expected, insulin resistance was greater in the RA patients than in healthy controls. Furthermore, IL-2 levels were significantly elevated and were highly positively correlated with fasting insulin levels. The authors suggest that this finding may cement the pathogenic role of IL-2 in insulin resistance. This may be a bit premature, but the strength of the correlations was clear.

The work of these two groups - encompassing an authoritative review and 3 original primary studies - strongly ties the dysregulation of inflammatory factors in RA to the conditions of insulin resistance and cardiovascular disease. The findings relating levels of disease control in non-rheumatoid arthritis patients further strengthens this connection as it ties the same factors to insulin resistance in the absence of the potent auto-immune disorder. Finally a specific cytokine (IL-2) was targeted for investigation and was found to be very strongly correlated with insulin resistance.

There are a number of other diseases and disorders that feature chronic, high levels of inflammatory factors. These range from simple infection to non-obese hypertension to chronic psychological stress. Examination of patients suffering from these disorders is important as it will help separate the connection between cytokines and insulin resistance from the potent RA disease state.

P. Hjemdahl[Hjemdahl 02] and R.Rosmond[Rosmond 03] have both written reviews on the topic of chronic stress and insulin resistance or diabetes. Hjemdahl writes that in some

individuals the allostatic load - or drive to adapt to physiological changes - may exceed their ability to adapt and result in deleterious outcomes. Stresses, be they physical or psychological, activate the hypothalamus-pituitary-adrenal (HPA) axis and result in, among other things, cortisol and catecholamine release, vagal withdrawal and activation of the renin-angiotensin system. Acutely this provides for fuel mobilization and blood shunting to muscle in preparation for action. If the stress is chronic, coping adaptations are lacking, or the ability to terminate the stress response is impaired, the allostatic load may lead to pathophysiology. The best known result of excessive stress is cardiovascular disease. It may be, however, that chronic stress leads to CV disorders by way of insulin resistance and the plurimetabolic syndrome.

Hjemdahl(Hjemdahl 02) reports on a study among working men that examined inflammatory markers and the metabolic syndrome. This study found a correlation between cortisol and catecholamine levels (assessed via excretory byproducts), IL-6 and c-Reactive protein and the metabolic syndrome. Psychosocial factors accounted for up to 37% of the variance between those subjects expressing the disorder and those who did not, suggesting that stress plays a substantial role in the etiology of the disease. The author closes by suggesting multiple mechanisms by which activation of the HPA axis might induce symptoms of the plurimetabolic syndrome. Increased sympathetic activity will decrease blood flow to non-working skeletal muscles, the primary mechanism for glucose disposal, thus engendering a form of insulin resistance. SNS activation also leads to lipolysis from central fat depots, resulting in increased blood lipid flux. As triglycerides have local anti-insulin action this can result in a further decrease in insulin

sensitivity. Additionally, chronic stress can affect the body in non-physiological ways such as reduction in appetite leading to poor diet or the seeking of food for comfort as opposed to food for nutrition. This could be a contributor to central obesity and aid its role in insulin resistance.

Roland Rosmond[(Rosmond 03)] suggests similar pathways in a review of the topic. In another study of middle-aged men it was found that those subjects with disrupted HPA regulation (as determined by cortisol peaking, circadian rhythm and feedback regulation) had an increased likelihood of central obesity, elevated fasting glucose and insulin, high triglycerides and above normal total cholesterol. These subjects also had elevated heart rate, blood pressure and sex steroid levels. The author suggests that the primary issue disrupting the HPA axis was an inability of feedback (by dexamethasone) to limit release of cortisol. While genetic factors strongly influence the ability of the HPA axis to self-regulate, the author suggests that chronic cortisol exposure might limit that ability in a time and dose dependant fashion.

Excess weight is considered by many health professionals to be an example of chronic stress and for some individuals it may well be a source of psychological stress. There are a number of adipokines that are known to increase IR, such as resistin, TNF-α, and c-Reactive protein.[(Azuma 03, Bokarewa 05, Ruan 04, Silswal 05)] These and other cytokines are released in particularly high levels from the adipose tissue of obese subjects. All of these can interfere with central processing of metabolic signals, alter HPA regulation or have direct effects on IR. In short, these subjects might have had high levels inflammatory factors or anti-insulinemic secretory products that led to their insulin resistance while

reducing the HPA axis activation once the disorder was fully developed.(Mino 02)

Limone et al(Limone 03) have recently examined insulin resistance in HIV-infected patients. Though potentially confounded by the large number of other metabolic and physiologic issues facing HIV patients, this relatively small study did find a connection between TNF-α and insulin resistance. HIV patients had similar fasting blood glucose levels as healthy controls, but significantly higher HOMA-IR scores. This is typical early in the pathogenesis of plurimetabolic syndrome and is a key indicator of insulin resistance. As HIV patients express a number of inflammatory factors at high levels, it was no surprise that TNF-α was significantly higher than in controls. There was also a fairly strong positive correlation between TNF-α and HOMA-IR (remembering that a high HOMA score is indicative of increasing insulin resistance), suggesting a link between the inflammation and insulin resistance. This stands to reason as TNF-α is known to interfere with insulin signaling in controlled experiments by blocking phosphorylation of insulin receptor substrates 1 and 2 (IRS-1 and IRS-2), thus providing a clear mechanism for blunting insulin-stimulated glucose uptake.

Insulin resistance is a growing concern among the industrialized nations of the world. It is strongly associated with obesity, hypertension, cardiovascular disease and death. Cases of Type II Diabetes now far outnumber Type I Diabetes, with nearly 19 in 20 diabetes cases being linked to insulin resistance.(ADA 07) and this trend is unlikely to stop any time soon. Direct treatments of insulin resistance have, for the most part, met with limited success and thus the eye of the health community has to focus on prevention. Diet intervention, exercise and the limiting smoking and alcohol consumption are the

keys to preventing this disorder.(Rosenberg 05) Even with this knowledge, however, cases of insulin resistance develop in people following significant changes in their lifestyle or other diseases and infections. The immune system and stress response system clearly have ties to the generation of insulin resistance. Control of inflammatory factors in arthritis patients is already a top priority, and the development of stress-coping strategies in the population as a whole may be the first step to limiting the impact of insulin resistance and the development of the metabolic syndrome.

Physical activity and vigorous physical training represents an exceptional bridge therapy for patients with insulin resistance/Type II diabetes and those with rheumatoid arthritis. The advantages of resistance and aerobic training have already been touch upon above, but it bears repeating that a regular exercise regimen can improve disease symptoms and quality of life in both patient groups. Furthermore, the literature indicates that regular exercise can exert an anti-inflammatory effect on the body, potentially reducing symptoms in an acute timeframe along with the chronic benefits previously detailed. Conraads et al.(Conraads 02) reported a significant decrease in TNF receptor levels, as well as functional class and workrate improvements, following a 4 month combined endurance/resistance training program. An exercise program as short as 4 weeks in insulin resistant patients resulted in improved insulin signaling, increased adiponectin levels and a reduction in circulating CRP, a marker of inflammation.(Oberbach 06) Other investigators have indicated that exercise not only limits the production of inflammatory agents but also induces acute increases in anti-inflammatory cytokines and "myokines".(Petersen 05) It has been suggested that as few as two to three bouts of resistance

exercise training per week can offer a significant protective benefit, helping to reduce the incidence of diabetes and heart disease as well as maintaining functionality and quality of life.(Winett 01)

As can be seen from the work discussed in this Introduction there is clear linkage between the conditions of rheumatoid arthritis and insulin resistance, quite possibly built on chronic inflammation and stress. Vigorous physical exercise has been linked to improvement in both adverse conditions, improving disease state and expression of symptoms. Given the similarities in outcomes and morbidity links between rheumatoid arthritis and insulin resistance, and the known therapeutic effect of exercise for those suffering from the individual diseases, continued investigation into the efficacy and potency of an exercise program for treatment of both diseases concurrently should hold value.

Centecor funded the Strength Training and Remicade study to assess the impact of an intensive, individualized resistance training program on the physical, mental, social and disease status of Rheumatoid Arthritis patients undergoing Remicade (infliximab) therapy. This study was implemented to test the primary hypothesis that a 16-week, progressive, individualized, intensive strength training program in RA patients taking Remicade™ would improve strength, body composition, disease activity, physical function, pain and quality of life outcomes as compared to RA patients on Remicade™ without the strength training program.

A second aim of this investigation and the focus of this dissertation was to assess the degree of association of several factors implicated in IR on the level of systemic

insulin resistance in RA patients currently undergoing a prescribed Remicade™ treatment regimen. A further intent of this study was to examine the changes in body composition, adiponectin, resistin, TNF-α, glucose and insulin following a 16-week progressive resistance training regimen in rheumatoid arthritis patients treated with Remicade™, testing the hypothesis that resistance training will result in an increase in lean mass while weight and fat mass will decrease, leading to a concomitant increase in adiponectin with decreases in resistin, TNF-α and insulin. Furthermore it was hypothesized that this effect would be seen only in those patients undergoing the exercise intervention, and that the control condition would offer no changes in measured variables.

A review of the pertinent literature, detail of the methodology used over the course of the study, a presentation of the resultant data and then discussion and conclusions are presented to complete this report.

CHAPTER II: REVIEW OF THE LITERATURE

INSULIN

Identity & Role

Insulin is a polypeptide hormone with 51 amino acid residues synthesized and secreted by the β-cells of the pancreas. These cells cluster in regions known as the Islets of Langerhans and make up only about 1-4% of the mass of the pancreas. The gene encoding the insulin precursor was the first polypeptide hormone cloned and it has been successfully integrated into animal models. Insulin is highly conserved (>92% homology) across mammalian species, with human insulin differing from porcine insulin in only 1 amino acid and from bovine insulin in just three residues.(Dranzin 89)

The primary goal of insulin is to maintain glucose homeostasis in body, particularly following the postprandial glucose load. This is achieved by expediting the uptake of glucose into muscle and adipose cells and reducing glucose production (via glycogenolysis and gluconeogenesis) in the liver.(Trout 07)

Synthesis

Insulin synthesis occurs in the β-cells of the structures know as "Islets of Langerhans" in the pancreas and it begins with pre-pro-insulin, a gene product synthesized in the endoplasmic reticulum. This protein undergoes enzymatic cleaving resulting in pro-insulin, which is then packaged into secretory granules. Once in the granules enzymes again cleave this precursor molecule, resulting in the final insulin protein. A byproduct of this reaction is C-peptide, a length of protein that was cleaved from between the center segment of pro-insulin which is no longer needed to link the "chains" of insulin together. C-peptide is a molecule with no known post-synthesis

function but it can be detected and quantified in the plasma. This combined with the fact that it is formed in equal molar amounts as insulin have led to it being used as a measure of insulin secretion.[Draznin 89, Trout 07]

Stimulus for release

Insulin secretion is stimulated by elevated blood glucose, as seen following meals or other ingestion of food. Glucose enters the β-cells of the pancreas via the constitutively expressed glucose transport channels GLUT2 and undergoes phosphorylation by glucokinase, resulting in glucose-6-phosphate. ATP is then generated by the metabolization of the G6P via the glycolytic pathway and Kreb's cycle, resulting in an increased ATP/ADP ratio. This signals for the closure of potassium channels in the cell membrane resulting in a depolarization, triggering the opening of voltage-gated calcium channels. Calcium then floods into the β-cell and induces the excytosis of the insulin vesicles and releasing the hormone into the bloodstream.[Trout 07]

Tissue targets

Once released, insulin travels through the bloodstream and binds to specific receptors on muscle and adipose cells, initiating intracellular cascades that result in a number of outcomes, dependant on the target tissue. The primary impact of insulin is seen in skeletal muscle, adipocytes and the liver. The primary goal of insulin action is to reestablish or maintain glucose homeostasis by promoting energy storage and inhibiting energy mobilization. Energy storage is induced in skeletal muscle and adipocytes through an up-regulation in glucose transport into the insulin-stimulated cells, while the decrease in mobilization is moderated by insulin action on adipocytes (via mechanisms

beyond those responsible for energy storage) and the liver. Secondary to this goal, insulin can also induce cell growth, protein expression and hormone modulation.(Ruan 03)

Receptors & Signaling Cascade

Insulin signaling is a complex cascade of events using the second messenger system, generating a specific and coordinated response to the binding of insulin to its receptor. A number of distinct outcomes result from the divergence of insulin signaling along several pathways, leading to glucose uptake, hepatic glucose production inhibition, hormonal pathway activation (or suppression), protein synthesis and cell growth.

This cascade of events begins with the binding of insulin to the extracellular portion of the insulin receptor, a dimerized 12-transmembrane domain protein that is located in the membrane of target tissue cells. This protein consists of an extracellular α subunit, responsible for binding insulin, and a transmembrane β subunit, responsible for transducing signal via tyrosine kinase activity. The expressed receptor consists of two receptor proteins connected via disulfide bonds, thus it is considered a hetero-tetrameric receptor. Binding of insulin to the α units of the receptor induces a conformational change which leads to autophosphorylation of tyrosine residues on the β subunits, activating the tyrosine kinase activity and generating responses within the cell.

Once the β subunits have become activated they bind and activate proteins such as Insulin Receptor Substrates 1 and 2 (IRS-1, IRS-2), the Shc protein and others. These proteins then serve as docking stations that bind and activate subsequent kinases that act as signal carriers and lead to insulin's ultimate effects on the cell. Glucose uptake in skeletal muscle is achieved through the IRS-1 cascade, wherein PI3K, a kinase, activates

another kinase, PDK-1, followed by Akt/PKB activation. This results in the translocation of the glucose transporter 4 (GLUT4) from intracellular vesicles to the cell membrane, and once the vesicles dock they are integrated into the membrane of the cell and glucose transport can occur.(Youngren 07)

General and Site-specific Action

Insulin promotes glucose uptake in adipocytes and myocytes using the glucose concentration gradient as the driving force for transport. Following binding of the insulin molecule to its receptor a cascade of intracellular reactions takes place resulting in the insertion of glucose transporters into the cellular membrane. These transport proteins then allow glucose to enter the cell. Once inside the cell the glucose is rapidly converted in triglycerides or glycogen, in adipocytes and myocytes respectively, allowing the concentration gradient to remain robust and keeping the flow of glucose into the cell high. (Ruan 03)

Additional cascades in the adipocytes act to increase lipoprotein lipase activity on the cell surface, inducing clearance of triglycerides/lipoproteins from the plasma, furthering the energy storage activity of insulin. Yet more mechanisms are in place in the adipocytes which insulin suppresses hormone-sensitive lipase activity within the cell, limiting release of free fatty acids from storage within the fat cell. (Ruan 03)

The glycogenolysis and gluconeogenesis pathways in the hepatic cells are likewise suppressed, further reducing energy mobilization in the body and restricting the amount of glucose entering the bloodstream. (Ruan 03)

In healthy individuals these actions are sufficient to maintain glucose

homeostasis. Those individuals with abnormally low or absent insulin synthesis or a blunted response to insulin frequently suffer from diabetes and its attendant symptoms and complications.

Agonists/Antagonists

Ruan and Lodish[(Ruan 03)] note in their 2003 review that insulin is the only major hormone that promotes energy storage and inhibits fuel mobilization while there are several antagonists that act contrary to insulin. Glucagon, epinephrine, growth hormone, glucocorticoids and sympathetic nervous system activation all act to mobilize energy, both glucose and fatty acids, from storage and diminish the insulin response. This antagonism occurs by metabolic effect at the target tissue level and, in some cases, the inhibition of insulin synthesis and release from the pancreas.

INSULIN RESISTANCE

Definition

Insulin resistance (IR) is best defined as the inability of a given amount of insulin (either native or exogenous) in a given individual to stimulate glucose uptake to the same extent as in a healthy member of the same population.[(Oncul 02)]

Locii of resistance

Both extracellular and intracellular factors can be implicated in the genesis of insulin resistance. Possible loci for action that degrades the effectiveness of insulin include interference with insulin synthesis/secretion, inactivation in the plasma, decreased receptor expression, decreased insulin binding affinity at the receptor, receptor antagonism/competition and modification of intracellular signal cascades. The complex signaling cascades that occur intra-cellularly provide several opportunities for modulation

or attenuation of insulin signaling.

Insulin resistance is unlikely to be the result of mutations in the insulin receptor. Instead, it is the complexity of the signaling cascades resulting from insulin binding to the receptor that poses the most likely candidates for dysregulation. It should be noted, however, that insulin receptor levels within the cell might account for some signal loss, those these deficits in protein expression are more likely to be related to increased degradation or decreased transcription rather than a gene mutation. The impact of agents upon insulin synthesis and secretion are generally beyond the scope of this review as they speak to issues beyond insulin resistance, but some cytokines implicated in resistance may have impacts on protein expression and will be discussed elsewhere in this work.

The insulin receptor tyrosine kinase activity is the most frequently examined locus of resistance, likely because of the 7 tyrosine residues on the β subunit of the receptor that are available as autophosphorylation sites, regulating diverse and distinct aspects of insulin receptor function. Proper phosphorylation is required to stabilize the receptor subunits and engender maximize substrate affinity. In particular, proper phosphorylation of tyrosine 972 is vital to the proper binding and activation of IRS-1, the receptor substrate best linked to glucose uptake. Though deficit in the IRS-1 protein is also considered as a locus for insulin resistance, impaired activation of the insulin receptor has been reported in nearly all models of human and animal insulin resistance. Biopsy and muscle strip samples from Type 2 diabetics, obese individuals without diabetes and obese insulin resistant patients all display decreased insulin receptor autophosphorylation and tyrosine kinase activity, casting suspicion on dysregulation of

the receptor complex as a contributing factor in resistance.[Youngren 07]

Impact

IR is considered a strong marker of pre-diabetes, a condition of impaired glucose tolerance that is a strong risk factor for the development of Type II diabetes. It is estimated that approximately 7% of the United States population, or 20.8 million people, have some form of diabetes, while nearly 54 million more are considered pre-diabetic. Patients with one of the diabetic diseases may develop a number of serious complications, including stroke, heart disease, kidney disease, blindness and neuropathies. Diabetes is the fifth-deadliest disease in the United States, claiming nearly 225,000 lives a year, and studies indicate that deaths secondary to diabetes are under-reported due to the host of secondary complications that accompany the disease.[ADA 07] Rosenberg et al.[Rosenberg 05] report that 80% of deaths in patients with diabetes are attributable to macrovascular complications secondary to their diabetic state, and that both women (3.6 fold) and men (1.8 fold) have a significantly higher risk of myocardial infarction than non-diabetics. Furthermore they report that patients with Type II diabetes but no prior history or incidence of heart disease have the same risk of undergoing a cardiac event as non-diabetics with established heart disease. In short, the fifth-deadliest disease in the United States has be conclusively linked with increasing incidence of heart disease, the first-deadliest disease.

Assessment

There are several methods available for the assessment of insulin resistance, varying in invasiveness, expense and principle. The euglycemic hyperinsulinemic clamp

is considered the standard against which most other methodologies are compared. The clamp assessment uses two intravenous lines – one to infuse glucose and insulin, the other to collect blood for assessment. Insulin is then infused into a fasted (12h) patient to simulate a postprandial state, which is then maintained for 2 to 4 hours. This level of infusion should suppress natural synthesis and release of insulin. A varying amount of 20% dextrose solution is infused to maintain euglycemia in the subject. Collected blood is frequently sampled and assessed for glucose levels and the amount of dextrose infusion is adjusted to maintain euglycemia. Analysis of the amount of glucose infused over the course of the test determines the subject's insulin resistance. Generally speaking, high infusion rate indicates high insulin sensitivity while lower infusion rates indicate a greater degree of insulin resistance. Normally insulin sensitive patients are expected to require between 6 and 12 mg/kg/min of infused solution, with insulin resistant patients requiring a lower infusion level.(Bloomgarden 06, Trout 07)

The Oral Glucose Tolerance Test (OGTT) is a simple, expedient and more cost-effective method of estimating insulin response. A fasted (8-14h) patient ingests a known volume of glucose, generally 75g, and is then kept in a rested, unfed state for 2 to 3 hours. Following this interval investigators assess the subject's plasma glucose and render a diagnosis on insulin action based on standardized plasma glucose values. A diagnosis of diabetes may be conferred if an individual's plasma glucose is 200 mg/dL or greater, and values between 140 and 199 mg/dL indicate impaired glucose tolerance. This basic assessment is popular among clinicians because of the ease of administration and the relatively low patient discomfort. It does not, however, address insulin secretion;

only overall insulin action is assessed. Some investigators have modified the OGTT protocol to include multiple blood draws both before and after the glucose load is given, and assay the samples collected for both glucose and insulin. This alteration in methodology provides greater insight into the insulin-glucose metabolism of a subject.[Trout 07]

There are two common methods in use that assess insulin action from a single blood draw, thus minimizing patient discomfort and time expenditure. Both QUICKI and HOMA-IR use plasma insulin and plasma glucose values from a single fasted patient blood draw. The QUICKI (QUantitative Insulin sensitivity ChecK Index) uses the formula $QUICKI = 1/(\log I_0 + \log G_0)$, where I_0 is the fasting insulin concentration and G_0 is the fasting glucose concentration. In this assessment, decreasing values indicate increasing insulin resistance.[Trout 07] The other ratio-based assessment is the homeostasis model for assessment of insulin resistance (HOMA-IR), using the formula $HOMA\text{-}IR = (G_0 \times I_0)/C$ where I_0 is the fasting insulin concentration, G_0 is the fasting glucose concentration and C is a constant, either 22.5 or 405, depending on the units used for glucose assessment (mmol/L or mg/dL respectively).[Bloomgarden 06, Matthews 85, Trout 07] Stern et al.[Stern 05] compiled clinical data and examined a number of variables to determine appropriate diagnostic cut-points for determination of insulin resistance via routine clinical measures. The guidelines suggested by the authors indicate that subjects with a HOMA-IR $\geq$ 4.65, or subjects with a HOMA-IR $\geq$ 3.60 and BMI $\geq$ 27.5 should be considered insulin resistant. A large sample cross-sectional study found that healthy subjects had a mean HOMA-IR of 2.1 compared to 4.3 in subjects with impaired glucose

tolerance and 8.3 in diabetic subjects.[Trout 07] While both QUICKI and HOMA-IR provide inexpensive and expedient methods of insulin action assessment, they lack insight into glucose-load stimulated insulin action. A combination of OGTT and HOMA-IR has been suggested as an improvement over HOMA-IR alone (and by extension, over QUICKI alone).[Bloomgarden 06]

Causes and correlates

It is known that a poorly balanced diet - particularly one high in fat and energy intake without balancing output - a sedentary lifestyle and central obesity can all play a role in the development of insulin resistance. It has been reported that glucose intake can lead to reactive oxygen species (ROS) generation and a transitory state of inflammation for up to 3 hours following ingestion. As described below, inflammation plays a role in increasing insulin resistance. Furthermore, a mixed fast-food meal, high in fat and calories, engenders an inflammatory state for up to 4 hours, having even greater likelihood of generating insulin resistance.[Dandona 04] Sedentary subjects, regardless of weight, have been shown to have greater levels of glucose, insulin and insulin resistance than active subjects of similar weight status. [Kavouras 07] Active overweight subjects in this study displayed similar levels of glucose with reduced levels of insulin as compared to sedentary lean subjects, underscoring the importance of physical activity in combating insulin resistance.[Kavouras 07]

There are a number of independent factors known to interfere with insulin signaling at the tissue level. The cytokines interleukin-2 (IL-2) and tumor necrosis factor alpha (TNF-α) display anti-insulinemic effects in humans.[Biarnes 05, Oncul 02, Ruan 03] It has

been suggested that the chronic state of inflammation seen in obese patients may play a part in generating insulin resistance. Plasma borne markers of inflammation such as TNF-α and IL-6 have been correlated with insulin resistance, and moreover it has been indicated that increases in these markers may predict the future development of obesity and diabetes. Adipose tissue, increased in the obese, releases TNF-α constitutively, thus leading to a condition in which the obese secrete more TNF-α than the non-obese. TNF-α can interfere with insulin action by suppressing signal transduction, thereby increasing insulin resistance and fostering adipose tissue expansion. Completing the cycle, it seems that insulin has an anti-inflammatory impact at the cellular level, and thus insulin resistance may reduce this impact and be, in effect, pro-inflammatory.(Csehi 05, Dandona 04, Plomgaard 05) The specific mechanism by which TNF-α interferes with insulin signaling is likely the inhibition of tyrosine phosphorylation of the insulin-receptor substrate IRS-1.(Hotamisligil 03) By blocking this phosphorylation event, the cascade leading to GLUT-4 translocation is derailed and glucose uptake is reduced, creating a condition of insulin resistance. Resistin, a small protein produced in adipose tissue and during inflammatory responses in the body, may also be related to insulin resistance in humans. Resistin has been strongly associated with obesity and insulin resistance in mice and it has been shown that super-physiological doses can lead to transitory insulin resistance in other models. Research in human patients has been less conclusive, but resistin has been strongly correlated with inflammation and there are indications that resistin levels may be correlated with insulin resistance as well.(Azuma 03, Bokarewa 05, Silswal 05) This suggests that disorders which feature dysregulation of these factors may express or contribute to

insulin resistance in those same patients.

Obesity

JS Rana et al.[Rana 07] discussed the interplay between obesity, inflammation, cardiovascular disease and diabetes in a recent review, noting that 1.2 billion people in the world are overweight and at least 300 million are overtly obese. Evidence indicates that many of these people are likely to have insulin resistance or Type II diabetes. An examination of nearly 7000 males without history of diabetes found that subjects with a BMI between 25 and 28 were more than twice as likely to develop Type II diabetes than subjects with BMI below 25, and the risk increased further with increasing BMI.[Wannamethee 99] Though obesity-linked insulin resistance may never develop into full Type II diabetes it has been recognized as an independent risk factor for morbidity, and has been associated with hypertension and cardiovascular disease.[Kavouras 07, Sowers 03]

A significant body of evidence has further identified abdominal or visceral fat as a prime determinant of insulin resistance and diabetes risk. Central obesity has been linked with hyperinsulinemia, insulin resistance, diabetic dyslipidemia, hypertension and inflammatory and prothrombotic states. The elevation of risk in abdominally obese subjects may be derived in part from the extensive list of circulatory lipid imbalances - decreased HDL-C, high serum triglycerides, increased free fatty acids - and inflammatory factors - elevated c-reactive protein, TNF-α and IL-6 - along with a host of other challenges to metabolism and homeostasis.[Despres 06, Sowers 07]

Several mechanisms have been put forth as the means by which obesity is linked to insulin resistance, spanning metabolic, endocrine, inflammatory, neural and cell-

signaling rationales. The elevated release of fatty acids from the adipose depots in the overweight and obese is frequently identified as a threat to insulin sensitivity. It has been reported that the increase in fatty acids can also limit glucose uptake in peripheral cells by increasing signaling molecules such as PKC and JNK while inhibiting NF-κB, resulting in increased serine phosphorylation of IRS-1, thus decreasing GLUT4 translocation to cell membranes and glucose uptake.(Gual 04, Qatanani 07) This alteration in signaling has also been associated with the accumulation of lipids in skeletal muscle and the liver, driving similar reactions as that seen in subjects with elevated plasma fatty acid content.(Greenfield 04, Gual 04) The hypertrophied adipocytes seen in the obese, particularly the abdominally obese, are resistant to the anti-lipolytic effects of insulin and are, in fact, hyper-lipolytic, resulting in an enhanced non-estrafied fatty acid (NEFA) flux to the liver. The increase in NEFA has been shown to increase hepatic glucose production and induce insulin resistance in the liver cells.(Despres 06, Kahn 06) These larger adipocytes have also been linked to increased production of resistin and TNF-α, with decreased production of adiponectin and leptin, suggesting a viscous cycle in which the obese, with larger adipocytes, secrete agents which increase insulin resistance, decrease sensitivity and lose signals intended to limit food intake.(Kadowaki 03) It has also be suggested that increased NEFA in the plasma, along with elevated plasma glucose, can have a degenerative effect on the β-cells of the pancreas, limiting the ability of the cells to respond to insulin resistance and decreasing insulin secretion, possibly to the point ablating secretion altogether.(Kahn 06) Shimabukuro et al.(Shimabukuro 98) found an association between FFA and β-cell apoptosis, implicating elevated plasma fat with the decompensation of the pancreas

following extended insulin resistance. Their rat cell-culture study determined that elevated FFA induces β-cell apoptosis through ceramide (an apoptosis messenger) formation by three times over that of control cells, strongly suggesting a link between FFA and both insulin resistance and decreased insulin secretion.

Evidence indicates that the chronic state of inflammation accompanying obesity is likely to interfere with insulin signaling, further exacerbating this condition. Hormone, adipokines and cytokine secretion is altered in the obese, generally favoring increases in those agents linked to insulin resistance (TNF-α, c-reactive protein, IL-6, resistin) and decreasing those linked to insulin sensitivity (adiponectin).(Despres 06, Greenfield 04, Kahn 06, Qatanani 07, Steinberg 07, Rana 07) The effects of these agents are discussed in detail elsewhere in this review.

Disease states

Insulin resistance is a growing concern among the industrialized nations of the world. It is strongly associated with obesity, hypertension, cardiovascular disease and death. Cases of Type II Diabetes now far outnumber Type I Diabetes, with nearly 19 in 20 diabetes cases being linked to insulin resistance.(ADA 07) and this trend is unlikely to stop any time soon. Direct treatments of insulin resistance have, for the most part, met with limited success and thus the eye of the health community has to focus on prevention. Diet intervention, exercise and the limiting smoking and alcohol consumption are the keys to preventing this disorder.(Rosenberg 05) Even with this knowledge, however, cases of insulin resistance develop in people following significant changes in their lifestyle or other diseases and infections. The immune system and stress response system clearly

have ties to the generation of insulin resistance, as discussed at length below, so control of inflammatory factors and the development of stress-coping strategies in the population as a whole may be useful in limiting the impact of insulin resistance and the development of the metabolic syndrome.

Treatment

There are several options and avenues of treatment for insulin resistance. These options can be categorized as lifestyle modification (including weight reduction), management of concomitant risk factors and glycemic control.

Weight reduction via diet and increased physical activity are frequently touted as the primary treatments. Reduction of dietary fat, cholesterol and total caloric intake are part of many treatment plans, and there is some indication that reducing both carbohydrate intake and glycemic index can be beneficial in improving the health of insulin resistant patients. It has been shown that an "achievable lifestyle change" involving the loss of 7% body weight and 150 minutes of moderate exercise per week can reduce the conversion of patients with impaired glucose tolerance to diabetes patients by as much as 58%. Other improvements associated with dietary restriction and increased exercise include reduction of body fat, improved blood lipid profile, decreased blood pressure and overall cardiac health.(Rosenberg 05)

In addition to caloric restriction, recommendations have been made suggesting the reducing overall carbohydrate intake and the glycemic index of foods consumed is of particular advantage to diabetic or insulin resistant patients. Foods with a high glycemic index have been associated with hyperinsulinemia, postprandial hypoglycemia and

increased hunger, all leading to increased food intake, β-cell dysfunction and dyslipidemia. These conditions are all factors affiliated with the metabolic syndrome and may be viewed as a common pathway for both diabetes and cardiovascular disease.(Brand-Miller 03)

The management of concomitant factors includes smoking cessation, avoiding excessive alcohol consumption, limiting sodium intake, blood pressure management and dyslipidemia management. In patients who are unable to control their blood pressure and lipid profile via diet and exercise alone, prescription of ACE-inhibitors and statins are a valid option for pharmacological control of these conditions, respectively. A regimen of aspirin therapy is also of potential benefit to insulin resistant or diabetic patients, as platelet aggregation is increased and fibrinolysis decreased in diabetes, favoring the formation of thromboses and potential stroke.(Rosenberg 05)

A broad host of pharmacological agents are used to improve glycemic control in both insulin resistant and diabetic patients, and are capable of reduction of hepatic glucose production, increased glucose clearance, stimulation of insulin secretion, and carbohydrate absorption blockade. The biguanides, including Metformin, reduce hepatic glucose production and modestly improve skeletal muscle glucose uptake. Though the mechanism of action is not clear, it appears that Metformin is linked to AMP kinase and induces increased fatty acid oxidation. In addition to improvements in blood glycemia there are indications that this drug has a modest beneficial effect on lipid profiles (↑ HDL, ↓ LDL, total cholesterol and triglycerides). A decrease in circulating insulin and C-reactive protein has also been reported with Metformin. No evidence of hypoglycemia

is seen with Metformin administration and it has not been associated with weight gain or other disadvantageous outcome. The primary side effects of these drugs are gastrointestinal distress and nausea.(Rosenberg 05)

The sulphonylureas act primarily by stimulating insulin release from the pancreatic β-cells, an effect that is enhanced by the presence of glucose. This class of drugs inhibits potassium channels in the β-cell membrane, resulting in a depolarization of the cell and a subsequent secretion of stored insulin. This enhanced secretion reduces hepatic glucose production and increases glucose uptake in those tissues sensitive to insulin. This can result in hyperinsulinemia and its usefulness may be mitigated in subjects with constitutively elevated insulin secretion, but the sulphonylureas have not been associated with increased cardiac event incidence.(Rosenberg 05, Stratton 00)

The α-glucosidase inhibitors reduce postparandial hyperglycemia by delaying absorption of carbohydrate from the digestive system. The limitation of glucose entering the blood may allow a normally overtaxed insulin clearance system the opportunity to maintain homeostasis. Though digestive side effects such as gastrointestinal bloating, flatulence and diarrhea may limit their attractiveness, these drugs have also been associated with decreased weight, BMI, blood pressure and triglyceride levels.(Rosenberg 05)

The members of a broad family of drugs called thiazolidinediones (TZD) are similar in action to Metformin but have greater and more wide-ranging impacts. This family includes drugs such as troglitazone, pioglitzone and rosiglitazone, all of which are potent agonists of PPAR-γ. The extensive array of effects of TZD includes increased lipid metabolism, enhanced skeletal muscle insulin sensitivity and reduced hepatic

glucose production. Additionally TZD administration reduces the levels of the inflammatory markers CRP and TNF-α, reduces pro-thromboembolic mediators PAI-1 and MMP and increases plasma adiponectin levels. There is also evidence that TZDs may improve pancreatic β-cell function and serve to protect these insulin-secreting cells, perhaps by reducing lipid deposits near the secretory cells, and preventing the loss of function frequently seen in advanced Type II diabetes. These drugs can result in weight gain, edema and rarely congestive heart failure and liver function deficit, and as such patients must be carefully screened prior to beginning a TZD regimen and should be closely monitored while using the drug.(Oh 07, Rosenberg 05)

Exogenous insulin is required by those patients with Type I diabetes and in certain cases of advanced or severe insulin resistance, often in an acute regimen. The use of injected or oral insulin can be combined with one of more of the other glycemic control regimens discussed above to assist in maintenance of glucose homeostasis. Care must be taken to insure that overdose and subsequent hypoglycemia does not occur, and the regimen of regular injections can be burdensome, but exogenous insulin is often a required part of the diabetic patient's life.(Rosenberg 05)

ARTHRITIS

Overview

Arthritis, from the Greek arthro-, meaning joint, and -it is, meaning inflammation, is a collection of over 100 joint-related conditions or diseases in which swelling and pain are primary symptoms. This term is applied to a number of diagnostically different conditions, rising from a variety of mechanisms and causes ranging from autoimmune disease to blood-borne systemic infections. Arthritic diseases include rheumatoid

arthritis, osteoarthritis, septic arthritis, ankylosing spondylitis, fibromyalgia and gout. Arthritis can develop following other systemic diseases, including lupus, hepatitis, Crohn's disease and others, adding an increased burden to patients already suffering from a debilitating condition. More than half of all patients suffering from diabetes or heart disease are also afflicted with some form of arthritis. The symptoms most common to all forms of arthritis include inflammation and pain secondary to swelling, fatigue and reduced mobility. Arthritis is the leading cause of disability among Americans, with over 19 million people reporting limitations due to arthritic conditions, affecting more than 5 percent of the working general population and over 30% of all arthritis patients.(CDC 07)

The Arthritis Foundation reports that over 46 million cases of arthritis have been documented in America alone and predict that as many as 8 million additional cases will be diagnosed over the next 10 years. The Centers for Disease Control (CDC) estimate that the financial impact of arthritis is $128 billion annually, and this cost has risen by $20 billion dollars since 1997. Medical bills, pharmacy expenses, missed work and lost wages account for the majority of this impact. Over 750,000 hospitalizations, 36 million ambulatory care visits and 9,500 deaths have been attributed directly to arthritis in the United States, underscoring the significant impact of this class of disease.(Arthritis Foundation, CDC 07)

RHEUMATOID ARTHRITIS

Definition

Rheumatoid arthritis (RA) is a common chronic autoimmune disorder, affecting approximately 1% of the worldwide population.(Burton 06, Orozco 06, Weinblatt 07) It is a systemic

disease of chronic inflammation in the lining of the joints and internal organs which can lead to the destruction of the affected joints, causing significant disability and impairment, decreasing quality of life and carrying increased risk of secondary morbidity and mortality.(Brennan 07, Burton 06, Gaffo 06, Orozco 06) The disease is affiliated with complications and conditions affecting the skin, cardiac and respiratory systems, nervous system and the circulation and requires wide-ranging and aggressive treatment.(Burton 06)

Diagnostic guidelines exist to aid physicians in qualifying RA and it is recommended that patients displaying 4 of the following 7 criteria for a period of time in excess of 6 weeks be classified as having RA:

1. Morning stiffness in and around the joints lasting at least 1 hour;
2. Subcutaneous soft tissue swelling in at least 3 joint areas;
3. At least 1 swollen area in the wrist, metacarpal or interphalageal joint;
4. Simultaneous involvement of joint areas on both sides of the body;
5. Subcutaneous nodules over bony prominences;
6. Presence of abnormal amounts of serum rheumatoid factor (RF); and
7. Radiographic changes on hand or wrist radiographs including erosion or decalcification in or near affected joints.(Burton 06, Weinblatt 07)

The erosions are often detectable within 4 months of disease onset and rapid diagnosis has been associated with improved disease outcomes, indicating a need for early detection and therapy.(Combe 07) By recognizing early signs and employing diagnostic tools such as radiographs, magnetic resonance imaging and blood tests (for rheumatoid factor, erythrocyte sedimentation and cytokines), primary care physicians can

detect RA quickly and prescribe an appropriate therapy. As it stands, patients generally go undiagnosed for 9-12 months after onset of symptoms and then wait several additional months for rheumatology appointments, resulting in a delay capable of seriously compromising their health and limiting the success of disease-modifying therapies.(Burton 06, Weinblatt 07)

Impact

A wealth of information on RA can be found at the Arthritis Foundation website (http://www.arthritis.org/). According to the foundation's online information, Rheumatoid Arthritis affects 2.1 million Americans, with women accounting for more than two-thirds of the US cases. Onset is generally seen in middle age and appears more frequently in older people but can affect children and young adults.(Arthritis Foundation 07) The gender bias of RA appears to be worldwide, or at the least common to developed countries.(Burton 06)

Patients with RA are 7 times more likely than age- and gender-matched controls to have greater than moderate disability, leading to unemployment or under-employment, impaired physical function and transportation difficulties. Estimates indicate that development of RA can reduce life expectancy by between 5 and 15 years. This disease is the most common of the inflammatory arthritic diseases and is responsible for a great deal of adverse impact on the physical, emotional and financial well-being of afflicted patients.(Burton 06, Weinblatt 07)

Etiology

Rheumatoid arthritis is a disease of uncertain origin. A genetic component has

been identified but the condition cannot be explained by inheritance alone. Reports show that only approximately 30% of identical twins both develop RA when one twin expresses the disease, indicating a significant environmental or idiopathic component to disease development.(Burton 06) Other investigators have reported that as much as 60% of disease susceptibility is related to genetic factors, and that first-degree relatives of RA patients have between a 2% and 12% chance of developing the disease. This represents an increased likelihood of RA development of 2-4 times that of the general population - and some authors report the risk to be as high as 15 times the general population. The major histocompatibility complex (MHC) genes have been identified as a genetic region of risk, specifically the human leukocyte antigen (HLA), and indications are that there are several of loci of interest. (Orozco 06, Weinblatt 07)

There still remains a significant component of disease risk that lies outside the genetic contribution. Burton and Lloyd(Burton 06) write that a commonly held theory is that an environmental trigger, often some form of infection, elicits an uncontrolled inflammatory cascade that in turn leads to the joint damage and chronic systemic effects of RA. They further report that links between RA and physical trauma or psychological stressors are difficult to verify but frequently occur in patient anecdotes. Development of RA has been linked to infectious agents such as the Epstein-Barr virus and rubella, as they have both been isolated from the synovial fluid of RA patients. A direct causal effect of these infections on the development of RA has not been proven, but it is theorized that this sort of immune system stress might be the trigger that initiates development of the disease.(Weinblatt 07)

A variety of other environmental risk factors have been identified from epidemiological studies and clinical case reports. In addition to the genetic risk factors, age and gender a number of lifestyle-linked factors have been identified. Studies have indicated an increased risk of RA development secondary to smoking in both women and men, with risk increasing with duration and frequency of smoking. Additionally it has been reported that people who had ever smoked were at elevated risk for the development of some form of polyarthritis.(Symmons 05, Voigt 94) Obesity has been implicated as a risk factor for RA development as well, but there are conflicting reports as to the validity of obesity as a risk. Data from multiple epidemiological studies found that obesity (as defined by BMI $\geq$ 30) is a significant risk factor in women, linked to a 1.4 times higher incidence of RA development.(Voigt 94) No such association was described in males. It has been reported that there is the possibility of a one to two year time window in which BMI indicates enhanced risk of disease development, potentially addressing the lack of association found in some studies.(Symmons 05)

Symmons' review(Symmons 05) of RA risk identifies specific dietary risk factors beyond caloric surfeit. It has been reported that subjects in the middle and high tertiles of vitamin C intake have only one-third the risk of RA development as those in the lowest tertile, and that those in the highest tertile of red meat consumption evidenced 2.3 times the risk of disease development as those in the lower tertiles. Alcohol consumption reports are conflicting, with some investigations reporting no associations while others indicate a reduced risk of disease development with increased alcohol consumption (average of over 14 alcoholic drinks per week) in postmenopausal subjects.(Voigt 94)

Of interest, it is generally seen that RA symptoms go into remission during pregnancy and that there is an increased incidence of RA development following parturition. Furthermore, it has been reported that women taking oral contraceptives have a relative risk of disease development of 0.49 compared to women who had never taken the pill. Subsequent analysis of pooled data suggest that this value is accurate, but it is uncertain if the benefit is due to the pill itself or if it is simply a marker for some other protective factor.(Symmons 05)

Symptoms

Symptoms besides pain include frequent fever, lack of appetite, difficulty moving, anemia, and of course swelling of the affected joints. The frequency, intensity and variety of symptoms expressed may vary over the course of the disease.

Early symptoms of rheumatoid arthritis include fatigue, stiffness (particularly in the morning or after prolonged rest) and pain, all improving with activity and motion. The disease causes pain, swelling, stiffness and potentially deformities in the joints of the upper and lower extremities. It generally affects at least 5 joints and is usually seen to have bilateral impact. The small joints of the wrist, hands and feet are the most likely to show damage or discomfort. Clinical impact on the hips or shoulders generally does not occur during the early phases of the disease, but the knees can be involved and affected.(Gaffo 06) Range of motion of the affected joints can be reduced secondary to obstruction of the anatomical features by the thickened synovium. There is seldom any overt clinical evidence of joint damage in the early stages of the disease and no signs of lost cartilage or bone are likely to be visible on radiographs.(Weinblatt 07)

Prolonged, especially untreated or uncontrolled, RA can lead to damage to the bones surrounding affected joints, often visible on radiographs as erosions which are used to assess the degree of disease progression and damage.(Gaffo 06) Subcutaneous rheumatoid nodules are another manifestation of the disease, typically painless and found on surfaces involved in extension and mechanical stress such as the elbow. These nodules occur in 20 to 35 percent of patients and are a marker of more severe RA. They tend to enlarge when the disease is active and can be exacerbated by methotrexate, a common RA treatment. These nodules may need to be surgically removed if they prove painful or debilitating, though they are known to reoccur.(Burton 06, Gaffo 06)

Rheumatoid arthritis is a systemic disease that has impacts throughout the body of afflicted patients. In addition to bone and joint damage, patients can suffer from vasculitis, an inflammation of the small blood vessels. This is generally low-grade and leads to small lesions on the hands and feet, frequently expressing in small hemorrhagic lesions around the nail beds. Dry eyes and mouth are irritating symptoms seen in RA patients, causing difficulties in swallowing, especially dry foods and medicine tablets and discomfort from bright lights. RA patients can be predisposed to chest infections and respiratory diseases, and as many as 10 percent of patients can have symptomatic and progressive alveolitis, resulting in reduced lung function and difficulty breathing. Rare but significant symptoms also include pericarditis (often asymptomatic), cervical cord compression resulting in pain, paraesthesia (pins and needles feeling) and weakness in the extremities and peripheral neuropathies. Anemia occurs in many RA patients secondary to their chronic disease and frequently does not respond well to iron

supplementation.(Burton 06)

In summation, rheumatoid arthritis expresses early symptoms primarily in the small joints of the patient, moving progressively to the larger joints and increasing in intensity and damage. As the disease progresses symptoms are seen in non-articular systems including the skin, cardio-respiratory system, sensory system and the circulation. Early detection and aggressive treatment is mandated to reduce the severity or eliminate the instance of advanced symptoms.

Disease Progression and Diagnostic Levels

Rheumatoid arthritis is a progressive disease, almost always resulting in worsening symptoms and advancing damage to the affected joints and bones. Patients with progressing RA are characterized by increased severity of symptoms, addition of new articular symptoms or affected regions and finally symptoms in systems beyond the articular system.

Early RA is characterized by symmetric swelling and pain in the small joints of the hands and feet, most frequently seen with pain or discomfort. As the disease progresses, this swelling and pain spreads to other joints in the hands and feet, leading to ever-increasing frequency of pain. Joint and tendon damage may cause weakness or decreased range of motion while compression of nerves caused by the swelling of the synovial lining can induce additional pain and discomfort, ultimately resulting in deformity and loss of function.(Weinblatt 07)

As the disease progresses larger joints, such as the elbow and shoulder, become affected. The symptoms here progress from swelling and pain to contractures, or

shortening of the muscles, leading to deformity and disability. In the shoulder swelling leads to pain and decreased range of motion with the possibility of effusions from the synovial capsule. In addition to disability and loss of function chronic shoulder pain and damage may cause difficulty sleeping with attendant fatigue and discomfort.(Weinblatt 07)

The knee joints are often affected in early RA, typically characterized by swelling and effusion with some synovial thickening. The muscles surrounding the knee may atrophy as the disease progresses, resulting in weakness, joint instability and limited mobility. This mobility impairment can be exacerbated by progressive swelling and deformity in the joints of the feet and ankle as well.(Weinblatt 07)

Disease progress is measured in a number of ways, using patient reports, physician examination and laboratory tests as benchmarks for assessment. Measurement of the erythrocyte sedimentation rate is a routine blood test used to assess disease control in RA patients, as are measures of inflammatory factions and antibodies (such as c-reactive protein, RF and anticyclic citrullinated peptide (anti-CCP)).(Weinblatt 07) A scoring system has been developed based on the number and severity of erosions and this system is used to assess both disease severity and the effectiveness of exogenous agents to control the progression of the disease.(Gaffo 06) Three modalities of imaging assessment are used to quantify erosion and assess disease progress - plain x-ray, ultrasonagraphy and MRI. Plain x-ray is the least expensive of the three but is best suited to more advanced RA patients as only overt lesion will be easily appreciable. Ultrasound can show synovial inflammation as well as bone lesions not visible on plain film, while MRI can also illuminate local areas of bone edema which are likely to advance to erosion with

excellent predictive strength.(Mitchell 07)

Additional scales have been developed to aid in arthritis research, either epidemiological or intervention based. In an effort to insure continuity of classification and applicability of results, these scales are accepted as a useful tool during study design, recruitment and outcome reporting. Though the scales are not driven by absolute values and are open to some interpretation, the criteria put forth allow for patient classification with a minimum amount of invasive or discomforting procedures. The measures indicated are meant to sample the range of symptoms in RA, provide a scale to measure change and serve to predict long-term outcomes or progression of the disease. Evaluation guidelines from the American College of Rheumatology (ACR) recommend assessment of 7 areas to determine current disease activity. These assessments are:

1. A count of tender joints;
2. A count of swollen joints;
3. Patient's assessment of pain;
4. Patient's assessment of global disease activity;
5. Physician's assessment of global disease activity;
6. Patient's assessment of physical function;
7. Assessment of acute-phase reactants (such as ESR or CRP).(Felson 93)

The ACR has also devised a function classification system to assess the impact of disease severity on the ability of patients to perform tasks of everyday life, delineated into 4 functional classes. Class I patients are able to perform all activities of daily life (self-care, vocational and avocational). Class II patients are able to perform self-care and

vocational tasks but have some impairment with avocational activities. Class III patients are able to perform self-care tasks but have impaired ability to perform vocational or avocational activities, while Class IV patients have some level of impairment in their ability to perform all activities of daily life. Definitions of vocational (including work, homemaking or schooling) and avocational (including leisure and entertainment) activities are age- and gender-specific but meant to be broad and encompassing.(Hochberg 92)

Co-morbidities

Rheumatoid arthritis has been linked to sedentary lifestyle with its attendant risks, insulin resistance and excessive cardiovascular disease (CVD), morbidity and mortality risk.(Dessein 03, Dessein/Moomal 02, Dessein/Joffe 02) Investigators have found as much as a 4-fold increased incidence rate for cardiovascular events in patients with fully developed RA and have reported that as heart disease prevalence is as high as 49% in this group.(Dessein 03) Others have reported that RA patients have 2.2 times the risk of CVD-related death than non-RA patients.(Snow 05) A significant amount of effort has been directed at uncovering the links between RA and CVD and it has be determined that the classic CVD risk factors (such as obesity, smoking, psychological stress) are insufficient to describe the risk situation for RA patients and that the chronic inflammatory state of these patients further jeopardized their cardiac health. Accelerated atherogenesis and sub-clinical atherosclerosis have been identified in RA patients and contribute to enhanced disease risk. Furthermore, it has been found that the traditional risk factors were insufficient to predict this atherosclerosis and that measures of the RA disease state were supplementary and improved predictive strength. Metabolic syndrome features, particularly insulin

resistance and triglyceride levels, were linked to plaque formation and growth frequency independent of other CVD risk elements. (Dessein/Veller 06, Gonzalez-Gay 05, Pamuk 06) Investigators have strongly recommended adopting treatment programs and regimens that address cardiovascular health in addition to pain, inflammation and disability in an effort to curtail the heightened risk of CVD development in RA patients, preferably by reducing adverse lifestyle risk factors and increasing physical activity.(Turesson 07)

There are indications that rheumatoid arthritis patients have a lower level of physical activity, particularly recreational physical activity, than healthy age-matched controls. Though this relationship is less definitive in younger patients and health professionals, it remains a serious concern.(Eurenius 05, Hootman 03, Turesson 07) In their 2003 review of nationwide surveys on physical activity and lifestyle, Hootman et al.(Hootman 03) reiterated the benefits of physical activity in decreasing morbidity and mortality related to several chronic diseases and presented public health recommendations for developing and maintaining physical fitness. There are several populations known to be at risk for physical inactivity and among those are women, older persons and patients with chronic diseases. Given that the epidemiological data on RA suggests women and older adults are most likely to be afflicted with the disease the authors wished to examine the confluence of inactivity and RA. They reported that over 32% of the respondents to three large scale surveys had been diagnosed with some form of arthritis and that among this group 30.8% were inactive, compared with 25.8% of patients without arthritis. Additionally 33% of women, persons $\geq$ 45 years old and the obese with arthritis were found to be inactive. Among non-arthritics this level of inactivity was only found in

subjects ≥ 75 years of age. Despite accumulated study results that indicate physical activity in RA patients for pain reduction, improved physical function, delayed disability and reduced comorbidity risk, patients with RA appear resistant to activity.

The authors[(Hootman 03)] suggest that fear of increased pain, particularly at the onset of an exercise program, or inappropriately being instructed to avoid activity may be the key reasons RA patients are inactive and that it is incumbent upon health professionals to reverse this position. This population in particular needs increased activity rates in order to manage symptoms, limit disease progression and reduce comorbidities such as cardiovascular disease and diabetes. An even high rate of insufficient activity was seen in an examination of self-reported activity among RA patients in Sweden. This survey of nearly 300 RA patients, both male and female, found that 47% of the sample was insufficiently active and that the vast majority of patients were found to be of only average or below average aerobic fitness as assessed by a battery of fitness tests.[(Eurenius 05)]

Lemmey et al.[(Lemmey 01)] found a significantly lower self-reported exercise level for rheumatic disorder patients as compared to healthy controls. The authors similarly found a significantly higher percentage of body fat in the rheumatic patients than the controls. This may be due in part to above-average protein catabolism seen in rheumatoid patients as well as decreased physical activity. In the absence of muscle-building exercise the catabolic processes of inflammatory disease may further predispose the patients to increased loss of fat-free mass and fat mass gain even beyond that of an otherwise healthy sedentary individual. Obesity and overweight incidence among RA patients is a topic of debate, though it is considered a risk factor by some experts.[(Symmons 05, Voight 94)]

It stands to reason that patients of a disease typified by chronic inflammation and decreased physical activity with the possibility of elevated body fat would be at increased risk for the development of insulin resistance. The metabolic syndrome is a cluster of cardiovascular risk factors predisposing patients to increased risk of cardiac events, atherosclerosis and premature mortality. Definitions of the metabolic syndrome vary somewhat, but the World Health Organization (WHO) includes insulin resistance as a key component. Given the link between inflammation and insulin resistance, investigators have assessed the incidence of insulin resistance in RA patients. As hypothesized, RA patients have been shown to have a higher prevalence of metabolic syndrome, a frequent precursor to type II diabetes and a contributor to cardiovascular disease. Patients with long-standing RA were found to have a 42% incidence rate of metabolic syndrome compared to only 11% in age- and gender-matched controls. This relationship was in evidence in patients with recently diagnosed RA as well, as these patients had a 31% incidence of metabolic syndrome. These relationships remained significant after adjustment for age, gender, race and BMI.(Chung 07) Elevated fasting plasma insulin, glucose and HOMA-IR were also reported by Oncul at al.(Oncul 02) in RA patients as compared to healthy controls, corroborating these findings and further highlighting insulin resistance as a key component of the metabolic syndrome.

An examination of insulin resistance and β-cell function yielded similar associations. The investigators in this study(Dessein/Joffe 06) reported a significant difference in insulin resistance between subjects with high-grade inflammation versus low-grade inflammation (as assessed by CRP levels). Regression analysis determined that

abdominal obesity and patient's assessment of disease activity, as recommended by the ACR above, were significant predictors of insulin resistance. Furthermore, tender joint count, swollen joint count and patient's assessment of disease activity were significantly associated with reduced β-cell function as assessed by the Homeostatic Model for Assessment of β-cell function (HOMA-B). These findings suggest that RA, particularly active or poorly controlled RA is associated with insulin resistance and decreased β-cell function.

The acute phase response, indicative of disease activity in RA, has been suggested as a link between the disease and the dyslipidemia and insulin resistance often seen in patients. An examination of arthritis patients and age-, gender- and race-matched controls reported significantly elevated BMI, fasting insulin, fasting glucose, HOMA-IR and triglycerides in arthritis patients as compared to controls. Additional, patients were found to reduced HDL cholesterol and a lower HDL/Total cholesterol ratio, suggesting dyslipidemia. ESR, a measure of arthritis disease activity, along with BMI, were found to be significant predictors of insulin resistance, indicating that the inflammatory disease is correlated with poor glucose tolerance and this contributes to increased CVD risk in the population.[(Dessein/Moomal 02)] Additional work by investigators involved in this study further reported that the degree of insulin resistance and other cardiovascular disease risk elements is greater in patients with rheumatoid arthritis as compared to age- and gender-matched osteoarthritis patients, highlighting the need for investigation into the links between RA and IR and preventative strategies to curb this risk.[(Dessein/Joffe 02)]

Not only is the inflammation of the RA disease state correlated with and

predictive of insulin resistance, there are indications that glucocorticoid treatment, frequently prescribed in the past and still used on occasion currently, is positively correlated with and predictive of insulin resistance. What was once thought to be simply a side-effect of other factors has been brought to the forefront of some investigations - insulin resistance is not just a byproduct of RA but a significant condition that independently and significantly increases risk of CVD development.(Dessein 05)

Pharmacological treatment

Treatment of rheumatoid arthritis symptoms generally begins with non-steroidal anti-inflammatory drugs (NSAIDs) prior to diagnosis and continuing throughout the progression of the disease. NSAIDs include over-the-counter drugs such as aspirin and ibuprofen, and offer rapid, though often incomplete, relief of pain and inflammation. Glucocorticoids have previously been widely and systematically prescribed for RA treatment and are still frequently used to limit pain and swelling and as a bridge to other therapies. Prednisone remains one of the most frequently prescribed glucocorticoid therapies. These drugs exhibit frequent, often severe adverse effects and are best used in low dosages along with other therapies or not at all. Disease-modifying antirhuematic drugs (DMARDs) are the primary initial therapy prescribed to RA patients. These drugs are slow-acting but address both symptom relief and slow clinical disease progression. They can be supplemented with NSAIDs for more rapid relief of pain. This category includes such agents as methotrexate and leflunomide, among others. Biological response modifiers are the newest pharmaceutical treatment option and are designed to target and block the mediators of disease symptoms and progression. By limiting the

activity of the disease these drugs are intended to reduce the frequency and intensity of symptoms as well as minimize or eliminate the progression and damage of the disease. A significant drawback to these drugs is that they are given via intravenous infusion and require regular clinic visits for administration. Infliximab (Remicade) and etanercept are the most common examples of biological response modifiers and are intended to inhibit the activity of TNF-α. A number of new agents are in development, including drugs targeting Il-1, Il-6 and B-cell function, as well as an anti-TNF-α drug that can be taken orally.(Emery 06, Gaffo 06)

Infliximab (Remicade)

Infliximab is a chimaeric monoclonal antibody to TNF-α comprised of 75% human (effector region) and 25% mouse (variable region binding site) protein. It binds with high specificity and affinity to both the soluble and membrane-bound forms of the cytokine while exhibiting no affinity for TNF-β, reducing the likelihood of non-specific, unintended effects. It has also been shown to lyse TNF-α producing cells in vitro, but this has not yet been shown in vivo.(Harriman 99, Markham 00, Keating 02)

Remicade, the trade name for infliximab, reduces the activity of TNF-α via dose proportional neutralization, reducing the action of the cytokine by binding to the molecule and preventing subsequent receptor binding. It is generally prescribed at doses ranging from 3 to 5 mg/kg, delivered via 2-hour IV infusion at regular intervals from 4 to 6 weeks under the supervision of trained medical professionals. Dosing is stepped up over the first 3 infusions, generally at 0, 2 and 6 weeks, before settling into a 6-week scheduled infusion at the final dosage. Tolerable dosing ranges from 0.01 to 10 mg/kg, and frequency of up to four-week infusion intervals may be considered in some patients.

The specificity, size and protein nature of the drug limits unintended effects and drug interactions while reducing the incidence of metabolite-related issues. Infliximab is generally well tolerated with abdominal pain, headache and nausea the most common side effects with an increased incidence over placebo of less than 5%.(Harriman 99, Markham 00, Keating 02, Micromedex)

This drug is currently FDA approved for treatment of Crohn's disease, ankylosing spondylitis, plaque psoriasis, rheumatoid arthritis and ulcerative colitis. Other indications for prescription include hidradentis suppurativa, juvenile idiopathic arthritis, systemic onset juvenile chronic arthritis and Wegener's granulomatosis.(Micromedex) Use as therapy for rheumatoid arthritis has been effective, significantly improving disease symptoms over methotrexate alone or with placebo with improvements seen as early as 2 weeks into the treatment regimen. (Harriman 99, Markham 00, Micromedex)

Other treatment options

Both aerobic and resistance training programs have been suggested for the management of RA symptoms and a reduction of disease comorbidities. It was once feared that any form of strenuous exercise could exacerbate disease symptoms and hasten tissue degradation in RA patients, but evidence now exists that indicates that various forms of exercise are not only safe but beneficial.(Jong 05, Stenstrom 03, Rall/Meydani 96, Rall/Roubenoff 96) A number of studies indicate that both aerobic and resistance training programs offer significant therapeutic benefit to RA patients including enhanced endurance, strength, joint stability and improved quality of life. For maximal effectiveness it is recommended that the training programs be sustained over time, performed with social support and

feature individualization for safety.(Hakkinen 04, Jong 05, Kettunen 04, Stenstrom 03, Rall/Meydani 96, Rall/Roubenoff 96)

The work of de Jong et at.(de Jong 04, de Jong 05) has been instrumental in detailing the improvements in RA disease state and symptoms during and after an exercise intervention. These studies found that an intensive weightbearing exercise intervention did not worsen any measures of disease state and, in fact, significantly reduced the radiological progression of the disease. Furthermore, subjects in the exercise group became more physically fit, gained functional ability and reduced their usage of glucocorticoid treatment. A follow-up study(de Jong 09) of the original patients found that the majority continued their exercise regimen and maintained strength gains acquired during the original intervention. While neither those who continued nor those who discontinued exercise were found to have maintained the same gains in aerobic fitness, gains in functional ability remained and no detrimental effects on disease activity or radiological damage was found subsequent to the original exercise intervention, providing additional reinforcement for the safety of resistance exercise in RA patients.

A recent review(Metsios 08) examined 40 original studies investigating the effect of strenuous exercise on disease state and characteristics in RA patients and confirmed that exercise, regardless of intensity, can have beneficial outcomes for RA patients. An array of exercise interventions varying in both mode (aerobic, resistance, combined) and intensity (low, medium and high) were presented as improving functional ability and disease characteristics without advancing disease progression. In light of the enhanced risk of cardiovascular disease seen with this disease, the authors recommend further study

in this arena particularly as relates to the impact of exercise programs on cardiovascular disease or risk factors in RA patients.

The time course required for exercise interventions to have a significant impact on disease state, quality of life assessment and aerobic fitness may be as short as four weeks. When compared to control subjects, patients undergoing a dynamic exercise program evidenced significantly improved functional and quality of life outcomes with gains in overall health and aerobic fitness. Although non-significant, the exercise intervention seemed to improve dexterity and disease activity as well. Radiological assessment via the simple narrowing erosion score (SNES) indicated that disease progression did not worsen in participants, further cementing that exercise activity improves quality of life in RA patients without enhancing disease progression.(Balliet 09)

TNF-α

Synthesis

Tumor necrosis factor alpha (TNF-α) is a multifunctional cytokine that is involved in inflammation, cell apoptosis and survival, cytotoxicity, mediation of synthesis of other cytokines (such as IL-1 and IL-6) and has been implicated in the genesis of insulin resistance. It was first investigated as an endotoxin-induced molecule that causes tumor necrosis (hence the nomenclature) and was subsequently found to be identical to cachectin, an agent secreted by macrophages.(Ruan 03) The initial divergence of nomenclature and anticipated function is due to the multiple sites of synthesis - adipocytes, macrophages, monocytes, T-cells, smooth muscle cells and fibroblasts - and the wide array of functions TNF-α can perform.(Popa 07) This cytokine is initially synthesized as a 26 kDa monomer bound to the membrane of the synthesizing cell. A

trimer is formed by cleaving of these monomers from the membrane by TNF-α converting enzyme, resulting in the final form of the cytokine. Though several cells in adipose tissue are capable of producing cytokines (such as stromal, endothelial and immune cells), synthesis of TNF-α in the adipose tissue is dominated by the adipocyte. The activity of TNF-α is modulated by its receptors, the soluble TNF receptor Type 1 (sTNFR1) and Type 2 (sTNFR2).[Ruan 03]

Gene transcription appears to be increased in the adipose tissue of obese animals and humans, though there are conflicting reports on the topic.[Warne 03] Hotamisligil et al[Hotamisligil 95] reported an increase in mRNA in obese subjects as compared to lean counterparts and further reported that TNF-α mRNA levels normalize after weight loss, suggesting a link between fat mass and gene transcription. Other studies[Kern 95, Koistinen 00] have failed to find any correlation between body mass and TNF-α mRNA levels, though the strength of these studies is limited by the use of Body Mass Index, a tenuous predictor of fat mass. In fact, Kern et al.[Kern 95] elucidated this limitation in their study in which BMI was not an accurate predictor of mRNA levels but a significant positive correlation was found between total body fat mass and TNFα mRNA.

Plasma levels of the cytokine were also found to be elevated in obese women as compared to lean controls.[Bastard 00] This would seem to indicate that translation is also up-regulated in obesity, providing evidence of potential interaction between adipose-tissue derived TNF-α and whole body insulin resistance in addition to the autocrine/paracrine effects at the adipocyte. Furthermore, significant elevations of soluble TNF receptors expression in both adipose tissue and the circulation have been

reported. Dzienis-Straczkowska et al.[Dzienis-Straczkowska 03] reported increases in both sTNFR1 and sTNFR2 in their investigation of the potential link between TNF-α and impaired glucose tolerance in obese subjects. They found that receptor levels were significantly higher in obese subjects versus lean subjects, and in obese subjects with impaired glucose tolerance versus obese subjects with normal glucose tolerance. Furthermore, the authors reported a significant, inverse correlation between receptor levels and insulin sensitivity. These findings were similar to those reported in a five-group study (control, obese, morbid obese, obese with type 2 diabetes, morbid obese with type 2 diabetes) using only women. The investigators in this study reported that all four investigational groups displayed increased sTNFR1 and sTNFR2 levels compared to controls and correlations between both receptor subtypes and BMI, percent fat, fasting insulin and fasting glucose.[Bullo 02] Other reports have indicated that sTNFR2 was increased in obese and insulin-resistant subjects and is correlated with waist-to-hip ratio (WHR), BMI, fat free mass (FFM) and insulin resistance while the sTNFR1 was not, although this study used both male and female subjects, suggesting possible gender differences.[Fernandez-Real 98]

Action

The immune reaction and inflammatory properties of TNF-α are substantial and diverse. In its cytokine role TNF-α is a protective and vital component of the immune reaction, helping the host resist bacterial, viral and parasitic infection by inducing synthesis and targeting appropriate immune agents to the area of infection. TNF-α stimulates the expression of adhesion molecules, such as V-CAM, on the endothelium,

allowing the docking of immune cells to the vasculature in the region undergoing pathogen attack. It is also able to up-regulate chemotactic factors (such as IL-8), prostaglandins and fibroblasts, all vital to the suppression of disease and the recovery from infection.(Brennen 92)

TNF-α exhibits a number of effects on adipose tissue, acting in an autocrine or paracrine manner. It has been implicated in the severe weight loss (cachexia) that accompanies several extreme pathological conditions such as cancer, congestive heart failure and chronic infection and it is because of these effects that TNF-α was also known as cachectin. In this role, TNF-α acts to decrease adipocyte mass via a number of distinct pathways. It has been reported to be pro-apoptotic to both preadipocytes and mature adipocytes while inhibiting adipogenesis. Furthermore, the cytokine acts to decrease transit of free fatty acids (FFA) from the circulation into adipocytes by decreasing expression of both lipoprotein lipase (LPL) and FFA transporters. LPL, expressed on the adipocyte cell surface, is required to convert circulating triglycerides and lipoproteins into transportable fatty acids, and the transporters are required for passage into the cell. In addition, TNF-α can work to deplete adipocyte stores of triglyceride, perhaps through some link to hormone-sensitive lipase, an enzyme expressed within the adipocyte that breaks down triglyceride into FFAs for export from the cell. In summary, TNF-α can work to shift lipid metabolism from storage to circulation, increasing the circulating levels of FFA/triglyceride and attempting to decrease fat mass.(Warne 03) The role of this cytokine in obesity is more elusive and elevated expression in that disease state may result from the inability to decrease fat mass as intended.

There is little question that TNF-α is a vitally important agent in protecting its host from infection, aiding in the recovery from injury and manipulating lipid metabolism. Difficulties arise when this factor is chronically stimulated, either via an established disease state (rheumatoid arthritis, for instance), chronic low grade inflammation, obesity or some other disadvantageous condition.

Correlates

TNF-α is thought to play a role in the development of insulin resistance and type 2 diabetes. It has been shown to induce insulin resistance in rodents in a reversible fashion, countered by troglitazone (an insulin-sensitizing drug) or TNF neutralization.(Dadona 04, Reynolds 04, Hotamisligil 93) TNF-α levels have been correlated with decreased insulin-mediated glucose disposal, advancing age and increased adiposity.(Reynolds 04 and more) Genetic knock-out of TNF-α expression has proven effective in improving insulin sensitivity in rodent models of obesity and Type II diabetes.(Ruan 03, Uysal 97) However, the administration of a TNF-α neutralizing antibody to obese Type II diabetics failed to improve insulin sensitivity. It has been suggested that this may be due to TNF-α autocrine and paracrine functionality in adipose tissue and that an exogenous antibody may not be able to affect the biological activity of the endogenous adipocyte-derived cytokine.(Ofei 96, Ruan 03) Exogenous neutralization of TNF-α has been effective in improving insulin sensitivity in animal models, however, suggesting that there may be a means by which the cytokines anti-insulinemic effect may be mitigated.(Hotamisligil 94, Hotamisligil 03, Ruan 03)

Circulating sTNFR1 and sTNFR2 levels have also been correlated with insulin

resistance and the receptors have been shown to impact the insulin signaling cascades in an adverse fashion. (Dzienis-Straczkowska 03, others)

It has been suggested that TNF-α is capable of inducing or exacerbating insulin resistance via one or more pathways. Systemically the expression of TNF-α can lead to elevated FFA in the circulation. These FFA have been shown to reduce glucose uptake and metabolism, inhibit insulin signaling and glycogen synthesis in muscle and promote hepatic glucose production.(Ruan 03) Additionally, FFA have been implicated in the progression of Type II diabetes. In animal models of the disease high plasma concentrations of FFA induced apoptosis in the β cells of the pancreas, the sole synthesis loci for insulin. This increase in cell death accelerated β cell failure throughout the organ and may be responsible for the ultimate defect of insulin production in advanced Type II diabetes.(Shimabukuro 98)

Locally TNF-α has been shown to inhibit insulin-stimulated tyrosine phosphorylation of the insulin receptor and insulin receptor substrate-1 (IRS-1). Reduced receptor and IRS-1 phosphorylation indicates a possible down-regulation in the translocation of glucose transporters to the cell surface and decreased glucose flux into the cell, be it adipocyte or myocytes.(Hotamisligil 96) Plomgaard et al.(Plomgaard 05) report that exogenous TNF-α induces insulin resistance in healthy subjects by altering the phosphorylation scheme of IRS-1 (increasing serine and decreasing tyrosine phosphorylation) and several kinases, notably p70 S6 kinase and c-jun kinase, resulting in impaired phosphorylation of Akt substrate 160, an important element in the translocation of GLUT4. Csehi et al.(Csehi 05) concurrently reported that TNF-α binding to its 55 kDa

receptor (TNF-R55) in its “death domain” is responsible for the serine phosphorylation of IRS-1 and the diminished intracellular response to insulin binding. Valverde et al.[(Valverde 98)] present a confounding finding resulting from their investigation into the impact of TNF-α on fetal adipocytes. They report that IRS-2 was hypophosphorylated in cells treated with TNF-α and exposed to insulin, but that IRS-1 phosphorylation was unaffected. The authors also indicated that GLUT4 mRNA expression was impaired by the TNF-α pretreatment and this impairment was sufficient to cancel the normal up-regulation in mRNA seen following insulin binding. This investigation suggests that tissue-specific effects on insulin sensitivity are possible and that these effects might well go beyond the realm of altered signaling and impact the expression of proteins and substrates required for signal transduction and glucose transport.

Other mechanisms of TNF-α induced insulin response impairment include down-regulation of IRS-1 protein expression, decreased PPAR-γ activity and decreased secretion of adiponectin from adipocytes (discussed below).[(Popa 07, Ruan 03)]

An examination of non-obese Japanese Type II diabetes patients published in 2005[(Ohya 05)] presented an opposing view. Systemic levels of TNF-α, sTNFR1 and sTNFR2 were not found to correlate with BMI, serum triglycerides, leptin, adiponectin or insulin resistance in these patients. The authors comment that these findings may be related to the fact that their subjects were uniformly non-obese and that their disease was well controlled. They do suggest, as have others, that systemic TNF-α activation does not present the impact on the induction or exacerbation of the disease that the localized autocinre/paracrine effect of TNF-α may carry.

RESISTIN

Synthesis

Resistin is a relatively recently discovered polypeptide of 114 amino acid residues (in its basic monomeric form) with a weight of 12.5 kDa.[Bokarewa 05, Kusminski 05] This protein, first highlighted in 2001, was originally described as an adipokine that provided a link between obesity and insulin resistance - hence its name. Subsequently it has been found that resistin is expressed at very low levels in human adipocytes, while monocytes, macrophages and bone marrow cells exhibit high levels of expression. Resistin can also be found expressed in lung tissue, endothelial cells and in the placenta.[Bokarewa 05] The relative contribution of these sources of resistin to the plasma levels of the protein remain uncertain and contentious, however, and there remains significant uncertainty into the impact of source-specific resistin on human physiology.[Kusminski 05]

The resistin molecule was originally detected as a disulphide linked homodimer, but recent investigation has found that there are two "assembly states" of resistin found in plasma. The high molecular mass (HMM) form is predominant in terms of amount, but the less common low molecular mass (LMM) form appears to be far more biologically active. This relationship suggests that bioactivity may be regulated via some form of processing wherein the HMM form is cleaved and altered into the LMM form prior to receptor binding and initiation.[Kusminski 05]

Several factors have been suggested which may up-regulate synthesis and secretion of resistin, including corticosteroids, testosterone, growth hormone, pro-inflammatory cytokines such as IL-6 and TNF-α, obesity, particularly abdominal obesity, and rheumatoid arthritis. Though it is certainly too early to be certain, it is possible that

the positive associations between obesity-resistin and RA-resistin might be linked through the pro-inflammatory cytokines.(Bokarewa 05) Leptin has been reported as a down-regulator of resistin mRNA and protein expression, at least in murine models, indicating both positive and negative modulatory effects on its synthesis.(Kusminski 05) Even these points are in contention, however, as effects of some factors have been shown to be contradictory in mouse or human models and standardization of protocols has not yet occurred to control for such variation.

Action

Investigations into the activity and mechanisms of action of resistin originally focused on adipocyte secretion and links to insulin resistance. Following the discovery that this protein is also synthesized in cells affiliated with the inflammation process, focus shifted to this arena as well. Thus far the vast majority of the literature on the subject has focused on associations and correlations rather than molecular or cellular actions.

The incubation of cells with resistin or the infusion of exogenous resistin into rodent models has resulted in the inducement of insulin resistance through as-yet uncertain mechanisms. Studies have shown that administration of resistin in vivo and transgenic over-expression of resistin in mice results in insulin resistance.(Kusminski 05, McTernan 06) Steppan et al.(Steppan 05) may have taken the first steps towards identifying a mechanism by which resistin can help induce insulin resistance. The authors performed an in vitro experiment in which they exposed 3T3-L1 adipocytes to resistin and assessed insulin signaling. The authors report that pre-incubation of these cultured cells with resistin resulted in decreased insulin sensitivity in a time- and dose-dependant manner,

and further report that this effect is not the result of insulin receptor antagonism or the byproduct of serine phosphorylation of IRS-1. Tyrosine phosphorylation was reduced, however, by ~40%, reducing P13K activity in a similar magnitude and thus limiting GLUT4 translocation and glucose uptake. Their data suggests that the resistin effect occurs via the suppressor of cytokine signaling (SOCS) molecules, a family of agents known to decrease insulin sensitivity and increase IRS-1 degradation. The investigators reported increased SOCS-3 gene expression following resistin incubation and a marked reduction in IRS-1 protein content. The use of a dominant negative SOCS-mutant cell impaired the ability of resistin to alter insulin signaling, lending more support to the hypothesis that this family of gene products was implicated in the resistin signaling pathway. Finally, the investigators confirmed their in vitro findings in vivo, injecting rodents with exogenous doses of resistin and reporting a transient increase in SOCS expression followed by normalization 8 hours after treatment. This investigation represents a breakthrough in resistin research and is certain to be used as a springboard for further investigation.

Correlates

Resistin levels have been inconsistently correlated with body composition, disease states and inflammation in human and rodent models. Human studies have shown increased resistin expression in abdominal obesity and have found positive correlations between plasma resistin levels and body fat content. A review of recent studies have shown higher serum resistin levels in obese subjects as compared to lean counterparts, positively correlated with increasing BMI and visceral fat area. Increased protein

expression and secretion has been seen in adipocytes isolated from obese subjects as well. Importantly, a significant reduction in resistin has been reported following weight loss in human subjects, indicating that the linkage between the protein and body mass may be bi-directional.(Kusminski 05) An examination of obese non-diabetic men in Japan reported that resistin levels were higher in the obese than lean controls and serum resistin correlated positively with BMI. Cross-sectional analysis of the obese subjects did not reveal any significant correlations between resistin and measures of adiposity or insulin resistance, but a longitudinal examination of a subset of obese subjects found change in serum resistin to be positively correlated with change in BMI, fat mass, percent fat, visceral fat, glucose and insulin. The strength of these correlations was undiminished by controlling for age, gender and baseline BMI. The authors conclude that resistin is related to adiposity in humans and their results support additional investigation into the role of resistin in insulin resistance.(Azuma 03)

These findings have not been universal and reports of studies in both human and rodent models have reported no appreciable association between obesity and resistin. Investigators have examined serum protein levels and mRNA levels independently, attempting to find associations with markers of adiposity including BMI, percent fat and fat mass. While some have been successful, others conclude no such association exists. Kusminski et al.(Kusminski 05) suggest that these findings may result from a variety of factors including, but not limited to, methodological limitations associated with the development of protocols to assess a newly discovered molecule, age- and gender-related discrepancies in mRNA and protein levels and the potential impact of cell origin on the mRNA-protein

expression ratio.

The relationship between resistin and insulin resistance is similarly muddled. Though a means of inducing insulin resistance in cultured cells has been described and exogenous resistin injection has generated insulin resistance in rodent models, investigations attempting to link biological levels of resistin and insulin sensitivity have been inconclusive. Early examinations of resistin in rodent models found circulating resistin elevated in models of obesity and insulin resistance, correlating with insulin and glucose levels.(Rajala 04) Other investigators found no such relationship, finding both mRNA and plasma levels of resistin to be unrelated to insulin sensitivity.(Kusminski 05, Lee 05) This conflicting results mirror what has been reported in human subjects, where some investigations have correlated resistin with insulin resistance in vitro and in vivo. It has further been reported that resistin levels were elevated by 20% in Type II diabetes patients by more than one research team.(Fujinami 04, Kusminski 05, McTernan 03) Again, other studies have failed to find any association between resistin and markers of insulin resistance or sensitivity.(Kusminski 05) Based on the large degree of conflict in the literature it is impossible to definitively state the role of resistin with regard to insulin sensitivity. It is possible that resistin may have localized effects (acting in an autocrine/paracrine manner like TNF-α) or that the relationship of resistin with IR in a systemic fashion may be related to the ratio of resistin isoforms, not overall plasma resistin levels.

The revelation that resistin mRNA was also present in a number of cells involved in the immune response and inflammation led investigators to assess its role in these areas. Again, the results of these investigations have not always been in concordance.

Bokarewa et al.[Bokarewa 05] examined resistin activity in both rodents and rheumatoid arthritis patients with inflammatory-disease-free controls. They report that PBMC exposure to resistin resulted in the induction of the genes coding for a number of other pro-inflammatory cytokines (including TNF-α and IL-6), confirming that resistin is a pro-inflammatory cytokine in its own right. The authors also determined that injection of resistin into the knee joint of healthy mice resulted in inflammation beyond that of injection trauma and induced arthritis in the knee, confirming the finding from in vitro treatment of cells isolated from human blood. Their examination of resistin levels in the RA subjects versus controls found that while serum levels were unchanged between the two, the synovial fluid resistin content was significantly higher in RA patients as compared to controls, suggesting that the cells of origin may speak to the disposition of secreted protein. A more recent investigation into the serum levels of resistin in RA patients did find a significant increase in resistin and found it correlated to inflammatory markers c-reactive protein and TNF-α. Furthermore, resistin was positively correlated to erythrocyte sedimentation rate, a measure of RA disease severity. The authors indicate that their findings help cement the role of resistin in the inflammatory process and its up-regulation in rheumatoid arthritis despite similar studies failing to report this outcome. They suggest that previous studies have less-rigorously controlled for drug therapies and that as their subjects were not using TNF-α antagonists and had less-well controlled disease indicates a more native state and engenders greater accuracy and power.[Migita 06]

ADIPONECTIN

Synthesis

It is now well accepted that adipose tissue is more than simply a storage depot for

energy-rich free fatty acids and triglycerides. A variety of bioactive agents are synthesized and released from adipocytes, capable of exerting impact on the body both locally, systemically or body-wide. These active molecules have been termed adipokines and include leptin, plasminogen activator inhibitor-1 (PAI-1), adipsin, resistin, the "adipocytokines" TNF-α and IL-6, and adipocyte complement-related protein (Acrp30), also called adiponectin.[Chang 06, Oh 07]

Adiponectin is a collagen-like protein that is secreted by white adipocytes and circulates in the blood at relatively high levels (serum concentrations from 2-20 μg/mL) in healthy adults. This 247 amino-acid protein is the product of the most abundant gene transcript in adipose tissue and has four domains; an amino-terminal signal sequence, a variable region, a collagenous domain and a carboxyterminal globular domain. This basic structure can then undergo modification into trimers, hexamers (disulphide bond-linked trimers) or "multimers" of high molecular weight (HMW). The monomeric form of adiponectin is seldom seen under normal conditions and usually requires heat denaturation to be detected. It has been suggested that these differing forms are likely to have different effects on target tissue and that the ratio of forms may somehow be linked to systemic insulin sensitivity.[Bruun 03, Chang 06, Oh 07] The mechanisms that underlie the synthesis and secretion of adiponectin, as well as the driving forces behind formation of the differing isoforms remain unclear.[Chang 06]

The amount of circulating adiponectin has been inversely correlated with hepatic fat and obesity and increases in response to significant weight loss, suggesting the presence of a feedback inhibition in which increasing body fat reduces adiponectin

synthesis or secretion.[Ahima 06, Lafontan 06, Oh 07] It has been suggested that TNF-α may play a role in this relationship as increasing levels of the cytokine have been correlated with decreasing amounts of adiponectin.[Oh 07, Ruan 03] Diseases that feature extreme weight loss (particularly fat loss) or redistribution of adipose tissue such as HIV infection may have a deleterious impact on adiponectin levels as well. Though the reduction in circulating protein in these cases may be a byproduct of overall fat loss, some decrease of mRNA has been reported as well, suggesting a cellular effect as well as an overall tissue effect. Some gender and race-related relationships have been seen as well. Males generally have lower relative adiponectin levels than females and seem to express a lower ratio of HMW isoforms, and Caucasians have been found to have higher levels of adiponectin as compared to BMI-matched Indo-Asians and blacks.[Oh 07]

Action

Adiponectin receptors are expressed in adipose tissue, skeletal muscle and the liver, and it is in these tissues that the effects of adiponectin binding are examined. Two receptor isoforms, AdipoR1 and AdipoR2, have been identified in human and animal models. The AdipoR1 is ubiquitously expressed, though at highest levels in skeletal muscle, and has a high affinity for binding the globular (trimer) form of adiponectin while the AdipoR2 is predominately expressed in the liver and exhibits intermediate affinity for all forms of adiponectin. Both receptors are 7-transmembrane domain proteins, binding adiponectin to the C-terminus in order to activate signaling.[Lafontan 06] It is noteworthy that this binding relationship is counter to that seen in G protein-coupled receptors and that the AdipoR1 and AdipoR2 do not appear to act through a G protein

signaling pathway.

Binding of adiponectin to its receptor has been shown to activate a number of intracellular mechanisms including AMP kinase (AMPK), p38 mitogen-activated protein kinase (p38 MAPK) and PPAR-α. Pathways activated by adiponectin lead to fatty acid oxidation and glucose uptake, among others, and the binding of the different adiponectin isoforms activate differing signal transduction pathways.(Lafontan 06)

Investigators have reported that expression levels of adiponectin receptors are reduced in subjects with a family history of Type II diabetes and are correlated negatively with insulin resistance, at least in skeletal muscle.(Civitarese 04, Kadowaki 06, Lafontan 06) There are other indications that AdipoR1 and AdipoR2 mRNA levels are positively associated with obesity, fasting glucose, lipid levels and insulin resistance.(Bluher 06) This conundrum needs to be further investigated to determine which, if either or both, relationship is accurate. It is possible that there are post-transcriptional processes at work that reduce the number of receptors in the cell membranes of target tissue in diabetes or insulin resistance.

Binding of adiponectin to one of the two receptor isoforms activates a number of biochemical processes. The binding of the globular trimeric form of adiponectin to AdipoR1 activates p38 MAPK and Rab5, both potential activators and up-regulators of the GLUT4 translocation pathway particularly in skeletal muscle. Activation of this pathway increases the amount of glucose transporter protein inserted into the cell membrane and should, by extension, improve glucose flux. By definition this up-regulation improves glucose tolerance by clearing sugars from the blood into the muscle

or liver where they can be stored as glycogen. The activation of AMPK leads to increased fatty acid oxidation in the mitochondria of skeletal muscle and liver cells, preventing lipid deposition in both tissues. Activation of AMPK systems can also decrease gluconeogenesis in the liver and further improve glucose uptake from the circulation. Adiponectin also activates PPARα, which in turn can activate a number of genes involved in fatty acid uptake and oxidation in both liver and muscle tissue. In summary, adiponectin activates a number of pathways in skeletal muscle and liver tissue that serve to clear fatty acids and triglycerides from the circulation while insuring that depositions in the liver and muscle are limited by increasing fat oxidation. Additionally, adiponectin acts to increase the signal driving GLUT4 translocation from intracellular stores to the cell surface, aiding in clearance of glucose from the bloodstream. By removing substrates that decrease insulin signaling and by increasing glucose flux into the activated cells, adiponectin addresses insulin resistance on both fronts.(Kadowaki 06, Lafontan 06)

Correlates

As mentioned previously, adiponectin levels are high in lean, healthy subjects and are decreased in the obese or morbidly underweight subjects. Similarly decreased circulating levels have been seen in insulin resistant subjects, patients with Type II diabetes, coronary artery disease and gestational diabetes.(Bruun 03, Kadowaki 06, Lafontan 06, Oh 07) A study by Williams et al.(Williams 04) suggests that low adiponectin levels in the early stages of pregnancy indicated an increased risk of developing gestational diabetes as compared to those women with high levels of adiponectin. Other studies have shown that

a decline in adiponectin precedes hyperglycemia in a model of genetically induced insulin resistance(Hotta 01), that decreased levels of the adipokine are correlated with increasing HOMA-IR and fasting glucose in non-diabetic young adults(Steffes 04) and that high levels of adiponectin are associated with reduced risk of Type II diabetes development in multiple ethnic groups.(Spranger 03)

Injection of exogenous adiponectin has been shown to improve insulin sensitivity in animal models of diabetes and lipoatrophy. Intraperitoneal injection of full-length adiponectin resulted in a significant reduction of blood glucose in both wild-type and diabetic mice, indicating a role in glucose clearance in both normal and impaired glucose tolerance subjects.(Berg 07) Similar results were reported following systemic infusion of the globular trimer isoforms in mouse models of obesity and diabetes, though in this instance administration of the full-length protein was not reported as effective.(Yamauchi 01)

The over-expression of adiponectin in transgenic mice has been shown to be protective against the development of high-fat-fed-induced insulin resistance. In mice over-expressing adiponectin and engineered to be leptin deficient (ob/ob, a model of obesity and Type II diabetes) the adipokine was protective against weight gain and ameliorated insulin resistance following a high fat diet. The crossed mice over-expressing adiponectin were also seen to have an increased insulin response to glucose, perhaps indicating a protective effect of the adipokine on β-cell function.(Yamauchi 03)

A cross-sectional examination of adiponectin levels in a study of health professionals(Pischon 04) found that subjects with high levels of adiponectin had a significantly reduced risk of heart attack, even following adjustment for cholesterol, BMI

and medical history. Adiponectin has been positively correlated with HDL-C while being inversely correlated with triglycerides, suggesting that the enhanced lipid clearance and prevention of fat deposition in muscle and liver by adiponectin may help limit or prevent atherosclerosis.(Oh 06) The findings of Yamauchi et al.(Yamauchi 03) support this hypothesis. A transgenic mouse model of atherosclerosis crossed with a line over-expressing adiponectin suffered significantly smaller atherosclerotic lesions that control mice of the disease model. This effect was seen without significant differences in plasma glucose, body weight or lipid profile, suggesting a direct effect on progression of the disease. Reports of in vitro work supports this possibility, as adiponectin appears to suppress the transformation of macrophages to foam cells, reduce monocyte adhesion to the endothelium and reduce macrophage cytokine production, all components of the development of vascular disease.(Oh 06)

In addition to the use of adiponectin as an exogenous or therapeutic agent, adiponectin has also been investigated as a target of other therapies. The administration of a number of different thiazolidinedione drugs (TZD) has been show to result in increased serum adiponectin, indicating that this is a generalized effect of the drug class and not limited to a single drug. Administration of metformin did not result in an increase in adiponectin, suggesting that the elevation seen with TZD treatment was not due to improvements in glycemic control but a direct effect of the drug. Though the pathway by which this effect occurs is unknown, increases in adipocyte adiponectin protein content suggests that TZD administration might increase synthesis and secretion of the adipokine. Increases in gene expression following troglitazone (a TZD) further

supports this possibility.[Kadowaki 06, Oh 06, Pajvani 04, Phillips 03]

The ratio of HMW/total adiponectin seems to be of some import in terms of insulin sensitivity. A volume of work out of the Scherer lab[Pajvani 04] has shown that the HMW isoforms of adiponectin has a higher predictive strength for insulin sensitivity, increases the recovery of insulin sensitivity following administration of a TZD drug regimen and has been shown to result in dose-dependant improvements in blood glucose when given exogenously to genetic knock-out mouse models (whereas the lower weight isoforms did not improve glucose levels). Other investigators have corroborated these findings, suggesting a significant role for this isoforms in adiponectin-mediated insulin sensitivity improvement. Glucose tolerance has been better correlated with levels of the HMW isoforms[Fisher 05], weight loss has been seen to enhance the HMW/MMW adiponectin ratio[Bobbert 05] and reduce LMW levels and mutations in the adiponectin gene leading to alterations in HMW production have been associated with Type 2 diabetes.[Lafontan 06, Kadowaki 06, Waki 03]

It has been suggested by several authors that TNF-α plays an inhibitory role on adiponectin, either decreasing synthesis or secretion or perhaps having some reducing effect in the circulation. An in vitro study by Bruun et al.[Bruun 03] reported that TNF-α and IL-6 plus soluble receptors induced a decrease in adiponectin mRNA levels in subcutaneous abdominal adipose tissue from healthy women (mean BMI = 25). This study also featured a clinical examination of lean and obese men, assessing among other variables, adiponectin and TNF-α. Though no significant differences were seen in TNF-α levels between the obese and lean subjects, the obese men had significantly lower

levels of adiponectin while exhibiting increase insulin resistance, increased fat mass and increased IL-6. Interestingly, the plasma level of adiponectin in the obese subjects inversely correlated with TNF-α levels while this relationship was absent in the lean control group. The lack of a significant difference between the two subject pools may be due in part to the relatively small sample size (10 lean, 19 obese), but even if the groups did not differ in circulating TNF-α, the increased fat mass of the obese group suggests an increase in TNF-α as discussed above, and the autocrine/paracrine action of the cytokine could easily be responsible for adiponectin deficit.

The findings of a 2005 study by Degawa-Yamauchi et al.[(Degawa-Yamauchi 05)] rebuts this finding and conclusion, suggesting that the impact of TNF-α on adiponectin levels is minor. The investigators examined the impact of TNF-α and dexamethasone on adiponectin mRNA in subcutaneous and omental adipocytes from subjects with a wide range of adiposities. They found a significant negative correlation in mRNA with BMI in subcutaneous adipocytes but no such correlation in omental cells. A modest decrease ($7.4 \pm 1.2\%$) in adiponectin was reported in subcutaneous adipocytes following TNF-α exposure but no effect was seen on omental cells. Dexamethasone, a glucocorticoid, similarly inhibited adiponectin release in subcutaneous, but not omental, adipocytes. From these results, the authors refute previous findings that TNF-α exerts a great impact on adiponectin synthesis and release and suggest that reported deficits of adiponectin in obese patients might be due to increased degradation or use of the protein. They do allow that it is possible that they did not see alteration in adiponectin synthesis or secretion in the cells harvested from obese subjects because they may already have been maximally

inhibited via autocrine/paracrine effects at the time of removal, and the exogenous dosing of TNF-α was unable to further inhibit the process.

Another avenue was investigated by Simons et al.[(Simons 05)] in their 2005 paper. The authors examined the impact of pro- and anti-inflammatory cytokines on leptin and adiponectin secretion in another in vitro experiment. Instead of using mature omental and subcutaneous adipocytes as above, they isolated preadipocytes for culture and experimentation. When cultured in adipogenic conditions, these cells matured into normal adipocytes and secreted leptin and adiponectin, increasing gradually as the maturation process advanced. Those preadipocytes isolated from lean donors secreted four times the adiponectin as the cells isolated from obese donors suggesting a significant effect of obesity on future adiponectin secretion even removed from the milieu of changes wrought on the system as a whole. That such an impact is observed in immature cells after maturation may hold significant value for future investigations. Additionally, this study brought into focus another clear point. The addition of anti-adipogenic agents such as TNF-α totally prevented adipogenesis and completely blocked adiponectin secretion. It is known that TNF-α inhibits maturation of preadipocytes[(Warne 03)], and it may be via this pathway that the cytokine decreases adiponectin levels in the obese. On a per-cell basis TNF-α's impact on adiponectin production and release may be moderate as shown by Degawa-Yamauchi study, but by limiting the number of mature cells available to produce adiponectin the reduction in secretion may be magnified. It remains noteworthy, however, that the Simons study did display a four-fold difference in mature adipocyte production of adiponectin absent any extracellular agents.

In addition to improved adiponectin secretion following healthy weight loss, a number of investigations have been made into the impact of exercise training on adiponectin expression and signaling. The results of these investigations have been varied and diverse. Oberbach et al.(Oberbach 06) reported a significant increase in adiponectin levels in subjects with impaired glucose tolerance or Type II diabetes following a 4 week combined aerobic/resistance training intervention. Regression analysis indicated that this increase in adiponectin was related to a decrease in fasting blood glucose and improvement of insulin sensitivity. Subjects with impaired glucose tolerance or Type II diabetes had significantly lower adiponectin levels at baseline as compared to normal glucose tolerance controls, and following the intervention the authors reported a near normalization of adiponectin levels. Fatouros et al.(Fatouros 05) reported that adiponectin increased in elderly subjects undergoing a high-intensity 6-month resistance training regimen, and that while low-intensity and moderate-intensity training programs run concurrently improved measures of body fat content they did not impact adiponectin or leptin levels. The percent adiponectin increase was related to the percent BMI decrease in the high-intensity exercise group, maintaining the expected relationship.

A study published by Hara et al.(Hara 05) in the 2005 examined the impact of aerobic training (8 weeks) or combined aerobic/resistance training (5 months) on body composition, functional performance and adiponectin in a group of young obese men. The authors report that fat mass and ventilatory threshold were significantly improved in both exercise groups versus untrained controls. Furthermore, weight, BMI, percent fat,

VO_{2Max} and power were all improved in the combined training group. Adiponectin was not found to be significantly different in any of the three conditions. It was noted, however, that there was a significant correlation between the change in fat mass and the change in adiponectin across the subjects, indicating that body composition is a key component of adiponectin change, not the exercise itself. This finding coincides with that of the Fatouros study above as the group with the greatest change in body composition had the significant change in circulating adiponectin.

Boudou et al.[(Boudou 03)] published a study of the impact of exercise and body composition change on the adiponectin levels in a small sample of middle-aged men with Type II diabetes. They reported significant change in visceral (omental) and subcutaneous fat following an 8-week cycling training program, as well as improved insulin sensitivity and increased leg muscle mass. No significant change in body weight or adiponectin was reported, counter to what was seen in the Fatouros and Hara studies mentioned previously. The authors did report a significant negative correlation between change in adiponectin and change in body weight in the trained group, but not with insulin sensitivity or adiposity variation. These represent confounding results, excepting the correlation between adiponectin and weight change, though it is possible that other significant relationships weren't seen because of the limited power of a 16-subject (8 control, 8 intervention) study.

A larger cohort (51 subject) study by Marcell et al.[(Marcell 05)] reported similar findings, however, using a similar subject characteristics. Subjects were divided into control, low-intensity and moderate-intensity exercise groups. The exercise program was

not regimented, allowing subjects to select the activities they preferred, but it was monitored in an effort to validate intensity. Modest improvements in body composition, fitness and insulin sensitivity were reported, without change in adiponectin or c-reactive protein levels, and the improvement in insulin sensitivity was credited to the change in body fat.

Following a 4-week aerobic training intervention in insulin resistant or Type II diabetic subjects investigators in 2006 reported alterations in adiponectin levels and adiponectin receptor expression.(Bluher 06) The authors of this study reported that prior to their intervention adiponectin was negatively associated and both the AdipoR1 and AdipoR2 mRNA levels were positively associated with obesity and insulin resistance. Following the training intervention, both adiponectin and receptor mRNA levels increased in skeletal muscle, suggesting a possible role in the improvement of insulin signaling following exercise. Furthermore, receptor mRNA levels increased transiently after long bouts of exercise (though it did not alter adiponectin levels), providing additional support for this possibility.

EXERCISE

Types of exercise

Aerobic exercise is generally accepted to include all forms of brisk physical activity that induce increased respiratory and cardiopulmonary activity, particularly when sustained over a period of time. The intent of voluntary aerobic exercise is to improve or maintain cardio-respiratory health, decrease weight or reduce disease risk. Arguably the most common form of voluntary exercise, aerobic exercise includes a range of activities such as running, swimming, bicycling and the like. Resistance exercise focuses on the

voluntary activation of skeletal muscles to move some load, either body mass or external weights, or overcome a resistance such as that provided by a "weight machine" or exercise bands. Once the purview of certain athletes and body builders, resistance exercise has been embraced by a wide range of people and is endorsed as a positive activity for the public health.(Winett 01)

Impact of aerobic exercise on insulin resistance and inflammatory disease

The beneficial effects of aerobic training and exercise are well documented and have been disseminated through virtually every form of media. Of specific interest to the current work is the relationship between exercise and insulin resistance and/or inflammatory disease. As previously discussed, obesity has been correlated with both inflammatory disease and insulin resistance, thus the reduction of obesity secondary to aerobic exercise reduces risk for development of these disorders. More specifically, Petersen and Pedersen(Petersen 04) reinforce the protective effects of regular exercise in reducing "all-cause" mortality, primarily by reduction of cardiovascular disease and type 2 diabetes risk. They suggest in their review of the topic that sustained regular exercise reduces the chronic low-grade inflammation seen in these disease states, down regulating production of TNF-α and other anti-insulinemic cytokines by reducing adipose tissue mass and stimulating IL-6 production via a TNF-independent pathway. Originally considered a cytokine linked to insulin resistance, the authors indicate that IL-6 synthesized in the muscle during and after exercise stimulates the appearance of anti-inflammatory cytokines in the blood, inhibits the production of TNF-α and enhances fat oxidation and lipolysis. Thus, the reduction of low-grade inflammation via even light

aerobic exercise such as walking may play a role in improving insulin sensitivity and reducing disease complications in inflammatory disorders. This conclusions are corroborated by the findings of Reynolds et al[(Reynolds 02)] and Straczkowski et al[(Straczkowski 01)] who independently found reductions in TNF-α and improvement in insulin sensitivity in subjects undertaking an aerobic exercise regimen.

Marcell et al[(Marcell 05)] reported improvements in insulin sensitivity following an aerobic training intervention, and that this improvement was not related to changes in CRP, an inflammatory marker, or adiponectin levels. Regression analysis of the data generated in this investigation confirmed that the change in insulin sensitivity was significantly related to the change in body fat content. The investigators expected to see a decrease in plasma CRP levels secondary to decreased body fat as they noted IL-6, a potent regulator of CRP, is strongly expressed by adipocytes and with decreased adiposity it was anticipated that IL-6, and therefore CRP, levels would decline. Thus they were surprised to see no changes in CRP levels despite a decrease in body fat, and no relationship between change in body fat or insulin sensitivity and CRP. This may be explained in part by the up-regulation of non-adipose tissue IL-6 suggested in the Petersen and Pedersen article cited above.

Interestingly, some aerobic exercise can transiently increase insulin resistance, persisting for up to 48 hours following the exercise bout. Excessive eccentric contractile exercise, such as running down hill or down stairs, or extremely prolonged exercise such as marathon running induces muscle cell damage. Decreased insulin receptor, IRS-1, PI3K and Akt phosphorylation are all evident in muscle cells following these activities,

leading to decreased insulin action within the cell and reduced GLUT-4 translocation and glucose uptake. Furthermore, TNF-α secretion is increased in the 48-hour period following these forms of exercise, increasing the inhibition of insulin signaling. These effects are, however, temporary and the persistent effects of exercise such as TNF-α reduction, insulin signaling and GLUT-4 expression increase outweigh the negative effects of this form of exercise.(Kirwan 03)

RESISTANCE EXERCISE

Principles

Resistance exercise is based on a principle of overload and adaptation. The basic goal of this form of exercise is to stimulate muscle activity by providing a modest overload of the muscles involved in a movement. Repeated and progressive overload (either in terms of resistance, frequency of movement or duration) stimulates a complex string of physiological adaptations that result in increased strength or muscle mass. This increase strength or mass is the adaptation to the exercise regimen and occurs during the recovery time between training sessions.(Winett 01)

There are indications that there is a threshold level of overload necessary to stimulate adaptation. This threshold is based on previous levels of activity, either of daily life or exercise sessions, and some researchers hypothesize that any additional volume of overload or exercise beyond that threshold is both unnecessary and potentially harmful. This potential for harm comes from the increased possibility of stress-induced injury and increased recovery time due to additional immunosupression.(Smith 00)

These researchers recommend that beginners or advanced trainees exercise particular regions or muscle groups twice a week. There is some evidence that a single

bout of training per week can have a beneficial effect, though likely of a lesser magnitude than a two bout per week regimen. Conversely, there is little evidence to support escalating the regimen to three bouts per week for a given major muscle group.(Feigenbaum 99) In each exercise bout it is recommended that the trainee perform a single "set" of movements against the prescribed resistance. Each movement consists of a concentric phase (moving the resistance) and an eccentric phase (returning the resistance to its initial point). One cycle through each phase is called a "repetition", and a group of repetitions, generally with a brief pause between each, is called a "set".(Feingenbaum 99, Winett 01) Following these recommendations, a trainee would perform a single set of each exercise, targeting a specific major muscle group, twice a week with bouts separated by 2-3 days, to achieve positive physical adaptation to the progressive overload.

The intensity of resistance exercise is an area of significant variability. Some participants prefer working with relatively heavy weights/resistances for a lower number of repetitions while others espouse a regimen of reduced weights/resistances for a higher number of repetitions. Research findings recommend only that moderate to high intensity exercise is most likely to result in positive adaptations, but a precise "intensity level" for optimal outcome has note been elucidated. It is noteworthy that intensity does not indicate force or speed of movement, but the degree of effort required to complete an activity. Both excessive force (as indicated by the amount of weight being moved or the force with which it is moved) and unduly rapid cadence can decrease the efficacy of the exercise and engender potential injury to the trainee. Recommendations are that a particular repetition of an exercise movement should take approximately 8 seconds – 4

seconds in the concentric phase and 4 seconds in the eccentric phase – and that each exercise be performed in sets of 6 to 10 repetitions. A proper amount of resistance is that at which performing repetitions beyond the prescribed set number is not possible.[Winett 01]

Health benefits

Though aerobic exercise has long been advocated and promoted for improving the public health, research has repeatedly demonstrated that resistance exercise offers significant quality of life improvement and the potential for disease reduction. Resistance exercise studies have shown favorable changes in risk factors for:

- Osteoporosis[Layne 99];
- Cardiovascular disease;
- Cancer; and
- Diabetes[Winett 01];

Resistance exercise has also been seen to be effective in combating back pain and injury risk[Carpenter 99, Pollock 99, Layne 99], improving quality of life and functional ability in the elderly or infirm, increasing mobility and balance and reducing overall mortality risk.

Impact of Resistance Exercise on Obesity

Credit for the exercise-related reduction of adipose tissue mass and incidence of obesity has traditionally been assigned to aerobic activities such as those discussed above. Some evidence exists, however, indicating that resistance training can have a beneficial impact on body composition via adipose mass reduction even in the absence of an aerobic exercise component. In their study of sedentary obese men, Banz et al[Banz 03] found a significant reduction in waist-to-hip ratio and total body fat without a significant change in body weight following a resistance training intervention. The reduction of adipose fat mass following resistance training has also been verified in both adults and

children in the absence of a concurrent aerobic training regimen.[Benson 08] A reduction in central or visceral fat has also been noted following resistance training and it has been suggested that continued fat loss or fat loss maintenance from diet and exercise interventions is enhanced through inclusion of resistance exercise in that regimen.[Winett 01]

Impact of Resistance Exercise on Inflammation

Bautmans et al[Bautmans 05] examined the impact of a resistance training regimen on cytokine and heat shock protein (Hsp) levels in an elderly population. They stated that chronic, low-grade inflammation is related to the development of sarcopenia and that intensive resistance training could be used to combat the strength deficit seen in the elderly. Given that exercise training elicits a significant release of TNF-α and IL-6, mediators of inflammation, but does not result in muscle wasting as seen in other inflammatory conditions, the authors hypothesized that changes in Hsp70 expression may be involved in protecting muscle from wasting and allowing positive adaptation and strength gains. Following a 6-week intervention the authors reported increases in strength and functional ability among their subject pool. They also found that TNF levels were unchanged by the exercise program but a tendency of decreased IL-6 levels and alterations in the expression of heat shock proteins were reported, in agreement with their hypothesis. Basal levels of Hsp70 post-training were decreased compared to the untrained state, but in conditions of heat shock (similar to that encountered during a bout of exercise or trauma/infection) Hsp70 expression was significantly greater following the training intervention. The authors concluded that the tendency for IL-6 decrease and the alteration in Hsp70 expression and activity might reflect an adaptive mechanism that

reduces basal inflammatory levels and lends greater cellular protection to pathological situations in resistance trained individuals.

A report published in 2002[(Conraads 02)] examined the impact of a combined aerobic and resistance training intervention on cytokines and cytokine receptor levels in patients with coronary heart failure (CHF). Both systemic and local inflammation are implicated in the pathogenesis and progression of CHF and circulating levels of cytokines and receptors have gained prognostic significance. Twenty-three patients with stable CHF due to coronary artery disease (CAD, n=12) or idiopathic dilated cardiomyopathy (IDCM, n=11) were enrolled in a non-randomized exercise intervention study. Eighteen age- and gender-matched patients with similar disease severity attending an out-patient clinic served as untrained controls. The training intervention consisted of a 3 session per week program that included 30 minutes of resistance training, 20 minutes of aerobic training and 10 minutes of warm-up and cool-down protocols. Functional ability, submaximal workrate and maximal workrate were improved following the 4-month training intervention. The investigators did not find a significant change in TNF-α or IL-6 levels from baseline values in either subgroup of patients. They did report, however, a decrease in soluble TNF-α receptor 1 (sTNFR1) and soluble TNF-α receptor 2 (sTNFR2) levels in the CAD patients. The receptor levels in the IDCM group were not significantly different from the CAS group at the onset of the intervention, but there the difference in mean receptor levels did approach significance ($p = 0.20$ and $p = 0.09$, respectively), suggesting a possibly heightened inflammatory state in the CAD group. TNF-α and sTNFR2 were significantly negatively correlated with peak oxygen uptake and maximal

workrate in the entire sample. In the CAD subgroup only, TNF-α and sTNFR1 change was significantly correlated with change in work efficiency, while TNF-α and sTNFR2 change correlated with change in maximal workrate. Though the study results do not show a reduction in inflammatory markers, it does indicate a reduction in receptor levels, suggesting a decrease in the inflammatory cascade activity. The authors state that their study indicates an anti-inflammatory effect of combined aerobic and resistance exercise, particularly in patients with inflammatory disease, and that improvements in work ability are related to this anti-inflammatory effect. The authors further suggest that additional study is required to accurately assess the impact of training on cytokine levels. They indicate that the commercially available ELISA assays for TNF-α are unable to distinguish between free and bound TNF-α and that the CHF patient pool has a wide variability in cytokine levels. As such, they cannot exclude the possibility of a decrease in free, bioactive TNF-α levels in their study and indicate that a much larger sample size is required to elucidate the impact of their combined exercise regimen on this cytokine.

Giannopoulou et al.[(Giannopoulou 05)] investigated the impacts of diet, exercise or combined diet and exercise on adipokines and cytokines in their 2005 study. A group of 33 postmenopausal Type II diabetic women were randomized into diet alone (D), exercise alone (E) or diet plus exercise (D+E) groups for a 14-week intervention. The exercise program consisted of 60 minute walking sessions performed three to four times per week. Following the intervention the authors found a significant decrease in c-reactive protein in all three groups and decrease in leptin levels in the D and D+E groups. The D and D+E groups exhibited weight loss while the E group did not, likely because of

the very modest intensity of the exercise intervention. Resistin, adiponectin and TNF-α levels did not change in any of the intervention conditions. From these findings the authors concluded that a typical exercise program with lifestyle modification induced few adipokines/cytokine changes in their population, suggesting that dramatic weight loss or clinical intervention is required to elicit these changes.

The body of work assessing the impact of exercise on markers of inflammation and related adipokines/cytokines offers few solid conclusions, though some evidence exists that resistance exercise does reduce appearance of some markers.(Olson 07) It appears that short-term interventions have little or no impact in cytokine levels, though interestingly it does appear that the functional ability of these cytokines may be altered by up-regulation of protective factors such as Hsp or the down-regulation of receptors required for TNF activity. It has been suggested that in order to achieve significant impact on basal adipokines/cytokine levels a long-term training program is required, preferably one that involved lifestyle modification and diet as well.

Impact of Resistance Exercise on Insulin resistance

Exercise and weight loss are frequently recommended as key elements in the treatment of diabetes and insulin resistance. A number of investigators have assessed the impact of various exercise regimens on measures of interest in this population.

Aerobic exercise is generally expected to result in weight loss, improved body composition and lipid profile and an improvement in general overall health. A 2002 study by Kang et al.(Kang 02) examined the impact of aerobic training and lifestyle education (LSE) on insulin resistance in obese adolescents. Subjects were randomized

into 3 groups - LSE only, LSE plus medium-intensity exercise and LSE plus high-intensity exercise. Following an 8-month intervention the authors reported that the subjects engaging in exercise had favorable changes in a number of lipid profile elements, but they did not report significant changes in weight, body fat, plasma insulin or glucose. Their study may have been limited by the age, gender and racial makeup of their sample and some degree of variation from expected effort levels in the exercise intervention (particularly the high-intensity group).

Nassis et al.[(Nassis 05)] performed a similar study, assessing the impact of a 12-week aerobic exercise intervention on measures of body composition and insulin sensitivity in overweight and obese girls. Following the intervention these investigators reported a significant improvement in insulin sensitivity (measured by OGTT and HOMA-IR) among the exercise cohort without appreciable change in body weight, percent body fat, serum adiponectin, IL-6, CRP or other inflammatory markers. The exercise program employed by the authors involved individual warm up activities followed by modified group games (such as volleyball, handball or basketball) performed while wearing heart rate monitors to track effort. An increase in lower-limb fat free mass was also reported and the authors suggest that an increase in skeletal muscle and an improvement in glucose clearance into skeletal muscle may account for the improved insulin sensitivity witnessed, absent changes in the other parameters. Similar findings were also reported by DiPietro et al.[(DiPietro 06)] in their study of the effect of aerobic training of varying intensity on insulin sensitivity in older women. Exercise dose was controlled (4/week, 300kcal/session) and resulted in no significant changes in weight or body composition.

Insulin sensitivity was significantly improved in the high-intensity group, suggesting an intensity association or threshold for improvement, at least in this population.

Reynolds et al[(Reynolds 02)] investigated the impact of resistance training on insulin-mediated glucose disposal and TNF-α levels in a small sample study in 2002. Eleven subjects were recruited into a 4-month supervised progressive resistance-training program. Prior to and following the intervention all subjects were assayed for insulin resistance (via hyperinsulinemic euglycemic clamp protocol), plasma TNF-α, sTNFR1 and sTNFR2. Additional variables such as anthropometric measure, maximal oxygen uptake (VO_{2Max}) and DXA body composition were assayed as well. Following the intervention subjects displayed increased lean body mass and increased strength (as assessed by single repetition maximum exercise) without overall change in body mass. No change was reported in any measure of blood pressure or VO_{2Max}. The authors found a significant improvement in glucose disposal rate after completion of the exercise training. Fasting plasma insulin was unaffected by the intervention, but fasting plasma glucose was significantly increased. TNF-α, sTNFR1, sTNFR2 and the ratio of sTNFR1:sTNFR2 were statistically unchanged over the course of the study. There was a tendency for TNF-α to decrease but this did not reach significance ($P = 0.118$). No correlations were found between TNF-α levels or change and insulin-mediated glucose disposal. Similarly, no relationships were found between receptor levels or changes and glucose disposal. This study indicates that resistance training can improve insulin signaling as measured by glucose uptake and it suggests that this improvement is independent of any changes in the TNF-related variables. The investigators allow that

regional reductions in TNF-α, such as in skeletal muscle, could impact glucose disposal without alteration of the plasma TNF-α levels. Furthermore, an acknowledged limitation of this study was the small number of participants. It is possible that with a larger sample size the tendency for TNF-α decrease may have reached significance. Regardless of TNF metabolism related changes, this study soundly endorses resistance training as a means of improving glucose disposal.

Fenicchia et al.[(Fenicchia 04)] used a short 6-week intervention to examine the impact of resistance training, both acutely and chronically, on glucose control. Briefly, they determined that an acute bout of strenuous resistance training could have a significant impact on glucose control and lead to a reduction in plasma glucose for up to 24 hours after the exercise bout. The authors did not report a significant impact on glucose clearance over the course of the intervention, but it has been put forth that training regimens of such short duration may be insufficient to achieve lasting effects. There were no significant changes in weight, percent fat or lean body mass following the intervention, suggesting that the duration was insufficient to achieve these adaptations.

A 16-week study by Ibanez et al.[(Ibanez 05)] found more expected changes among their subjects. A small sample of older males with Type II diabetes were recruited and underwent a supervised 16-week progressive resistance training intervention, meeting twice a week for approximately 1 hour per session. Significant gains in strength as assessed by 1RM testing were seen during the training. Following the intervention body weight was unchanged but percent body fat, subcutaneous abdominal fat and visceral abdominal fat all significantly decreased, indicating an increase in lean body mass.

Fasting plasma glucose decreased and insulin sensitivity, as assessed by a frequently-sampled IV glucose tolerance test, improved over the course of the intervention. Though the authors admit limitations in their study (small sample size and lack of a true control group), they are confident their results are valid and indicate a clear improvement in insulin sensitivity following an effective progressive resistance training intervention.

When resistance training is combined with weight loss[(Dunstan 02)] or aerobic exercise[(Cuff 03)] in patients with Type II diabetes the effect is a significant improvement in whole-body glycemic control when compared with weight loss only and aerobic exercise only, respectively. In the Dunstan[(Dunstan 02)] report, subjects undergoing a resistance training regimen while adhering to a healthy eating plan lost a similar amount of weight and fat mass as diet-only group but also gained a significant amount of lean body mass over the diet-only subjects. Additionally, though there were no significant differences in fasting glucose, fasting insulin or serum lipids, the exercise + diet group saw a greater reduction in glycosylated hemoglobin (HbA_{1c}, a measure of glycemic control where lower values indicate more normal glucose homeostasis) than they diet-only group. This suggests some degree of improvement in overall glucose homeostasis in the absence of significant over changes in insulin and glucose. In the study run by Cuff et al.[(Cuff 03)] subjects were randomized into aerobic exercise (Ae), aerobic exercise plus resistance training (Ae + RT) or control groups. Both exercise groups had significantly decreased subcutaneous and visceral adipose tissue and increased muscle density, though the Ae + RT group was found to have a significantly higher increase in muscle density over the Ae group as well. This increase was associated with improved glucose clearance, supporting

the authors' hypothesis that a combined exercise regimen would offer greater improvement in glucose clearance than aerobic exercise alone.

An 8-week circuit training regimen (a combination of aerobic and resistance training elements) was similarly found to improve strength while decreasing skinfolds, percent body fat, waist-to-hip ratio, glycosylated hemoglobin and fasting blood glucose in patients with Type II diabetes. This study suggests that even short-duration training regimens, if sufficiently intensive, can have a positive impact on the health of diabetic patients.(Maiorana 02)

In summation, it is clear that intensive exercise is associated with improved insulin sensitivity and glucose homeostasis. The means by which this improvement occurs, and the preferred modality of exercise are less clear, but evidence supports the inclusion of progressive resistance training in the exercise prescription for diabetic or insulin resistant patients. Though not exhaustively examined, it does not appear that any alteration in cytokines or adipokines is involved in this improvement, suggesting differing paths of action. It is worth noting that the exercise programs used in the research detailed above may have been of insufficient length to engender the adaptations necessary to see change in cytokines and adipokines, but that is speculation which must be addressed by future investigations.

Impact of Resistance Exercise on Rheumatoid arthritis

Several examples of the benefits of resistance exercise for patients with RA have already been presented above. However, further discussion of the impact of weightbearing exercise on inflammatory factors in RA patients is warranted. A pair of

studies from 1996[Rall/Meydani 96, Rall/Roubenoff 96] examined the impact of resistance training in aging subjects and rheumatoid arthritis patients. In the parent study, 24 subjects (8 healthy young adults, 8 healthy elderly adults and 8 adults with rheumatoid arthritis) were recruited into a 12-week resistance exercise intervention. Six healthy elderly subjects served as a non-resistance exercise control group. The investigators examined protein degradation, TNF-α, growth hormone, glucagon, IL-6 and a number of other measures of inflammation and cytokine production. The authors reported no significant alterations in any measure of immune response or markers of inflammation following the intervention. They did report that adults with rheumatoid arthritis did exhibit increased rates of protein breakdown than their healthy counterparts, though this relationship was not in evidence in RA patients undergoing methotrexate therapy. This increased protein catabolism was not evident following the strength training intervention, suggesting that some adaptation to training attenuates this breakdown. The investigators further reported that regression analysis showed that TNF-α levels were positively correlated ($r = 0.47$, $P = 0.01$) with this catabolism. No rationale for the oblivation of this catabolism is put forth, though it is possible (given the information related previously on the decrease in sTNFR levels following training) that even if TNF-α plasma levels are not altered, the activity of the cytokine may be impacted by the training regimen. The authors note that, if nothing else, their investigation lends support to the thought that patients with well-controlled rheumatoid arthritis are able to tolerate progressive resistance training and that positive outcomes on strength and muscle mass are obtainable.

CHAPTER III: RESEARCH METHODOLOGY

HYPOTHESES AND INTENT

The present study was implemented to test the primary hypothesis that a 16-week, progressive, individualized, intensive strength training program in RA patients taking Remicade™ would improve strength, body composition, disease activity, physical function, pain and quality of life outcomes as compared to RA patients on Remicade™ without the strength training program.

The second purpose of this investigation and the focus of this dissertation was to assess the degree of association of several factors implicated in IR on the level of systemic insulin resistance in RA patients currently undergoing a prescribed Remicade™ treatment regimen. A further intent of this study was to examine the changes in body composition, adiponectin, resistin, TNF-α, glucose and insulin following a 16-week progressive resistance training regimen in rheumatoid arthritis patients treated with Remicade™, testing the hypothesis that lean mass will increase while weight and fat mass will decrease, leading to a concomitant increase in adiponectin with decreases in resistin, TNF-α and insulin. Finally, it was hypothesized that this effect would be seen only in those patients undergoing the exercise intervention, and that these variables would remain unchanged in the control condition.

STUDY DESIGN

The STaR study was a partially randomized controlled trial, with all subjects self-selected for Remicade treatment. Following initial testing subjects were randomized to exercise intervention (detailed later) or control treatment in a 2:1 ratio to allow clear characterization of any exercise effect. All subjects maintained their Remicade treatment

throughout the course of the trial and continued to receive normal medical care from their physician/rheumatologist. Subjects were encouraged to continue their prescribed course of therapy while participating in the study.

Subject Eligibility and Recruitment

Adult rheumatoid arthritis (RA) patients, as determined by American College of Rheumatology (ACR) criteria and diagnosed by a certified physician, were eligible for inclusion. Potential subjects had to be Functional Class I or II according to American Rheumatology Association (ARA, now ACR) standards, on stable Remicade therapy for a minimum of four months and anticipating remaining on therapy. Criteria for exclusion included significant non-arthritis health conditions including heart disease, high blood pressure, diabetes, osteoporosis or cancer contraindicating exercise. Additional exclusion criteria included need for canes or other assistive devices and intent to leave the region prior to the end of the trial. Subjects who had a body mass index (BMI) of 40 or greater, or who had participated in a previous aerobic conditioning or strength training program of 150+ minutes a week were also excluded from participation.

Potential subjects were recruited through media, direct mailings, materials presented in physician's office and through direct recruitment with participating rheumatologists and the project director. Financial compensation was not offered to potential subjects, and no promises of disease improvement were made. One hundred RA patients were screened and 33 were determined to be eligible. Primary exclusions were for transportation difficulties, part-time residency or insufficient time on Remicade. Written consent from each subject's rheumatologist or primary care physician was

required and written informed consent was given by the subject prior to entry into the study. One of these 33 did not pass the study physical exam and 2 did not complete baseline testing (1 because of family commitments and the other because of infection), leaving 30 patients to be randomized into the trial.

Subject Population

Of the 30 people randomized into the study, 24 subjects (19 women and 5 men) completed the assessments. Twenty were originally randomized to exercise and ten were randomized to control treatment, with 16 exercisers and 8 controls completing the assessments. Subject ages were between 29 and 75 (mean 51 ± 12.8 years) with disease duration ranging from 2.4 to 39.0 years (mean 14.0 ± 10.2 years). The majority of the subjects were Caucasian (95.8%), including 16.7% of Hispanic ethnicity. Three-quarters of the subjects were employed and nearly half (41.7%) had completed college.

One subject had arthroplasties in both weight-bearing and nonweight-bearing joints. Four of the 24 subjects who completed the trial were taking prednisone along with the Remicade therapy, 21 were taking methotrexate, 13 were taking non-steroidal anti-inflammatory drugs (NSAIDs) and 3 were taking other disease modifying anti-rheumatic drugs (DMARDs). Seven patients in the exercise group were taking a calcium supplement.

SUBJECT ASSESSMENT

Subjects underwent assessments and testing at baseline, 8 weeks (mid-intervention) and 16 weeks (post-intervention). Baseline and post-intervention testing was the most rigorous and time-consuming, requiring approximately six hours divided

over three to four visits. The mid-intervention assessment consisted of only questionnaires and required approximately one hour to complete.

Questionnaires and Surveys

Subjects completed several questionnaires and surveys over the course of the trial during their scheduled assessment visits at each testing time point. In general terms, these assessments were categorized as evaluating Health and Disease Status, Diet and Exercise or Mental Health and Attitude. The questionnaires were self-administered following brief instruction and a staff member was available for direction if required. The forms and surveys used are detailed in Appendix A. The results generated from these questionnaires and surveys are detailed in another work.(Flint-Wagner 05)

Muscle Strength

Functional muscle strength was assessed in the exercise group using the three repetition maximum (3RM) weight. This was chosen over the more common single repetition maximum (1RM) to avoid injury and accommodate the reported difficulty of RA patients to produce a single maximal effort.(Stenstrom 03, Minor 89) This test was performed in the same facility used for the supervised intervention program and was administered by the same certified trainers used during the intervention.

Strength in five movements engaging different muscle groups were assessed by the 3RM test – machine leg press, 55° incline dumbbell press (left arm and right arm) and dumbbell hammer curl (left arm and right arm). The testing protocol began with a light aerobic warm-up (treadmill walk) followed by a set of 3-5 repetitions of the selected exercise at 40-60% of expected maximum (selected by supervising trainer). A 2-minute rest and stretch followed, and then a higher-intensity set (60-80% of expected maximum).

A final 3-minute rest period followed, then 3 repetition sets began with the weight increasing incrementally from the high-intensity set weight. The 3RM test result was the final weight at which the subject could complete 3 repetition using proper form and movement. All of the subjects were scheduled such that the 3RM testing was not done on the same day as the peak torque strength testing (dynamometer testing) or grip strength testing to limit fatigue cross-contaminating results.

Peak Torque

Functional dynamic muscle strength was assessed in exercise and control groups via a Biodex Isokinetic Dynamometer (Biodex Systems, Shirley NY). Peak torque averaged over trial sets (expressed in newtons) was the resultant data. Knee extension and elbow flexion were assessed bilaterally, with data recorded individually for each limb.

For all tests the patients were seated comfortably and secured to the dynamometer chair via lap and shoulder belts. Chair position and dynamometer location was adjusted vertically, laterally and longitudinally to ensure that the axis of rotation was properly aligned with the joint being tested. Range of motion was assessed and set through the computer interface and care was taken to avoid hyperextension of any limbs in an effort to avoid exacerbating disease effects. All positional data was recorded to ensure identical testing position at subsequent appointments for that subject.

During the trials a belt was secured to the active limb (at the thigh or bicep as appropriate) to mitigate large limb action and ensure accuracy. Prior to the knee extension trials leg limb weights were measured via computer interface and used as a correction factor in the software determination of torque. During the elbow flexion trials

the subject was allowed to select the grip style (thumb wrapped around the grip or thumb on top of the grip) used so as to accommodate any hand deformity. This information was recorded and all trials with each arm were performed using the same grip style.

Following positioning and securing of the subject to the dynamometer, each subject was allowed to familiarize himself or herself with the instrument. Two to five warm-up repetitions were performed at sub-maximal effort, again assessing comfort of the patient. Two sets of 5 maximal contractions were then performed at 60°/sec angular velocity. Three minutes of rest were allowed between sets for the knee extension trials, and three minutes rest was also allowed between leg sides (time required to reset the machine and re-seat the subject). Ninety seconds rest was allowed between elbow flexion trials, and three minutes rest allowed between sides. Maximal effort was required for both the flexion and extension phase of each movement in all trials.

Subjects received real-time visual feedback via computer monitor graphic representations of data (red or blue bars) and prior to the assessment have been encouraged to provide maximal effort. No verbal encouragement was given during the trial to ensure consistency across trials and subjects. Following the completion of all trials (knee and elbow, bilaterally) subjects completed a pain visual analog scale (VAS) and rating of perceived exertion (RPE). The same technician performed all dynamometer assessments. Subjects were scheduled such that the dynamometer testing was not done on the same day as the functional muscle strength testing (3RM) or grip strength testing to avoid fatigue cross-contaminating results.

Grip Strength

Isometric grip strength was assessed using the hand dynamometer on the FOCUS system (Baseline, Irvington NY). The FOCUS system is a multi-component, computerized collection of physical function tests used to assess ability/disability in a range of activities and situations. Subjects were tested in a standing position with elbow extended (but not to maximum extension) with the dynamometer positioned on a shelf at standing elbow height. The non-active hand was allowed to be placed atop the dynamometer to allow for stabilization during the test. The handle was perpendicular to the longitudinal axis of the forearm. Subjects were instructed to squeeze the handle of the dynamometer when told to begin and hold the grip until instructed to stop. Each set consisted of 3 maximum voluntary contractions (MVC) lasting 3 seconds, with 5 seconds of rest between trials. Subjects received real time visual feedback via a computer monitor. No verbal encouragement was given during the trials to ensure consistency across trials. The average force generated across the 3 trials for each set (in pounds of pressure) was recorded as the absolute grip force.

Subjects were scheduled such that the grip strength testing was not done on the same day as the functional muscle strength testing (3RM) or peak torque strength testing to avoid potential cross-contamination of results by fatigue.

Mobility

The timed 50-foot walk test is a standard measure of function in RA patients as walk times tend to increase with disease activity.[(Cush 90)] In the present study, the 50-foot walk was also used to assess stride length to allow computation of distance walked during

activities of daily life for the subjects and aerobic output during walking exercise (steps counted via pedometer).

A distance of 60 feet was measured out on a flat, firm walking surface with tape markings at 0', 10' and 60'. Subjects were positioned at the starting point and fitted with a zeroed pedometer. The test administrator provided a count down and "go" command. Time was kept via stopwatch but was not triggered until the subject reached the 10' mark. This initial 10' distance was included in the test to normalize subject stride length and ablate any reaction-time component at the start. Steps taken during this distance were counted by eye and recorded. Time required to complete was recorded in seconds, to the nearest tenth. Subjects were instructed to stop and hold position upon passing the 60' mark. A reading was taken from the pedometer at this point, steps taken during the initial 10' distance were subtracted and the 50' walk test time and steps were recorded. The same technician administered all tests.

Functional Movement

A combined strength and functional mobility test was designed by the study staff to assess the ability to perform activities of daily life, including lifting and setting down items of weight and walking while carrying weight. The "box carrying test" was developed to combine these factors by having subjects lift a weight-loaded box from a shelf, carry it on a 50' circuit returning to the point of origin, and then place the box back on the same shelf. The shelf height was determined by the anatomical markers of the specific subject, aligning the shelf top with the top of the subject's forearm while standing with upper arms perpendicular to the ground and elbows bent at a 90° angle. At

the conclusion of each circuit additional weight was added to the box and 15 seconds of rest were allowed. The subject then completed, if possible, another circuit. There were six circuits possible, and if the subject completed the final circuit the test was terminated.

Assessment consisted of two separate components – time required to complete each circuit and number of circuits completed. The subjects were instructed to walk the circuits at a relaxed pace, and the time elapsed was used in part to assess changes in walking rate with load value. Time was computer calculated based on the removal and replacement of the weighted box on the shelf.

The box was custom-built for the test, measuring 9” x 23” x 5” and was designed to be carried in front of the body with the weight resting on the forearms and upper arms. This alleviated the need to use the wrists or hands to lift or support the weight to remove localized joint pain or fatigue as a confounding element. Hands were allowed to stabilize the box and hold it comfortably to the body. The width of the box was such that it was simple to set the box on the shelf without worry of overbalancing or missing the shelf.

The first circuit was made with the box empty (6.2 lbs of weight), and on subsequent circuits weight was added as follows (aggregate weight in parentheses): +5.0 lbs (11.2 lbs), +2.5 lbs (13.7 lbs), +2.5 lbs (16.2 lbs), +5.0 lbs (21.2 lbs) and +5.0 lbs (26.2 lbs). Subjects continued until they were unable to finish due to pain, upper or lower body fatigue, inability to lift the box or altered posture required to carry or move the box. A pain VAS was administered both before and after the test. The same technician administered all trials.

Anthropometry

Height, weight and waist circumference were assessed in all subjects. Height was measured to the nearest 0.1 cm using a Shorr stadiometer. Subjects removed footwear and any hair accessories that might have caused an erroneous reading and were placed facing away from the stadiometer with their weight centered below them to prevent leaning. The subject's head was aligned in the Frankfurt plane such that the line between the lower border of the orbit and the tragus of the ears were parallel with the ground, and their arms hung in a relaxed posture at their sides. The measurement board was lowered to the top of the subject's head and the resultant value was recorded. The subject stepped away and the process was repeated for a second trial. The average of the two values was used as the criterion.

Weight was assessed on a Seca model 880 digital scale (Seca, Hamburg, Germany), assessed in duplicate with the average reading to the nearest 0.1 kg used as the criterion. Subjects were weighed in normal clothing minus footwear. The scale was calibrated daily and zeroed prior to each trial.

Body mass index (BMI) was calculated from height and weight measures as mass (kg) divided by height (m) squared.

Waist circumference was measured with an anthropometric tape at the midpoint between the bottom of the ribcage and the top of the iliac crest. Clothing was removed so as to not alter the result. The measurement was taken following a normal expiration and recorded to the nearest 0.1 cm. All measurements were made in duplicate with the subject relaxed and tape repositioned between each trial.

Body Composition Assessment

Dual-energy x-ray absorptiometry (DXA) scanning and analysis was used to assess body fat, muscle mass and bone mineral content. Whole body and regional fat tissue, total fat free mass (FFM) and total and regional lean soft tissue were assessed. Appendicular skeletal muscle was estimated from arm and leg lean soft tissue, and bone mineral content and density (BMC/BMD) in the spine, forearm and femur were also assessed. All scans were made using the Hologic QDR 4500W (Hologic Inc., Bedford MA) using supplied software v9.09D. All whole body scans were run at medium speed, as were all specific regions unless the thickness/depth of the specific area being measured exceeded 24 cm, in which case the spine or femur were assessed at slow speed.

Two experienced and trained technicians performed all measures, and the technician that performed a scan also performed the computer analysis of that scan.

Blood Analysis

Following an overnight fast, blood draws were performed on each subject by a certified phlebotomist. The samples were then sent to a study laboratory where they were centrifuged with HISTOPAQUE at 2000rpm for 30 minutes at 18-20° C. The plasma layer was extracted and samples were stored at -80° C. Samples were thawed, vortexed and re-aliquotted at a later date and remained at -80° C until needed for further analysis. The samples were exposed to only this one thaw-freeze cycle prior to use.

Fasting insulin was quantified via sandwich ELISA (Cat. # EZHI-14K, LINCO Research, St. Charles, MO). This assay is based on the capture of insulin molecules by an antibody coated on the wells of a microtiter plate. The amount of insulin captured is

measured by the spectrophotometrically assessed activity of horseradish peroxidase following conjugation to biotinylated antibodies bound to the insulin molecules. The treated plates were read at 450nm on an Anthos Labtec Lucy 2 luminometer and analyzed with the provided ADAP software. Plasma was drawn from aliquots prepared as previously described. Commercial quality controls were assessed in triplicate while subject samples were run in duplicate. Control samples all fell within accepted ranges. Inter-assay coefficient of variation was 1.60 and intra-assay coefficients of variation ranged from 3.46 to 3.78.

Fasting glucose was quantified using the glucose oxidation principle via Beckman Glucose Analyzer 2 (Beckman-Coulter , Brea, CA), reported in mg/dL, then converted to mmol/L. The principle of the procedure is the measurement of oxygen depletion during an oxidation reaction as measured by the Beckman Oxygen Electrode. The rate of oxygen depletion during the mixing of a known quantity of glucose oxidase and the tested sample is linked to amount of glucose present in the sample. The assessment and calculation is completed by the analyzer. Plasma was drawn from aliquots prepared as previously described. Commercial quality controls were assessed in duplicate at the beginning and end of each trial session. Subject samples were run in duplicate and were immediately run again if results were outside of 10 percent variation. Inter-assay coefficient of variation was 5.60 while intra-assay coefficients of variation ranged from 1.56 to 2.68.

Insulin sensitivity was assessed via the Homeostatic Model for Assessment of Insulin Resistance (HOMA-IR) first presented by Matthews et al.[(Matthews, 1985)] This model

allows for quantification of insulin action within a subject without the invasiveness and time commitment of the euglycemic clamp procedure. This model is defined as: HOMA-IR = FI x FG/22.5 where FI is fasting insulin, measured in uU/mL and FG is fasting glucose, measured in mmol/L.

Adiponectin (Acrp30) was quantified using Quantikine sandwich ELISA (Cat. # DRP300, R & D Systems, Minneapolis, MN). This assay is based on the capture of adiponectin molecules by a mouse antibody coated on the wells of a microtiter plate. The amount of adiponectin captured is measured by the spectrophotometrically assessed activity of horseradish peroxidase following conjugation to biotinylated antibodies bound to the adiponectin molecules. The treated plates were read at 450nm on an Anthos Labtec Lucy 2 luminometer and analyzed with the provided ADAP software. Plasma was drawn from aliquots prepared as previously described. Commercial quality controls were assessed in triplicate while subject samples were run in duplicate. Control samples all fell within accepted ranges. Inter-assay coefficient of variation was 7.90 and intra-assay coefficients of variation ranged from 5.40 to 7.04.

Resistin was also quantified using Quantikine sandwich ELISA (Cat. # DRSN00, R & D Systems, Minneapolis, MN). This assay is based on the capture of adiponectin molecules by a mouse antibody coated on the wells of a microtiter plate. The amount of resistin captured is measured by the spectrophotometrically assessed activity of horseradish peroxidase following conjugation to biotinylated antibodies bound to the resistin molecules. The treated plates were read at 450nm on an Anthos Labtec Lucy 2 luminometer and analyzed with the provided ADAP software. Plasma was drawn from

aliquots prepared as previously described. Commercial quality controls were assessed in triplicate while subject samples were run in duplicate. Control samples all fell within accepted ranges. Inter-assay coefficient of variation was 8.62 and intra-assay coefficients of variation ranged from 3.39 to 6.01.

Tumor-necrosis factor alpha (TNF-α) was quantified using Quantikine high-sensitivity sandwich ELISA (Cat. # HSTA00C, R & D Systems, Minneapolis, MN). Samples were pipetted into TNF-α antibody coated microtiter plate wells, binding TNF-α to the wells. Unbound substances were washed away and an enzyme-linked polyclonal antibody was added to the wells, the plate was again washed and a substrate solution (lyophilized NADPH) added. Following incubation, an amplifier was added and color develops. A stop solution was added and the treated plates were read at 490nm on an Anthos Labtec Lucy 2 luminometer and analyzed with the provided ADAP software. Plasma was drawn from aliquots prepared as previously described. Commercial quality controls were assessed in triplicate while subject samples were run in duplicate. Inter-assay coefficient of variation was 12.42 and intra-assay coefficients of variation ranged from 7.00 to 10.10. Though high, these are similar to the expected values presented in the literature accompanying the assay kit.

EXERCISE INTERVENTION

An innovative, progressive, individualized, thorough and professionally monitored exercise program was the heart of the trial intervention. Subjects randomized to the exercise intervention were required to train in a hospital supported exercise and rehabilitation facility featuring a wide range of exercise machines (both resistance-based

and aerobic) as well as free weights. Subjects were scheduled to visit the training center on three non-consecutive days each week, generally Monday, Wednesday and Friday. Each scheduled session included warm-up exercises, eight resistance training exercises, an aerobic training segment, abdominal exercises and a cool-down including both walking and stretching. Each appointment was approximately 75 minutes long and included 30 minutes of aerobic activity and 40 minutes of resistance training. The importance of the warm-up and cool-down was explained and reinforced by the staff and was a requirement of the program. Dedicated exercise outside of these sessions was limited to range of motion (ROM) exercises performed 2-3 times per week, selected from a list of recommendations focusing on joints commonly affected by RA. Normal outside activity was allowed.

All training sessions were undertaken in the presence of a certified trainer who was also a study staff member. The subject to trainer ratio never exceeded 4:1 allowing for full supervision, safety and the development of rapport with the subjects during the training regimen. All subjects were also required to attend both a 2-hour introductory training seminar and program overview and an individual session with a trainer, including a facility orientation and assessment of individual fitness needs, prior to beginning the intervention. An illustrated exercise manual was provided to the subjects at the training seminar.

Resistance Training

The resistance training program featured 8 exercises performed in 2 sets of 6-8 slow repetitions (2 to 3 second movements), with 30 to 60 seconds rest between sets

preferred. This scheme was chosen to strike a balance between strength/muscle size gains and muscular endurance. Subjects were provided with three means of completing each of the eight exercises in an effort to allow subjects to exercise, regardless of functional ability or disease flare-ups. "Option 1" generally involved only the use of provided Therabands for exercise and was reserved for absolute minimal functional ability (due to pain or flare-up) or for those days when the facility was unavailable. "Option 2" included use of both the Theraband and other weights/machines to enhance the training over Option 1. "Option 3", the use of full resistance via free weight or resistance exercise machine, was the preferred exercise.

Subjects were able to intermix Options as required, thus allowing someone suffering from hand/wrist issues to use Options 1 or 2 on exercises focusing on those areas while still using Option 3 on lower body exercises. It was hoped that this scheme would maximize training efficiency and outcomes even in the face of changing disease states. Furthermore, Options 1 and 2 provided a way to ramp subjects up from introductory movements or functional ability to full function and maximum resistance. Additionally, assistive devices such as wrist guards or weight gloves were made available to those subjects that required them in an effort to limit injury and encourage compliance and successful training.

The exercises, muscle group(s) affected, rationale for inclusion in the program and optional exercises were:

- Leg Press – Quadricep and gluteal muscles. Leg strength is important for stance, walking, climbing and rising from the seated position. It may also help preserve

hip, knee and ankle joints and reduce injury and fall risk.

- Option 1: Chair Stand. Subjects rise from the seated position from a chair or bench without using arms or momentum from torso. Focus is on maintaining posture and balance throughout the movement. Subjects were allowed, if necessary, to place pillows on the chair to increase height. Repetitions start from the seated position, stand, sit.
- Option 2: Step Up. Using a step platform, subjects step up from floor to platform, leading up and down first with the right leg and then with the left. Subjects may advance the difficulty of Option 2 by increasing height or number of steps. A single repetition consists of step up (right foot, left foot), step down (right foot, left foot), step up (left foot, right foot), step down (left foot, right foot).
- Option 3: Seated Leg Press. Subjects used the leg press machine, stabilizing their legs with a rehabilitation ball or their arm placement. Weight stacks were set based on personal progression (initially determined by trainer). A single repetition was extension (care taken to not lock knees) then lowering weight such that knees reach 90°. The purpose of leg stabilization was to prevent the knees from turning inwards during the lowering of the weight. Shoulder stabilizers were available as well.

- Incline Dumbbell Press – Deltiods, pectoralis major, triceps, trapezius and serratus anterior. Shoulder strength is necessary for lifting and carrying items, and helps reduce the difficulty of other arm movements or exercises.

- Option 1: Theraband Chest Press. While seated or standing, subjects wrapped a Theraband behind their back and under their arms. With hands at shoulder height, subjects extended arms away from body, stretching the Theraband. A repetition was one extension, a one second pause, then a slow return to base position.
- Option 2: Seated Incline Two Arm Ball Press. Seated on an incline bench with the back positioned at 50°, the subject held a weighted medicine ball or physioball, as determined by their ability. With one hand on either side of the ball it was pressed away from the subject's chest, extending arms upward over head level. A slow retraction to the chest completed one repetition.
- Option 3: Seated Incline One Arm Dumbbell Press. Seated on an incline bench with the back positioned at 55°, subjects hold a dumbbell in one hand. The weight is pressed straight upwards to near-full extension, then lowered back to the chest. Subjects completed an entire set with one arm, then switched to the opposite arm.

- Hip Adduction – Thigh adductors (longus, brevis, magnus, pectineus, gracilis) and gluteal muscles. Strengthening these muscles improves lateral motion.
  - Option 1a: Theraband. Subjects secured their Theraband to a stable tower and tie the opposite end to their right ankle, drawing the band taunt. With feet spaced hip width apart, the subjects moved the secured leg inward, touching the left knee with the right. One transit in and back to starting

position was a repetition. Subjects alternated legs by sets.

- Option 1b: Lying Down. Subjects were positioned on the floor, back down, with legs perpendicular to the floor. Legs were opened to form a "V" (as wide as possible while maintaining posture) then closed.
- Option 2: Hip Adduction Machine. Subjects performed adduction exercises in a seated machine, adducting both legs at the same time, using weight as determined by their individual program.
- Option 3: Adduction with Cable Pulleys. Subjects used a weight tower with pulley and weight stack. This exercise was performed while standing and was similar to Option 1a with the addition of weights.

- Hip Abduction – Abductor muscles, gluteal muscles, tensor fasciae latae, sartorius and rectus femoris. Strenghtening these muscles improves lateral motion.
  - Option 1: As Hip Adduction Option 1a, except the Theraband extended across the near leg and motion was away from the center.
  - Option 2: As Hip Adduction Option 2, except with abduction machine.
  - Option 3: As Hip Adduction Option 3, except the cable extended across the near leg and motion was away from the center.
- Row – Latissimus dorsi, teres major, trapezius, rhomboid major, deltoideus, biceps brachii, brachiordiasis, brachilais. Back and arm musculature is important for posture, stability and pulling actions. Strength training these muscle groups may help limit injury or pain.
  - Option 1: Theraband Seated Row. Subjects sat on the edge of a chair or

bench with the Theraband secured under their feet. Grasping both ends, the subject drew their elbows back and squeezed their shoulder blades together. Following a one second hold, they slowly returned to base position and completed the repetition.

- Option 2: Seated Row Machine. Subjects were seated at machine with feet braced against footplate. The subject then grasped the machine handle with both hands and drew it taut. Weight was set based on individual progression. The handle was then drawn in to the body using the back muscles over the arm muscles. A pause and return to base position completed the repetition.
- Option 3: One Arm Dumbbell Row. Subjects performed this exercise using single dumbbells while standing near, or kneeling on (with one leg) a bench. While bent forward at the hips, the subject started with the weight hanging at the side, then pulled the weight up to waist level, then lowered it to starting position to complete the repetition. Subjects alternated arms by sets.

- Calf Raise – Gastocenemius and soleus. Strengthening the calf improves walking ability and improves stability and safety when walking or climbing stairs.
  - Option 1: Calf Raise Without Weight. Subject could perform this option while seated (buttocks on edge of chair, back not on back rest) or while standing near a wall for support. Starting with heels flat on the floor, subjects raised both heels, bringing their feet to tiptoes. The position was

held for a moment and then returned to base to complete one repetition.

- Option 2: Two-Legged Calf Raise with Dumbbells. Subjects stood on a foam board positioned near a wall with dumbbells (weight determined by individual progression) in each hand. Starting with heels flat on the floor, subjects raised both heels, bringing their feet to tiptoes. The position was held for a moment and then returned to base to complete one repetition.
- Option 3: One-Legged Calf Raise with Dumbbells. As Option 2 above, except the subject stood on one leg while holding the other bent at a 90° angle behind the body. In Option 3 the dumbbell was held only in the hand on the side being exercised.

- Hammer Curl – Biceps brachii, brachialis and brachioradialis. Strengthening the muscles of the arm assists in lifting and carrying items in front of the body.
  - Option 1: Theraband bicep curls. Subjects were seated on the edge of a chair or bench with the Theraband secured beneath their feet. With the free ends of the band grasped in both hands and elbows tucked near the torso, the subjects curled their hands upwards towards the shoulders. After holding the position for one second, the subjects returned to base position and completed the repetition.
  - Option 2: Hammer Curl with Wrist Cuff Weights. Subjects stood comfortably with weight cuffs attached to their wrists. With elbows held near torso each arm was sequentially curled towards the shoulder, position held and then returned to base position. The subject then repeated the

movement with the other arm. One curl with each arm comprised a repetition.

- Hammer Curl with Dumbbells. As Option 2 above, replacing wrist cuff weights with dumbbells, weight determined by individual progression.

- Leg Curl – Biceps femoris, semimenbranous, semitendinous and sartorius. These muscles are important in walking and help support the knee and hip joints.
  - Option 1: Seated Heel Drag. Subjects performed this exercise while sitting back in a chair. One leg was extended on the floor in front of them while the other was remained at normal seated posture. The subject dragged the heel of the extended leg back to full compression, then lifted the leg and squeezed the calf against the edge of the chair. The leg was then extended back to base position, completing the repetition. Subjects alternated legs by sets.
  - Option 2: Leg Curl with Cable Pulley or Theraband. Subjects stood facing a secure tower with either a Theraband or cable secured to their active leg. While facing the tower, subjects moved to a point where the band or cable was taut, and then pulled back the active leg and raised it towards their buttocks. A slow return to base position completed a repetition. If using the cable pulley, weight was determined by individual progression. Subjects alternated legs by sets.
  - Option 3: Machine Seated Leg Curl. Subjects were seated at the leg curl machine with back and buttocks resting against the back chair pad and

both ankles placed against the lower roller pad. Handles on either side of the body were available for stability and support. Subjects moved legs from initial position to 90° flexion, and then returned to starting position, completing a repetition. Weight was determined by individual progression.

Abdominal Exercise

Similarly, there were three options made available for abdominal exercises, and three specific exercises within each option level. Subjects were to perform two of three exercises at their selected option during each training session. Difficulty could be enhanced by holding positions for a longer period of time (up to 8-10 seconds) than baseline (3-5 seconds).

- Option 1 – Theraband
    - Theraband Abs. Subjects looped a Theraband around a tower and held both ends of the taut band over their shoulders while facing away from the tower. Using their abdominal muscles the subjects pulled forward with back straight and arms extended. Holding and returning to base position completed a repetition.
    - Marching in Place. With their back against a wall and feet hip width apart, subjects contracted their abdominal muscles and raised one leg to a 90° angle, held the position and then returned to base position. The exercise was then repeated with the other leg, and this constituted a single repetition.

- Wall Pelvic Tilt. Subjects stood with their back to a wall and feet hip width apart. Arms were placed out to the side with the palms facing the wall. The subject then contracted the abdominal muscles and pressed the small of their back into the wall. Following a 3-5 second hold the subject returned to base position, completing the repetition.

- Option 2
  - Reverse Crunch. Subjects were positioned with their backs on a floor mat and legs raised into the air with knees slightly bent. With arms resting on the floor, subjects lifted their buttocks off the floor 1-2" and held position for 3-5 seconds, then returned to base position to complete the repetition.
  - Bicycles. With the back on the floor mat, subjects raised their legs perpendicular to the floor. Subjects then completed cyclic motions as though they were peddling a bicycle. Every 6 cycles counted as one repetition.
  - Ab Twists. Subjects were positioned with their backs on a floor mat and knees bent at a 60° angle (feet flat on the floor). Keeping the knees bent, subjects were to move both knees to the right side of the body such that they touched the mat, then back to center position, then to the left side of the body and then back to center to complete the repetition.
- Option 3
  - Ball Crunch. Subjects were seated on a physioball with feet flat on the floor then slowly leaned backwards until their back was securely against

the ball from tailbone to shoulders. Once positioned, subjects curled up and forward slowly until their shoulder blades were off the ball. Following a brief hold at this position, the subject returned to base position and completed a repetition.

- Lower Ab Hold. Subjects started back down on a floor mat with legs elevated and knees slightly bent. Arms were held out to the sides and the lower back was kept in contact with the mat by contraction of the abdominal muscles.. Subjects were to lower their legs until they felt their lower back begin to lift away from the mat, and then return to the starting position. This arc of movement constituted a repetition.
- Bench Knee Ups. Subjects were seated on the edge of a lengthwise bench, leaning backwards and supporting their trunk with a hand on each edge of the bench. Subjects lifted their legs no higher than the height of the bench and then contracted the abdominal muscles and brought the upper body and knees together. To complete the repetition the subjects returned to the extended-leg starting position.

Aerobic Training

This study used walking as the primary aerobic training (including warm-up and cool-down activity, along with stretching), and subjects were encouraged to walk as much outside of training sessions as they might like. A pedometer was provided to all exercise group subjects at the onset of the intervention and was theirs to keep. When walking to exercise, subjects were encouraged to walk briskly to be sure their activity was in the moderate to vigorous range. Proper posture and gait were emphasized,

particularly given the impact RA can have on mobility and body position. Pedometer readings were included as part of the exercise logs and training reports.

Individual Progression

Subjects advanced to higher Options, greater weights or higher intensity/duration as dictated by their responses to trainer evaluations. Increasing the weight used in an exercise occurred when the subject could perform all repetitions for all sets in a given exercise in proper form in two consecutive training sessions, and with a Rating of Perceived Exertion (RPE) ≤ 4. Setting and recording weekly goals for weight helped facilitate this process. Aerobic activity intensity or duration was increased when the subject could complete their current regimen with RPE ≤ 3.

Monitoring and Support

Subjects in the exercise intervention completed Exercise Logs each week indicating exercise and physical activity, both within and outside of the prescribed regimen. These logs included options selected, sets, repetitions and weights used for all strength and abdominal exercises, and type, duration and intensity of aerobic exercises performed. These logs were submitted to the training staff weekly and were used by the study staff to quantify comprehensive exercise "dose". Trainers also recorded notes on each subject for each scheduled exercise session, detailing attendance/compliance, modifications to the exercise regimen, injuries or barriers to successful training and any other issues or noteworthy events that may have occurred. These notes served to provide a professional and unbiased assessment of the quality of intervention for each subject.

A support program featuring social reinforcement and subject motivators was

instituted and continued throughout the course of the intervention. Incentives, awards and personal reinforcement strategies were employed to encourage compliance and attendance at training sessions. The inclusion of friends and family in the support of the patient was encouraged, as was input from other active exercisers. The program focused on increasing education, skill, and self-efficacy to reduce anxiety or training stress and social support, modeling and incentive programs to motivate participants and keep them entertained and interested by the intervention. Support events included motivational meals, personal notes from the staff, social gatherings and light competitions.

Compliance, as assessed by exercise logs and trainer's notes, was discussed at regular staff meetings that focused on addressing problems and eliminating obstacles. Issues relating to motivation, attendance or barriers to performance were then addressed with the subjects in the hope of creating an amicable solution and returning the subject to full participation and compliance. Attendance issues were addressed as quickly as possible to maintain the integrity of the intervention.

Exit Evaluation

Following the completion of all assessments the subjects were asked to respond to a final questionnaire. All subjects completed a 22-item assessment of their overall satisfaction with the staff, study requirements, office/lab visits and what, if any, changes they would recommend. Those subjects in the exercise intervention completed an additional 38 items assessing their satisfaction with the training regimen, trainers and facility. All evaluations were scored on a 1 (Strongly Disagree) to 5 (Strongly Agree) scale.

DATA ANALYSIS

All data was analyzed using SPSS statistical software package v14.0 (SPSS Inc, Chicago, Il., 2005). Distributions and frequencies were used to describe the subject sample and to assess normalcy of distribution. Independent sample T-tests were used to assess possible differences between intervention and control condition subjects at a given time point. Paired sample T-tests were used to assess possible differences across the course of the intervention in the same subject condition. Linear regression models were used to assess impact of independent variables on selected dependent variables.

CHAPTER IV: RESULTS

This section presents the data gathered for this study, organized first by data category and then chronology. This is done to allow clear and immediate comparisons between pre- and post-intervention data on a given variable of interest. The demographic data are presented first followed by the strength training results, showing the impact of the intervention on the muscle strength of the exercise participants. The body weight and anthropometric characteristics, including DXA body composition data are then presented, followed by the results of the glucose metabolism, adipokine and cytokine assays. The correlative relationships among all the variables assessed are presented, followed by multivariate regression analysis testing models of interest in prediction of HOMA-IR. The results gathered from the numerous surveys and questionnaires are not included in this report, nor are the functional ability data (50' walk and box-carrying test) or physician assessment results. Those data are presented in detail elsewhere.(Flint-Wagner 02, Flint-Wagner 09)

Given the relatively small sample size, correlations are presented using the maximum number of subjects available for a particular comparison. As not all subjects completed all assessments this resulted in sample size variances among correlations, even within a given correlation table. These "pairwise" comparisons provide the greatest likelihood of discerning accurate relationships between two given variables within the table or list, but may limit the ability to compare the relative strength of that relationship to other variable pairs. The sample size for each comparison is indicated in the legend for the table in which it occurs.

SECTION I - DEMOGRAPHICS

Thirty subjects (25 female, 5 male) were initially recruited. Age and disease duration demographics are detailed in tables I-a and I-b. The mean age was 51 ± 14.36 years with a minimum of 29 and a maximum of 80.12. Patient's average elapsed time since disease diagnosis was 13.67 ± 9.90 years. The subjects had been undergoing Remicade treatment for a minimum of 8 months to a maximum of 60 months, averaging 23.36 ± 12.15 months. Two subjects were uncertain of their duration of treatment but had been treated for at least eight months.

Table I-b displays the demographic data separated by subject gender. Mean age, disease duration and Remicade treatment time were similar between genders, and no significant differences were found between males and females.

Subjects were randomized in a 2-to-1 fashion to exercise or control condition. This was done without consideration to age, disease duration, Remicade treatment time or gender. One subject in each condition did not have complete Remicade treatment data, but as noted above was certain to have been undergoing treatment for at least 8 months.

Table I-c shows the demographic data for the exercise and control groups. There were no significant differences between the two groups. Mean ages, disease durations and Remicade treatment time in the control and exercise groups were within ten percent of one another and the standard deviations in all cases were similar.

Table I-a Subject Demographics

	n	Min	Max	Mean	SD
Age yrs.	30	29.02	80.12	51.81	14.36
RA yrs.	30	2.38	39.43	13.67	9.90
Remicade mos.	28	8.00	60.00	23.36	12.15

Table I-b Subject Demographics by Gender

	Female					Male				
	n	Min	Max	Mean	SD	n	Min	Max	Mean	SD
Age yrs.	25	29.02	80.12	51.99	14.86	5	33.68	66.03	50.89	12.97
RA yrs.	25	2.38	31.17	13.47	9.21	5	5.00	39.43	14.62	14.14
Remicade mos.	24	8.00	60.00	22.50	2.29	4	12.00	36.00	28.50	11.36

Table I-c Subject Demographics by Randomized Grouping

	Exercise					Control				
	n	Min	Max	Mean	SD	n	Min	Max	Mean	SD
Age yrs.	17	29.02	72.83	51.58	12.98	8	33.68	74.58	48.91	12.62
RA yrs.	17	3.13	39.43	14.80	10.76	8	2.38	31.17	13.47	9.21
Remicade mos.	16	8.00	60.00	24.63	13.48	7	12.00	36.00	22.29	11.34

SECTION II - STRENGTH

Strength was assessed via a 3-repetition maximum (3-RM) test in the exercise group after randomization and again following the intervention. Table II-a presents the baseline 3-RM data including the range of results. Not all subjects were able to complete all 3-RM tests due to pain or mobility issues. It is worth noting the significant variation in 3RM weights in all exercises, indicating a wide range of initial strength values in the population. As expected, males were considerably stronger than females in all 5 tests at baseline (data not shown).

3-RM testing was repeated during mid-intervention assessments. Strength, as reflected in 3RM values was significantly increased ($p < 0.01$) for each exercise. This data is presented in Table II-b, including a recapitulation of the baseline data for ease of comparison. Minimum and maximum 3RM values as well as the group means increased in each exercise as well, demonstrating improvement in each exercise among all of the participants, including the weakest and strongest participants at baseline.

Following the 16-week intervention the exercise group subjects again performed the 3-RM test. These data are detailed in Table II-c along with a recapitulation of the baseline data for purposes of comparison. Again not all subjects were able to complete all 3-RM tests due to pain or mobility issues at the time of testing. Subjects were bi-laterally consistent in both the Military Press and Hammer Curl tests. Paired-sample T-tests confirmed that results were significantly higher than baseline following the intervention period in all five tests. Increases in 3-RM values were also significant between the mid-intervention and post-intervention tests, at the $p < 0.01$ level for Leg Press and Military Press (both left and right sides) and at the $p < 0.05$ level for the

Hammer Curl (both left and right), indicating a continued increase in strength throughout the course of the exercise intervention.

Table II-d shows the change in 3-RM weights for all 5 test modalities. All values increased significantly from baseline to follow-up ($p < 0.01$). The magnitude of change ranged from 5.37 ± 3.73 kg (hammer curl – right) to 117.72 ± 60.44 kg (leg press). The mean percentage increase in each exercise from baseline ranged from 33% (Hammer Curl – Left) to 50% (Military Press – Left) with Leg Press in the middle at 41.6% increase. The majority of this increase occurred during the first half of the intervention, but the increase in strength from midpoint to completion was still appreciable, ranging from nearly 8% (Military Press – Left) to 20% (Military Press – Right).

Figures IIa-IIe present a graphical representation of the strength increases in each exercise. Figure IIa depicts the change in leg press 3RM values for each subject from baseline to midpoint evaluation to the post-intervention testing. Each line indicates a single subject's test results. Though there is some variation, the figure clearly indicates the increase in strength among virtually the entire sample from time point to time point. Every subject ended the intervention with an increase in leg press 3RM as compared to baseline, and virtually every subject improved from the midpoint assessment to the end of the intervention as well.

Figures IIb and IIc present the Military Press 3RM data, left and right sides respectively. Again a clear bilateral improvement is visible in virtually every subject from baseline to post-intervention, with the majority of patients also improving from the

midpoint assessment to the final 3RM test. Table IIb shows the clear separation between the male and female exercise participants, though this is not as obvious in Figure IIc.

The Hammer Curl 3RM data is presented in Figures IId and IIe in similar fashion. As in the other exercises, virtually every patient's strength improved from baseline to midpoint and from midpoint to post-intervention, though this is not absolute. As in the military press figures there is a clear visual distinction between the male and female patients in regards to their strength data.

Data regarding peak torque, hand strength and measures of functional ability including the 50' walk test are not presented in the current work and are detailed elsewhere.(Flint-Wagner 09)

Table II-a Baseline 3RM in kg

	n	Min	Max	Mean	SD
Leg Press	16	170	460	283	87
Military Press – L	17	8	42	20	9
Military Press – R	17	12	40	20	8
Hammer Curl – L	17	6	32	15	7
Hammer Curl – R	17	9	32	16	6

Table II-b Midpoint 3RM in kg

	Baseline		Midpoint		
	Mean	SD	Mean	SD	n
Leg Press	283	87	356	88	15
Military Press – L	20	9	26	10	16
Military Press – R	20	8	25	8	16
Hammer Curl – L	15	7	18	7	17
Hammer Curl – R	16	6	18	6	17

All results significantly different from baseline at $p < 0.01$

Table II-c Post-Intervention 3RM in kg

	Baseline		Post		
	Mean	SD	Mean	SD	n
Leg Press	283	87	404	82	14
Military Press – L	20	9	28	12	15
Military Press – R	20	8	30	10	15
Hammer Curl – L	15	7	20	9	15
Hammer Curl – R	16	6	21	9	15

All results significantly different from baseline at $p < 0.01$

Table II-d Change in 3RM Results (Baseline to Completion) in kg

	n	Min	Max	Mean ± SD	% change
Leg Press	13	20	230	118 ± 60	
Military Press – L	15	0	20	10 ± 6	
Military Press – R	15	-5	17	9 ± 5	
Hammer Curl – L	15	0	15	5 ± 4	
Hammer Curl – R	15	1	15	6 ± 3	

Figure IIa - Leg Press 3RM Values

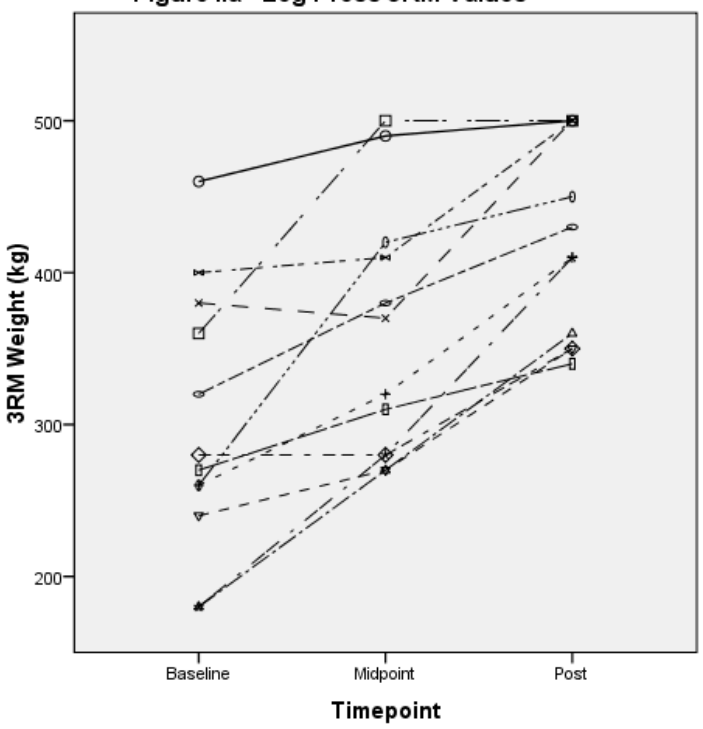


Figure IIb - Military Press (Left) 3RM Values

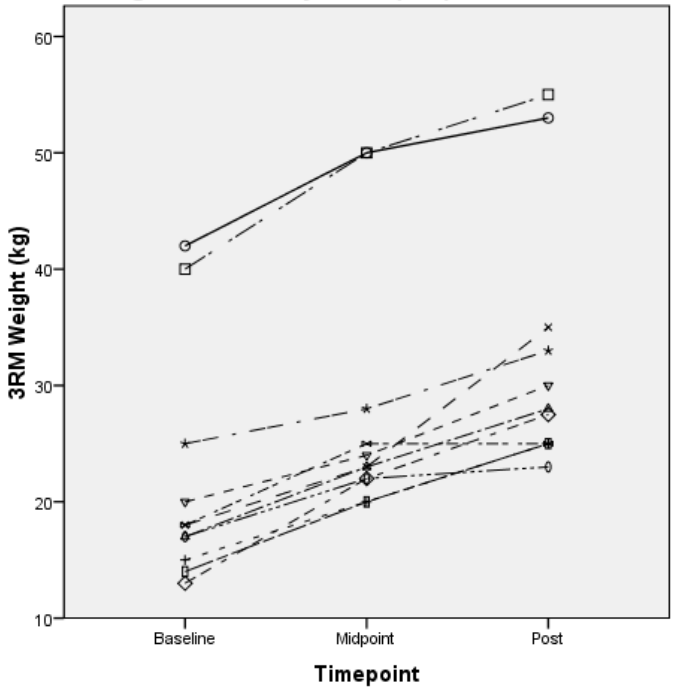


Figure IIc - Military Press (Right) 3RM Values

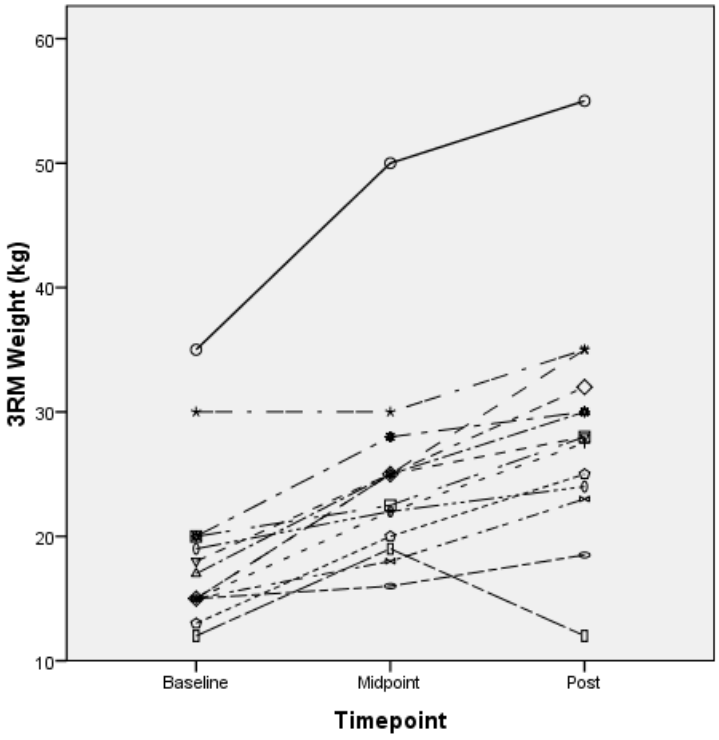
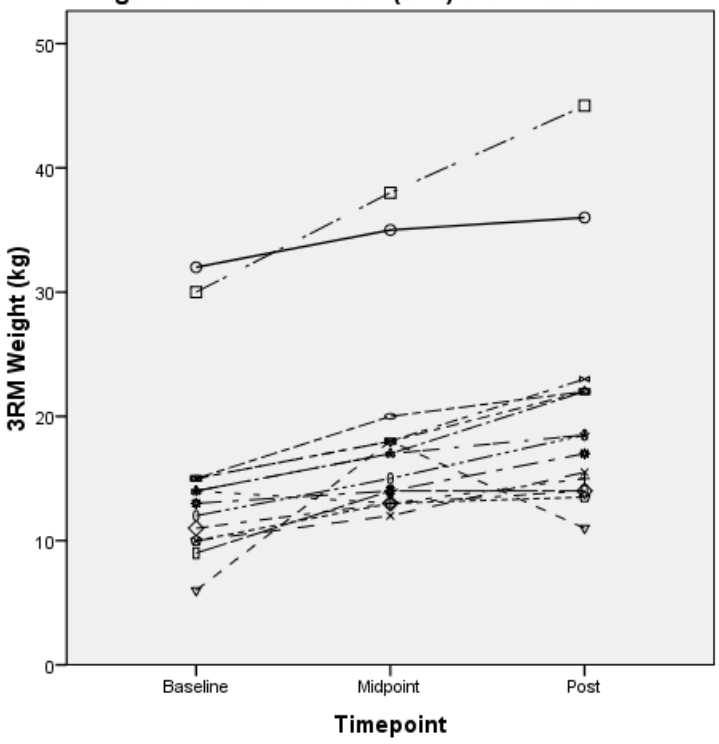


Figure IId - Hammer Curl (Left) 3RM Values



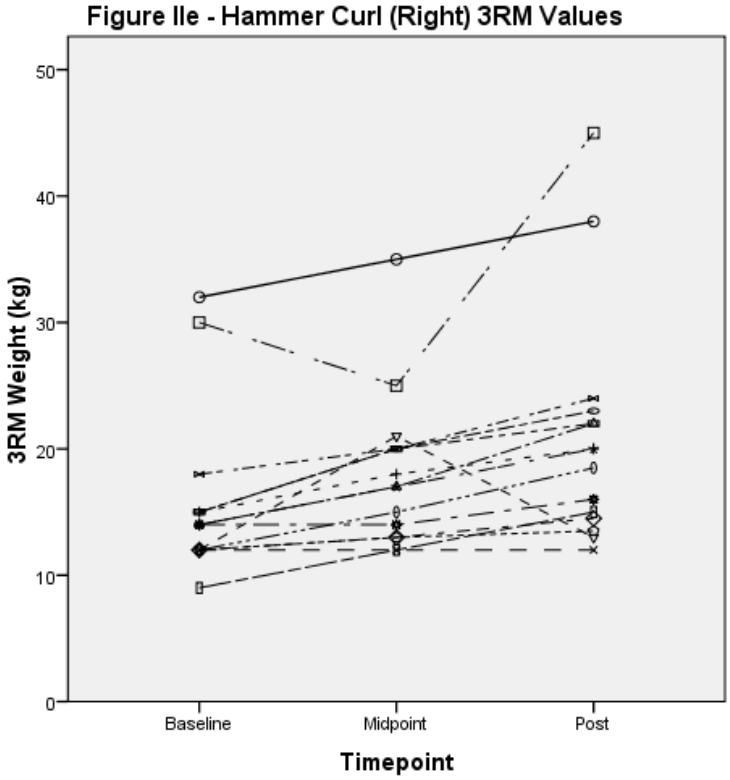


Figure IIe - Hammer Curl (Right) 3RM Values
3RM Weight (kg)
50
40
30
20
10
0
Baseline
Midpoint
Post
Timepoint

SECTION III - WEIGHT AND ANTHROPOMETRY

Subjects underwent weight, anthropometry and body composition assessment prior to randomization and again following the intervention period. Table III-a details the subject pool at baseline. Only those patients randomized into the study are included. Three patients randomized to the exercise group did not complete their DXA assessment, and two patients did not have a baseline waist circumference measurement.

Initial measurement indicated that the subject pool was generally "overweight" according to BMI conventions (BMI $\geq$ 25) with an average weight of 73.2 kg. Average fat mass was near 27.5 kg, representing better than 35% of the total mass. The range of values for all assessed variables was significant, indicating a wide array of patient sizes.

As might be expected, there were significant differences in weights and lean masses between the female and male subjects. Table III-b details weight and anthropometry findings by gender. Female average weight (68.86 $\pm$ 16.01 kg) was much lower than male average weight (93.85 $\pm$ 4.77 kg) significantly different at $p < 0.01$. Total lean mass (41.29 $\pm$ 5.35 kg vs. 60.71 $\pm$ 5.71 kg) and trunk lean mass (21.50 $\pm$ .51 kg and 30.80 $\pm$ 1.88 kg) were also significantly different between genders at $p < 0.01$. The difference in abdominal fat mass between genders approached significance (t-value 2.027, $p = 0.056$). Total and trunk fat masses were relatively similar between the two groups.

Table III-c provides weight and anthropometry data for the randomized subjects as divided into Exercise and Control populations. The exercise population started with 17 patients (15 female, 2 male) while 8 patients (5 female, 3 male) were randomized to the control population. Both pools of patients contained widely ranging initial weights

and body compositions, spanning more than 45 kg in each pool. Independent sample t-testing found no significant differences in any of these assessed variables at baseline, though trunk lean tissue mass and total fat mass approached significance ($t = 2.011$, $p = 0.065$ and $t = -1.960$, $p = 0.066$ respectively).

Correlations between these variables were examined in the combined subject pool. Table III-d highlights the relationships among measures of weight and size in the study participants. Body weight was highly correlated ($p < 0.01$) with BMI, waist circumference, total fat mass and measures of lean mass. Weight was not found to be correlated with percent fat in this group. BMI correlated significantly with all measures except total lean mass and trunk lean mass. Waist circumference was significantly correlated with all measures of weight and body composition except percent body fat. As expected there was significant correlation among all measures of body fat. Similarly, total lean mass and trunk lean mass were tightly correlated ($r = 0.99$, $p < 0.01$).

Subjects underwent weight, anthropometry and body composition assessment again following the intervention period. This data is detailed in Table III-e below. Two control subjects and two exercise subjects did not complete the post-intervention assessments at all while an additional control subject did not undergo post-intervention DXA analysis. The groups were again compared via independent sample t-testing and no significant differences were found between the control and exercise group means. Mean weights were 70.1 kg (exercise) and 70.3 kg (control), with BMI at 25.9 and 24.7, respectively. None of the variables assessed in the control group showed significant change (as assessed by paired sample t-test), with only trunk fat mass approaching

significance (t = 1.719, p = 0.184). In the exercise group trunk fat mass decreased significantly (t = 2.885, p = 0.020), and the decrease in total fat mass (t = 2.029, p = 0.077) and increase in trunk lean mass (t = -2.197, p = 0.059) approached significance. The other measures were statistically unchanged.

Table III-f summarizes the magnitude of change in each of the weight and body composition variables. There were no significant differences found between groups in any measurement of change in these variables of interest. Sample sizes following attrition were reduced and the unavailability of body composition data on several subjects exacerbates the effect of subject drop-out on the data analysis power.

Correlations among weight and anthropometry were again examined in control (Table III-g) and Exercise (Table III-h) subjects. The post-intervention correlations are presented to address the possibility that the resistance training program may have elicited a significant alteration in the relationship between lean mass, fat mass and total mass among the subjects that underwent the intervention. As in the baseline assessments, the R-values for weight correlation with the other variables of interest were very high, exceeding 0.8 in all cases. BMI significantly correlated with waist circumference, total fat mass, trunk fat mass and trunk lean tissue, driven perhaps by the 2 male subjects in the control group. Trunk fat was strongly correlated with weight, BMI, waist circumference and total fat and with an improved sample size, abdominal fat as well (r-value = 0.93).

In the exercise group measures of weight and fatness were tightly inter-correlated as they were prior to the intervention. Weight was a significant correlate of all other

measures at the $p < 0.01$ level. Total lean mass and trunk lean mass were tightly correlated, as expected, and were significantly correlated with trunk fat and abdominal fat mass, though not with total fat mass.

Tables III-i and III-j present the correlative data for change among the measures of weight and anthropometry. In the control subjects the only significant correlations are among measures of fatness (total fat mass, trunk fat mass and abdominal fat mass) and between weight and waist circumference. Analysis of the exercise subjects indicated similar relationships between change in total fat mass with regard to change in weight and change in trunk fat mass. Change in total lean mass was significantly correlated with change in trunk lean mass. Beyond these, there were no significant relationships found.

Table III-a Baseline Weight and Anthropometric Characteristics

	n	Min	Max	Mean	SD
Weight (kg)	25	45.2	101.1	73.2	16.7
BMI (kg/cm^2)	25	19.1	37.0	26.9	5.2
Waist (cm)	23	70.4	117.2	91.5	14.8
Fat-Total (kg)	22	9.22	42.12	27.44	9.14
Fat-Trunk (kg)	22	2.88	22.18	13.16	5.46
Fat-Abd (kg)	22	0.28	6.09	2.15	1.36
Percent Fat	22	17.88	48.84	36.04	8.43
Lean-Total (kg)	22	33.08	70.85	45.26	9.90
Lean-Trunk (kg)	22	17.61	34.09	23.43	4.66

Table III-b Baseline Weight and Anthropometry by Gender

	Female			Male		
	n	Mean	SD	n	Mean	SD
Weight (kg)*	20	68.03	14.44	5	93.85	4.77
BMI (kg/cm^2)	20	26.23	5.60	5	29.39	2.01
Waist (cm)*	18	87.2	13.5	5	107.0	7.1
Fat-Total (kg)	17	27.27	9.99	5	28.02	6.21
Fat-Trunk (kg)	17	12.22	5.58	5	16.32	3.93
Fat-Abd (kg)	17	1.86	1.10	5	3.16	1.77
Percent Fat	17	37.66	8.46	5	30.52	6.12
Lean-Total (kg)*	17	40.71	4.90	5	60.71	5.71
Lean-Trunk (kg)*	17	21.27	2.39	5	30.80	1.88

* - Significant difference between genders at $p < 0.05$

Table III-c Baseline Weight and Anthropometry by Randomized Grouping

	Exercise					Control				
	n	Min	Max	Mean	SD	n	Min	Max	Mean	SD
Weight (kg)	17	45.2	101.1	71.5	17.3	8	50.8	96.2	76.7	16.0
BMI (kg/cm^2)	17	19.1	36.9	27.3	5.8	8	19.2	28.9	25.7	3.6
Waist (cm)	16	73.7	117.2	92.1	14.7	8	70.4	110.2	90.0	16.3
Fat-Total (kg)	14	11.06	42.12	30.02	9.21	8	9.22	31.00	22.93	7.50
Fat-Trunk (kg)	14	4.58	22.18	14.08	5.45	8	2.88	17.04	11.54	5.43
Fat-Abd (kg)	14	0.44	6.09	2.38	1.44	7	0.28	3.41	1.66	1.08
Percent Fat	14	24.14	48.84	39.51	6.87	8	17.88	38.91	29.97	7.70
Lean-Total (kg)	14	33.08	59.01	42.43	8.35	8	40.20	70.85	50.21	10.98
Lean-Trunk (kg)	14	17.61	30.58	21.98	4.11	8	21.19	34.09	25.99	4.71

Table III-d Baseline Weight Correlates in All Subjects (r-value)

	Weight	BMI	Waist[1]	Fat Total	Fat Trunk	Fat Abd	% Fat	Lean Total	Lean Trunk
Weight	-	0.84[b]	0.90[b]	0.74[b]	0.85[a]	0.78[a]	0.32	0.82[b]	0.80[b]
BMI		-	0.84[b]	0.91[b]	0.89[b]	0.80[a]	0.69[b]	0.39	0.37
Waist			-	0.76[b]	0.90[b]	0.86[b]	0.44	0.60[b]	0.62[b]
Fat - Total				-	0.91[b]	0.82[b]	0.86[b]	0.21	0.20
Fat - Trunk					-	0.92[b]	0.66[b]	0.46[a]	0.47[a]
Fat - Abd						-	0.61[b]	0.41	0.44
% Fat							-	-0.27	-0.28
Lean Total								-	0.98[b]
Lean Trunk									-

n = 22

[a] - $p < 0.05$ [b] - $p < 0.01$

Table III-e Post-Intervention Weight and Anthropometry by Randomized Grouping

	Exercise			Control		
	n	Mean	SD	n	Mean	SD
Weight (kg)	15	70.1	17.3	6	76.4	16.9
BMI (kg/cm^2)	15	26.2	5.5	6	25.6	3.8
Fat-Total (kg)	12	26.98	8.15	5	19.32	6.18
Fat-Trunk (kg)	12	12.87	5.08	5	9.62	4.84
Fat-Abd (kg)	12	2.51	1.50	4	1.67	0.99
% Fat	12	37.37	6.10	5	24.95	4.45
Lean-Total (kg)	12	42.26	9.18	5	54.66	13.40
Lean-Trunk (kg)	12	22.31	4.95	5	27.54	6.75

No significant differences found between groups

Table III-f Change in Weight and Anthropometry by Randomized Grouping

	Exercise			Control		
	n	Mean	SD	n	Mean	SD
Weight (kg)	15	-0.58	1.73	6	0.045	2.49
BMI (kg/cm^2)	15	-0.52	1.30	6	0.51	0.96
Fat-Total (kg)	10	-1.07	1.70	5	-1.01	2.11
Fat-Trunk (kg)	10	-0.70	0.85	5	-1.01	1.58
Fat-Abd (kg)	10	0.07	0.36	4	0.26	0.41
% Fat	10	-1.27	1.86	5	-0.83	2.11
Lean-Total (kg)	10	0.83	1.48	5	0.61	1.20
Lean-Trunk (kg)	10	0.82	1.02	5	0.04	1.43

No significant differences found between groups

Table III-g Post-Intervention Weight Correlates in Control Subjects (r-value)

	Weight	BMI	Waist	Fat Total	Fat Trunk	Fat Abd[1]	% Fat	Lean Total	Lean Trunk
Weight	-	0.94[b]	0.85	0.86	0.94[a]	0.81	0.31	0.96[b]	0.98[b]
BMI		-	0.95[a]	0.90[a]	0.98[b]	0.82	0.42	0.87	0.89[a]
Waist			-	0.94	0.99[a]	0.87	0.66	0.88	0.90
Fat Total				-	0.97[b]	0.97[a]	0.75	0.68	0.73
Fat Trunk					-	0.93	0.57	0.82	0.86
Fat Abd						-	0.88	0.62	0.68
% Fat							-	0.04	0.14
Lean Total								-	0.99[b]
Lean Trunk									-

n = 5 for all comparison except [1] where n = 4
[a] - $p < 0.05$ [b] - $p < 0.01$

Table III-h Post-Intervention Weight Correlates in Exercise Subjects (r-value)

	Weight	BMI	Waist	Fat Total[1]	Fat Trunk[1]	Fat Abd[1]	% Fat[1]	Lean Total[1]	Lean Trunk[1]
Weight	-	0.89[b]	0.77[b]	0.82[b]	0.88[b]	0.90[b]	0.33	0.89[b]	0.88[b]
BMI		-	0.66[a]	0.73[a]	0.79[b]	0.75[a]	0.26	0.76[a]	0.74[a]
Waist			-	0.82[b]	0.74[b]	0.81[b]	0.51	0.56	0.50
Fat Total				-	0.92[b]	0.86[b]	0.81[b]	0.48	0.46
Fat Trunk					-	0.95[b]	0.63[a]	0.61	0.63[a]
Fat Abd						-	0.50	0.69[a]	0.71[b]
% Fat							-	-0.13	-0.13
Lean Total								-	0.99[b]
Lean Trunk									-

n = 15 for all comparison except [1] where n = 12
[a] - $p < 0.05$ [b] - $p < 0.01$

Table III-i Post-Intervention Weight Change Correlates in Control Subjects (r-value)

	ΔWeight	ΔBMI	ΔWaist[1]	ΔFat Total	ΔFat Trunk	ΔFat Abd[1]	Δ% Fat	ΔLean Total	ΔLean Trunk
ΔWeight	-	0.76	0.94[a]	0.73	0.59	0.67	0.69	-0.17	-0.45
ΔBMI		-	0.59	0.19	-0.03	0.15	0.10	0.41	-0.22
ΔWaist			-	0.81	0.65	0.78	0.80	-0.21	-0.52
ΔFat Total				-	0.97[b]	0.99[b]	0.97[b]	-0.45	-0.24
ΔFat Trunk					-	0.97[a]	0.94[a]	-0.55	-0.16
ΔFat Abd						-	0.94	-0.31	-0.12
Δ% Fat							-	-0.68	-0.43
ΔLean Total								-	0.67
ΔLean Trunk									-

n = 5 for all comparison except [1] where n = 4
[a] - $p < 0.05$ [b] - $p < 0.01$

Table III-j Post-Intervention Weight Change Correlates in Exercise Subjects (r-value)

	ΔWeight	ΔBMI	ΔWaist	ΔFat Total	ΔFat Trunk	ΔFat Abd	Δ% Fat	ΔLean Total	ΔLean Trunk
ΔWeight	-	0.25	0.33	0.74[a]	0.47	0.41	0.45	0.54	0.38
ΔBMI		-	-0.31	-0.53	-0.56	-0.41	-0.67	0.67	0.57
ΔWaist			-	0.36	-0.20	0.50	0.07	0.25	-0.03
ΔFat Total				-	0.82[b]	0.58	0.90[b]	-0.11	-0.15
ΔFat Trunk					-	0.23	0.87[b]	-0.45	-0.25
ΔFat - Abd						-	0.48	0.20	0.17
Δ% Fat							-	-0.46	-0.29
ΔLean Total								-	0.70[a]
ΔLean Trunk									-

n = 10

[a] - $p < 0.05$ [b] - $p < 0.01$

SECTION IV - BLOOD ASSAYS

Blood was drawn from overnight (12h) fasted subjects for analysis as described in the methodology chapter. Baseline assay results for glucose, insulin, HoMA-IR, adiponectin, resistin and TNF-α are shown in Table IV-a. Insulin data was not available for one subject at baseline. Their initial sample results fell below the range of assay sensitivity on initial and follow-up assays. Fasting glucose averaged 87.28 ± 25.71 mg/dL, a result that would be considered near the high end of the typical healthy population but given the age range and arthritis status of the subjects in this data pool it is not unexpected. HOMA-IR averaged 0.85 ± 1.07, well within the range of normal insulin sensitivity. There were some subjects displaying insulin resistance, however, as indicated by an HOMA-IR value above 3.0.

Table IV-b shows the blood variables differentiated by gender. Significant differences between female and male subjects appear in glucose (92.11 ± 23.95 mg/dL and 60.38 ± 18.93 mg/dL respectively) at $p < 0.05$. Insulin and HoMA-IR differences were not statistically significant, nor were those in adiponectin or resistin. TNF-α was significantly higher in females (13.43 ± 12.37 ng/mL) than males (6.21 ± 3.59 ng/mL) at $p < 0.05$. Differences were assessed via independent sample t-test.

There were no significant differences in blood variables between the randomized exercise and control conditions at baseline, as indicated in Table IV-c. Again, one subject in the exercise condition did not have baseline insulin data as detailed above. As HOMA-IR requires insulin values for calculation that patient is likewise missing a baseline HOMA-IR value.

Table IV-d presents the correlation among blood assay variables for all randomized subjects at baseline. Insulin was found to be significantly correlated with HOMA-IR ($p < 0.01$), an unsurprising finding as the calculation of HOMA relies very strongly on the insulin value. Glucose is not as strong a mathematical factor in HOMA determination, but was still significantly correlated ($p < 0.05$). Adiponectin was not significantly correlated with insulin or HOMA-IR, but the direction of the relationship as indicated by the sign of the r-values was appropriate given the review of literature. Resistin was significantly positively correlated with both insulin and HOMA-IR ($p = 0.08$), but TNF-α was not found to be correlated with any other variables of interest.

Table IV-e provides the post-intervention blood variable data differentiated by intervention condition. In addition to the four subjects that did not complete the intervention, two subjects displayed insulin data that was significantly outside the range of normal expected results (21.09 uU/mL and 13.46 uU/mL). These values were substantially higher than their baseline results, increasing 12.92 uU/mL and 7.18 uU/mL respectively. Retesting of their samples resulted in results similar to those seen in the initial post-intervention test. These data points have been excluded from analysis as they indicate one of the following possibilities: (a) error in blood collection or processing, (b) error in blood analysis, or (c) non-adherence with the fasting protocol. While it is possible that these subjects did develop extreme insulin resistance over the course of the intervention it is extremely unlikely that this is not artifact.

There were again no significant differences in blood variables between the two intervention conditions at the post-intervention time point, nor were there any significant differences seen in changes in blood variables between the two conditions (Table IV-f).

Significant baseline to post-intervention differences did exist within the exercise grouping. Glucose increased over the course of the study from 86.77 ± 7.76 mg/dL to 105.62 mg/dL in the subjects who completed the exercise intervention ($p = 0.04$), and resistin levels increased from 16.10 ± 4.18 ng/mL to 17.67 ± 3.85 ng/mL in those same subjects ($p = 0.10$). In the control condition glucose was the only variable to show a marked change, as glucose increased from 72.25 ± 3.52 mg/dL to 97.63 ± 14.29 mg/dL ($p = 0.058$) among those subjects who underwent both baseline and post-intervention testing. No other blood variables displayed significant change between those time points.

There were no significant correlations among the blood variables in control subjects following the intervention period as detailed in Table IV-g. The only significant correlation among the exercise subjects was between fasting plasma glucose and adiponectin (-0.605, $p < 0.05$). This data is presented in Table IV-h.

Among the control subjects there were no significant correlations among change in blood variables (Table IV-i) reported other than the expected insulin/HOMA-IR link. It is worth noting, though, that change in adiponectin and resistin displayed a very high r-value (0.89) as did change in resistin and TNF-α (-0.83) indicating the possibility of a relationship had the n-value been of greater magnitude. Change in glucose and TNF-α also had a similarly high R-value (0.83).

Correlation values among change in blood variables in the exercise subjects are displayed in Table IV-j. Again, change in fasting plasma insulin and HOMA-IR are tightly correlated due to the strong impact of insulin in the calculation of HOMA-IR. Change in adiponectin significantly correlated with change in fasting plasma glucose ($p < 0.01$) and change in TNF-α ($p < 0.05$) among these subjects.

Table IV-a Baseline Blood Variables

	n	Min	Max	Mean	SD
Glucose (mg/dL)	21	34.50	138.50	87.67	26.80
Insulin (uU/mL)	20	0.51	13.71	3.56	3.62
HoMA - IR	20	0.06	4.69	0.85	1.07
Adiponectin (μg/mL)	21	0.64	18.80	6.97	5.10
Resistin (ng/mL)	21	9.64	23.00	15.23	3.96
TNF-α (pg/mL)	21	0.72	54.81	12.79	12.74

Table IV-b Baseline Blood Variables by Gender

	Female			Male		
	n	Mean	SD	n	Mean	SD
Glucose (mg/dL)*	17	94.09	24.50	4	60.38	18.93
Insulin (uU/mL)	17	3.21	3.35	3	5.55	5.28
HoMA - IR	17	0.86	1.13	3	0.83	0.79
Adiponectin (μg/mL)	17	7.76	5.21	4	3.59	3.04
Resistin (ng/mL)	17	14.79	3.49	4	17.10	5.82
TNF-α (pg/mL)*	17	14.33	13.68	4	6.21	3.59

* - significant differences $p < 0.05$

Table IV-c Baseline Blood Variables by Randomized Grouping

	Exercise			Control		
	n	Mean	SD	n	Mean	SD
Glucose (mg/dL)	15	94.27	29.06	6	71.17	7.09
Insulin (uU/mL)	14	3.34	3.65	6	4.07	3.83
HoMA - IR	14	0.93	1.24	6	0.67	0.55
Adiponectin (μg/mL)	15	7.15	5.51	6	6.52	4.30
Resistin (ng/mL)	15	15.94	3.98	6	13.45	3.62
TNF-α (pg/mL)	15	10.20	9.31	6	19.26	18.34

No significant differences found between groups

Table IV-d Baseline Blood Correlates (r-value)

	Glucose	Insulin	HoMA-IR	Adiponectin	Resistin	TNF-α
Glucose	-	0.26	0.50[c]	0.11	-0.13	-0.06
Insulin		-	0.92[c]	-0.12	0.35[a]	-0.15
HoMA - IR			-	-0.10	0.35[a]	-0.18
Adiponectin				-	0.19	0.25
Resistin					-	-0.12
TNF-α						-

n = 26

[a] - $p < 0.10$ [b] - $p < 0.05$ [c] - $p < 0.01$

Table IV-e Post-Intervention Blood Variables by Randomized Grouping

	Exercise			Control		
	n	Mean	SD	n	Mean	SD
Glucose (mg/dL)	13	105.62	17.03	4	97.63	14.29
Insulin (uU/mL)	13	3.51	2.14	4	2.34	1.73
HoMA - IR	13	0.93	0.64	4	0.59	0.46
Adiponectin (μg/mL)	13	7.86	4.15	4	11.61	5.64
Resistin (pg/mL)	13	17.67	3.85	4	16.00	6.79
TNF-α (ng/mL)	13	10.57	6.26	4	14.63	8.71

No significant differences between groups

Table IV-f Change in Blood Variables by Randomized Grouping

	Exercise			Control		
	n	Mean	SD	n	Mean	SD
Glucose (mg/dL)	13	15.85	24.84	4	25.37	16.94
Insulin (uU/mL)	12	0.30	2.37	4	0.15	1.92
HoMA - IR	12	0.09	0.64	4	0.20	0.42
Adiponectin (μg/mL)	13	1.32	3.86	4	4.13	5.39
Resistin (pg/mL)	13	1.57	3.17	4	4.36	7.41
TNF-α (ng/mL)	13	1.01	12.78	4	-9.33	13.26

No significant differences were found between groups

Table IV-g Post-Intervention Blood Correlates in Control Subjects (r-value)

	Glucose	Insulin	HoMA-IR	Adiponectin	Resistin	TNF-α
Glucose	-	0.56	0.69	-0.25	-0.75	-0.71
Insulin		-	0.99[a]	0.66	-0.10	-0.81
HoMA - IR			-	0.53	-0.23	-0.84
Adiponectin				-	0.48	-0.37
Resistin					-	0.61
TNF-α						-

n = 4

[a] - $p < 0.05$ [b] - $p < 0.01$

Table IV-h Post-Intervention Blood Correlates in Exercise Subjects (r-value)

	Glucose	Insulin	HoMA-IR	Adiponectin	Resistin	TNF-α
Glucose	-	0.18	0.35	-0.61[a]	-0.22	-0.04
Insulin		-	0.98[b]	-0.10	0.44	0.37
HoMA - IR			-	-0.18	0.35	0.37
Adiponectin				-	0.22	0.19
Resistin					-	-0.18
TNF-α						-

n = 13
[a] - $p < 0.05$ [b] - $p < 0.01$

Table IV-i Change in Blood Variable Correlates in Control Subjects (r-value)

	ΔGlucose	ΔInsulin	ΔHoMA-IR	ΔAdiponectin	ΔResistin	ΔTNF-α
ΔGlucose	-	-0.05	0.36	-0.26	-0.57	0.83
ΔInsulin		-	0.91[a]	0.54	0.21	0.20
ΔHoMA - IR			-	0.44	0.01	0.50
ΔAdiponectin				-	0.89	-0.49
ΔResistin					-	-0.83
ΔTNF-α						-

n = 4
[a] - $p < 0.05$ [b] - $p < 0.01$

Table IV-j Change in Blood Variable Correlates in Exercise Subjects (r-value)

	ΔGlucose	ΔInsulin[1]	ΔHoMA-IR[1]	ΔAdiponectin	ΔResistin	ΔTNF-α
ΔGlucose	-	0.37	0.47	0.73[b]	-0.29	0.42
ΔInsulin		-	0.99[b]	0.49	0.44	0.04
ΔHoMA - IR			-	0.53	0.39	0.10
ΔAdiponectin				-	-0.35	0.59[a]
ΔResistin					-	-0.51
ΔTNF-α						-

n = 13 except [1] where n = 12
[a] – $p < 0.05$ [b] – $p < 0.01$

SECTION V - INTRAVARIABLE RELATIONSHIPS

Correlations were assessed among the demographics, measures of weight/anthropometry and levels of blood variables at baseline and post-intervention time points. The correlations of variables as related to demographics as well as relationships among the variables of interest in the entire subject population prior to intervention are presented in tables V-a, V-b and V-c.

No significant correlations were found among measures of weight/anthropometry and demographics. As indicated in Table V-b, Resistin was significantly positively correlated with age in years ($p < 0.05$) and duration of Remicade treatment in months ($p < 0.01$), indicating increased resistin levels with advancing age or extended Remicade therapy. No other relationships of significance were found as related to demographics and the variables of interest. These relationships were not re-examined following the intervention as it is reasonable to assume that they would not have changed based on a brief intervention period.

Table V-c presents correlation coefficients indicating relationships among weight/anthropometry measures and the blood variables of interest among the entire population. Plasma glucose levels were positively correlated with percent fat ($p < 0.05$) but not with other measures of weight or body composition. HOMA-IR was found to be significantly positively correlated with waist circumference and trunk fat ($p < 0.05$), suggesting an increase in insulin resistance with increased central fat. Abdominal fat from DXA assessment, however, was not found to be significantly correlated with HOMA-IR. Adiponectin was significantly negatively correlated with most every measure of weight and body composition, and this relationship was strongest with

weight, abdominal fat and total lean mass. Resistin, like HOMA-IR, was positively and significantly correlated with waist circumference and trunk fat mass, suggesting an increase in plasma resistin levels with increased central fat. The correlations of insulin levels with waist circumference ($r = 0.41$, $p = 0.056$) and insulin levels with trunk fat mass ($r = 0.41$, $p = 0.085$) approached significance, as did the relationship between total fat mass and HOMA-IR ($r = 0.43$, $p = 0.068$).

Table V-d reports the correlation values found when examining the changes in these same variables following the intervention period (change versus change). The control subject pool was reduced in size by attrition and missing data, resulting in no significant value in examining these relationships. As such, only the data in the Exercise subjects is presented for review.

Among the exercise subjects the change in trunk lean mass was significantly negatively correlated with change in fasting plasma glucose, insulin, HOMA-IR and adiponectin. The change in total lean mass was correlated with the change in TNF-α and the relationship between change in lean trunk mass and change in TNF-α approached significance ($r = 0.61$, $p = 0.084$), as did the correlation between change in BMI with change in HOMA-IR ($r = 0.63$, $p = 0.054$) and change in BMI with change in insulin ($r = 0.60$, $p = 0.067$). No other relationships approached significance.

Table V-a Demographics & Weight/Anthropometry Correlates (r-value)

	Weight[1]	BMI[1]	Waist[2]	Fat Total	Fat Trunk	Fat Abd	Lean Total	Lean Trunk
Age	-0.12	-0.15	0.19	-0.06	0.04	0.05	-0.11	-0.02
RA Years	-0.18	-0.21	-0.04	-0.09	0.03	0.06	0.03	0.11
Remicade Mos	0.25	0.15	0.17	0.11	0.12	0.12	0.27	0.28

[1] - n = 30, [2] - n = 27, for all other comparisons n = 23
[a] - $p < 0.05$ [b] - $p < 0.01$

Table V-b Demographics & Blood Variable Correlates (r-value)

	Glucose	Insulin[1]	HoMA-IR[1]	Adiponectin	Resistin	TNF-α
Age	0.10	0.08	0.11	0.36	0.43[a]	-0.01
RA Years	0.23	-0.04	0.02	0.21	0.28	0.15
Remicade Mos	-0.29	-0.11	-0.19	0.06	0.50[b]	0.17

n = 26 except [1] where n = 25
[a] - $p < 0.05$ [b] - $p < 0.01$

Table V-c Weight & Blood Variable Correlates in Pooled Subjects (r-value)

	Weight[1]	BMI[1]	Waist[2]	Fat Total	Fat Trunk	Fat Abd	% Fat	Lean Total	Lean Trunk
Glucose	-0.07	0.24	0.13	0.31	0.26	0.12	0.47[a]	-0.31	-0.32
Insulin	0.26	0.29	0.41	0.31	0.41	0.21	0.14	0.33	0.33
HoMA – IR	0.22	0.35	0.44[a]	0.43	0.52[a]	0.28	0.34	0.16	0.17
Adiponectin	-0.52[b]	-0.50[a]	-0.35	-0.46[a]	-0.56[a]	-0.53[b]	-0.25	-0.57[b]	-0.52[a]
Resistin	0.24	0.16	0.44[a]	0.41	0.45[a]	0.19	0.32	0.26	0.30
TNF - α	-0.23	-0.26	-0.32	-0.39	-0.43	-0.32	-0.29	-0.30	-0.26

[1] - n = 26, [2] – n = 23, for all other comparisons n = 20
[a] - $p < 0.05$ [b] - $p < 0.01$

Table V-d Change in Weight/Blood Variable Correlates in Exercise Subjects (r-value)

	ΔWeight[1]	ΔBMI[1]	ΔWaist[1]	ΔFat Total	ΔFat Trunk	ΔFat Abd	Δ% Fat	ΔLean Total	ΔLean Trunk
ΔGlucose	0.21	0.43	0.04	-0.29	-0.37	0.19	-0.37	0.58	0.80[b]
ΔInsulin	0.42	0.60	-0.22	-0.01	-0.08	0.28	-0.10	0.45	0.74[a]
ΔHoMA – IR	0.42	0.63	-0.20	-0.12	-0.17	0.26	-0.18	0.46	0.78[a]
ΔAdiponectin	0.16	0.11	-0.12	-0.10	-0.12	0.40	-0.19	0.56	0.75[a]
ΔResistin	0.27	0.31	0.01	0.36	0.48	-0.25	0.44	-0.39	-0.22
ΔTNF - α	-0.24	-0.19	0.28	0.19	0.33	0.20	-0.39	-0.67[a]	-0.61

[1] = n = 11, for all other comparisons n = 9
[a] - $p < 0.05$ [b] - $p < 0.01$

SECTION VI - REGRESSION ANALYSIS

Linear regression analysis was used to examine the significance of a body composition and adipokines in predicting HOMA-IR in the subject population at baseline following randomization. The initial models consisted of one measure of anthropometry or body composition (weight, BMI, waist circumference, total fat mass, trunk fat mass or abdominal fat mass), age, years of RA, duration of Remicade treatment and the three adipokines (adiponectin, resistin and TNF-α). Each model thus began with 7 variables. Variables were then removed in a backward regression based on the significance of the variable in predicting HOMA-IR until only variables found to be significant predictors remained in the final model. Table VI-a presents the 6 models developed by the regression analysis.

Despite the nearly significant correlation between resistin and HOMA-IR observed in the pooled subjects, resistin was not found to be a significant predictor. Similarly, adiponectin, TNF-α and age were found to be non-significant. Of the anthropometric and body composition variables trunk fat was found to be most significant predictor, though abdominal fat, total fat and BMI all resulted in significant predictive strength when substituted for trunk fat.

Multivariate model testing found that a two-component model using trunk fat and Remicade duration was best suited for prediction. The model had an adjusted $r^2 = 0.342$ and ANOVA indicates significance ($P = .014$). Trunk fat ($t = 2.994$, $P < .01$) was the stronger of the two components, while Remicade duration ($t = -2.030$, $P < .05$) had an effect counter that of trunk fat. Using forward regression the addition of adiponectin,

resistin or TNF-α to this model resulted in a decrease in predictive strength. The addition of other anthropometric measures resulted in co-linearity and did not improve the model.

Linear regression analysis was also employed to examine predictors of change in the index of insulin resistance. Table VI-b presents the regression models derived to assess the impact of change in variables of interest on the change in HOMA-IR. The variables were selected based both on anticipated impact as derived from the review of literature and relationships (or lack thereof) quantified from analysis of this data. Variables were removed in order of reverse significance until all variables remaining in the model were reported as significant.

The variables Δ total fat, Δ adiponectin and Δ trunk fat were removed in order as each was found to be non-significant in regards to the prediction of change in HOMA-IR. That left Model 4, containing as independent variables Δ total lean mass, Δ resistin and Δ TNF-α. Each was found to be significant in the prediction of change in HOMA-IR (significance determined at $p < 0.05$). The results of ANOVA indicate that the model approaches significance ($p = 0.063$) and carries weight in the prediction of HOMA-IR change with an adjusted $r^2 = 0.464$. The change in lean tissue mass the most significant predictor of change in insulin sensitivity, followed by change in TNF-α and then change in resistin. Removal of resistin or TNF-α from the model did not improve the predictive strength or enhance the significance of the model, in fact reducing both qualities. Inclusion of baseline HOMA-IR eclipsed the impact of all other variables of change when performing regression with ΔHOMA-IR as the dependent variable, indicating that

HOMA-IR prior to intervention was the most significant predictor of HOMA-IR change following intervention.

Table VI-a Regression Models for Prediction of HOMA-IR

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
	β	Sig	β	Sig	β	Sig	β	Sig	β	Sig	β	Sig
Trunk Fat	0.739	.04	0.739	.03	0.690	.03	0.725	.01	0.635	.01	0.581	.01
Remicade Dur.	-0.511	.12	-0.523	.07	-0.488	.07	-0.419	.05	-0.412	.05	-0.394	.05
Age	-0.367	.25	-0.380	.18	-0.352	.19	-0.338	.19	-0.261	.19		
Adiponectin	0.164	.61	0.160	.60	0.140	.63	0.147	.60				
Resistin	0.488	.64	0.159	.58	0.125	.64						
TNF-α	0.111	.67	0.103	.67								
RA Duration	-0.032	.91										
Intercept	0.681	.63	0.687	.61	0.927	.44	1.158	.28	1.270	.22	0.200	.75
Significance	0.228		0.135		0.077		0.039		0.018		0.014	
SEE	0.965		0.925		0.896		0.870		0.849		0.872	
Adjusted R^2	0.194		0.261		0.307		0.345		0.376		0.342	

Table VI-b Regression Models for Prediction of Change in HOMA-IR

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6	
	β	Sig	β	Sig	β	Sig	β	Sig	β	Sig	β	Sig
Δ Lean Mass	-1.506	.09	-1.528	.06	-1.618	.02	-1.644	.01	-0.798	.09	-0.463	.20
Δ Resistin	-1.410	.14	-1.383	.10	-1.354	.08	-1.396	.05			0.119	.73
Δ TNF-α	-2.348	.09	-2.253	.06	-2.280	.04	-2.249	.03	-0.521	.24		
Δ Trunk Fat	0.456	.68	0.147	.67	0.146	.64						
Δ Adiponectin	0.133	.75	0.122	.74								
Δ Total Fat	-0.288	.77										
Intercept	-0.581	.17	-0.514	.10	-0.511	.07	-0.439	.04	-0.243	.24	-0.118	.53
Significance	0.426		0.260		0.137		0.063		0.209		0.410	
SEE	0.466		0.422		0.390		0.368		0.462		0.503	
Adjusted R^2	0.141		0.295		0.398		0.464		0.155		0.000	

CHAPTER IV: DISCUSSION

STRENGTH

The primary aim of the intervention condition in this study was to engage the subjects in an intensive, progressive and individualized strength training regimen and to examine the impact of that regimen on weight, body fat, lean mass, markers of inflammation and measures of glucose metabolism. As such, the efficacy of the intervention was of paramount importance. If the training program did not increase the strength of the participants, demonstrating that they did exercise and achieve an adaptation, few useful conclusions regarding the impact of the program on the variables of interest can be drawn.

Post-intervention testing showed a clear and significant increase in weight lifted in all exercises ranging from a 31% increase (hammer curl, right arm) to a 50% increase (military press, right arm). Virtually every participant increased in strength from the baseline assessment to the post-intervention period in every exercise, regardless of initial strength, with many of the exercisers exhibiting strength increases in excess of 100% of their initial result. A previous study in a similar cohort of RA patients found a 12-week training regimen resulted in strength increases 48% greater than those reported in the control subjects in that study, though the study in question did rely on only the 1RM test of strength.(Rall 1996) The improvement in strength detailed in the Rall, et al, study is greater than that shown in other, perhaps more limited studies. Hayase et al. (Hayase 02) reported 1RM gains in leg press and bench press in the range of 10-12% following a 10-week training regimen in women. This study intervention did not provide the same degree of individualization or training duration as the current study but did exhibit

significant improvement in muscle strength. A more lengthy and intensive exercise intervention was employed by Greiwe et al.[(Greiwe, 01)] in their investigation of the impact of resistance training in the elderly. Their 3-month intervention led to strength gains ranging from 18-28% (bench press and leg press respectively) in subjects classified as frail, but generally healthy. Their cohort presented similar training obstacles as RA patients in that they suffer from limited ability to perform activities of every day life and, from an training standpoint, are not always able to complete exercises without risk of pain or injury. The authors of a study featuring a 6-week intervention in a similar group of elderly subjects present data showing significant strength gains up to 81% (leg press). Measurements of muscle power as assessed by isokinetic dynamometer tests found increases from 21-24% of baseline, dependent on the test applied.[(Bautmans, 2005)] The increase in power clearly indicates a significant increase in muscle strength, but the magnitude of gain in absolute weight suggests that some portion of the improvement is related to the subjects gaining mastery of the exercise techniques. Though not presented in detail in the present work, participants in the exercise group also improved peak torque as assessed by isokinetic dynamometer and hand strength.[(Flint-Wagner 09)]

Though increased familiarity with the exercises and improvement in technique can account for a significant portion of early gains in weight lifted, the inclusion of a midpoint assessment several weeks into the intervention allays concerns that gains in weight lifted are simply a byproduct of increased weight lifting expertise. Improvement in 3RM weight continued from the midpoint to the post-intervention assessment, confirming an actual increase in strength, as an increase limited to mastery of the exercise

protocol almost certainly would have been temporally limited to the first few weeks of the intervention.

This legitimate gain in strength, as opposed to improved neural skill, is further corroborated by a tendency for lean body mass, both total and trunk, to increase with increasing 3RM values. These increases in lean body mass in the exercise group did not achieve statistical significance, though the increase in trunk lean body mass did approach a significant level ($p = 0.059$). Other investigations reviewed also indicated a tendency for increases in lean body mass of a similar magnitude, though these did not always achieve significance[(Reynolds 2004, Greiwe 2001)]. These changes are indicated as typical and expected by Winett et al[(Winett 2001)] in their review of the primary literature regarding health-related benefits of resistance training.

The personalization and supervision of the exercise regimen was one of the greatest strengths of the current study. The special nature of the RA patients requires a degree of flexibility and presentation of exercise options generally not required by other groups due in no small part to the mobility limitations imposed on these exercisers by the disease. The presence of qualified trainers dedicated to both maximizing the impact of the training intervention and offering personal encouragement can not be overstated. Both post-intervention survey and anecdotal accounts indicate that the trainers encouraged compliance and effort while working to make the training experience more enjoyable for the participants.

Furthermore, in order to be maximally effective a resistance exercise regimen must be progressive, both in terms of training volume (either number of repetitions or

single repetition weight) and in terms of exercise complexity (e.g. moving from machines to free weights). The expertise of the trainers was applied to increasing the workload of the exercisers as well as advancing them from more basic to more comprehensive or intensive exercises. Their presence and guidance eliminated the guesswork regarding weight loads and progressions that would normally be employed by a novice exerciser and maximized the efficacy of the 16-week training program for virtually all of the intervention subjects.

The design of the training intervention presented exercisers with several options for each muscle group or movement. This provision allowed exercisers to complete their workout in all areas despite pain or limited mobility secondary to disease flare-ups. In other programs an exerciser may have had to skip any number of exercises or perhaps even the entire bout, but in the current study they were able to continue to participate in the intervention on a regular basis. The inclusion of exercise options also helps combat a sense of boredom or repetition by allowing the exercisers to vary their routines while still completing an appropriate amount of exercise.

WEIGHT AND ANTHROPOMETRY

Weight and BMI

Body weight, BMI and waist circumference were not significantly reduced in either the intervention or control groups. This was not unexpected as the goal of the exercise intervention was not a decrease in absolute weight but an increase in muscle strength. Though there were no significant baseline-to-completion changes in BMI in either group, there was a tendency for subjects in the intervention group to decrease BMI (-0.51 ± 1.30) while those in the control group increased BMI (0.51 ± 0.96). The

difference in change in BMI between groups was nearly significant ($p = 0.098$), though weight change was not. In the control group one subject lost an exceptional amount of weight (4.16 kg) while others generally increased weight. Eliminating this subject's data alters the control group weight change from a gain of 0.045 ± 2.49 kg to a gain of 0.89 ± 0.70 kg, and while this filtered value is still not significantly different from the exercise group (-0.58 ± 1.73kg) it does approach significance ($p = 0.11$).

The effect on change in BMI data was not as pronounced since the weight lost by the subject accounted for only a small portion of the subject's total mass, limiting the impact on BMI and reducing the effect of the subject on the control pool's mean BMI value and standard deviation. Even so, and with the reduction of statistical power caused by removing a subject from analysis, the p-value following filtering was reduced from 0.098 to 0.089.

The subjects in both the exercise and control groups were instructed to maintain normal activity and lifestyle (aside from the intervention) and were specifically instructed to not engage in any new weight loss program or regimen. Clearly some subjects' weight changed over the months of the study and that is an unavoidable confounding variable. Given the small sample size in the study, however, subjects who displayed significant changes in mass or weight could not be excluded from analysis on that basis alone.

Fat Mass

Average percent fat mass was statistically unchanged in the control group (-0.83%, $p = 0.43$) despite two subjects losing a notable percentage of their body fat (2.95% and 3.11%). This includes the previously mentioned subject with the exceptionally high weight loss as well as a second subject who did not have a significant

change in overall weight but clearly altered their body composition. The reduction in percentage of body fat in the intervention group was nearly significant (-1.27%, $p = 0.06$), though the sample size and unexpectedly high degree of variability precluded it from reaching standard levels of significance. Change in percent fat was not statistically different between study conditions.

Total body fat mass was not appreciably altered in the control group over the course of the study ($\Delta = -1.01 \pm 2.11$ kg, $p = 0.34$) despite the impact of the two control subjects mentioned above. Though it did not achieve significance ($p = 0.77$), the change in total fat mass in the exercise group was similar in magnitude to that seen in the control group, but with a more consistent distribution ($\Delta = -1.07 \pm 1.70$ kg).

The trend to reduce body fat percentage and total fat mass in the exercise group was likely the result of fat loss in the trunk region, as the intervention group reduced trunk fat by 0.70 ± 0.85 kg ($p = 0.029$). The control group had a mean trunk fat loss of slightly over 1 kg (± 1.57 kg, $p = 0.19$) but this was not significant, due in part to the large standard deviation determined for this small sample. The change in abdominal fat was not statistically different between groups.

Though abdominal fat specifically was not significantly reduced in this study the overall loss of trunk fat and near significant loss of total fat mass ($p = 0.077$) in the exercise group seems a reasonable expectation following an intensive exercise program, even if it is not one tailored to weight loss. This finding is corroborated by published findings from other studies which link resistance training to decreased abdominal fat, particularly as part of an overall exercise regimen.(Hayase 02, Park 03, Winett 01) The majority of

the literature surveyed involved concomitant resistance and aerobic training, more typical of exercise programs prescribed or recommended by physicians, trainers and mass media publications, particularly when discussed as part of the treatment for a disease or condition. The moderate walking component used in this intervention was perhaps less strenuous than the aerobic elements of the other studies surveyed, decreasing the impact of the intervention on body fat measures. However, using a conservative guideline of 400 kcal/hr, typical for a 150-lb subject performing strenuous housework, exercise participants would be estimated to spend at least 1500 kcal/week (based on 3 sessions per week at 75 minutes per session) in the exercise program.

In their study, Ibanez et al[(Ibanez 05)] employed a progressive resistance training program similar in duration to the current study in Type 2 diabetic men. The authors found that 2 training sessions per week resulted in a significant decrease in abdominal fat mass (via computed tomography) as well as skinfold thickness following the intervention without a substantial change in total body mass. The change in abdominal fat was reported to be near 10% reduction, more than twice the 5% decrease seen in the current study, possibly due in part to the greater homogeneity of the subjects in that study (all males within a smaller age range).

A 6-week resistance training program in diabetic women reported a modest change in body fat (approximately 2.5%) without a change in overall body weight, in line with the current study if extrapolated to a greater duration. Again, their study benefited from inclusion of only a single gender (all female) in a more narrow age range. As such, even though the sample size was smaller (n = 7) fat mass and weight results were more

consistent and achieved significance while those reported in the current work did not, despite similar magnitudes of change.[Fenicchia 04]

Park et al[Park 03], Cuff et al[Cuff 03] and Maiorana et al[Maiorana 02] each reported on combined exercise programs in either obese or diabetic patients. Each reported decreases in measures of body fatness and/or central fatness (abdominal fat, abdominal and visceral fat, and waist-to-hip ratio, respectively) following mixed resistance and aerobic interventions that were not always accompanied by total weight loss.

Lean Mass

The reduction of fat mass with a conservation of total mass suggests quite clearly that changes must have occurred in the lean tissue compartment. Lean total mass did tend to increase in the exercise group by approximately 2% ($\Delta = 0.83 \pm 1.48$ kg, $p = 0.11$) but the increase did not reach statistical significance. Nearly all of this increase was reflected in the trunk lean mass as this compartment did increase by nearly 4%, a significant difference from pre- to post-intervention ($\Delta = 0.82 \pm 1.02$ kg, $p = 0.03$). This may indicate that the upper body workout regimen represented a greater increase over pre-intervention usage of the affected muscle groups than the lower body exercise. The control group did also exhibit a non-significant increase in total lean mass (approximately 1%) while trunk lean mass was virtually unchanged. Again, a limited control subject sample size and incomplete data impugned the statistical power and limits the strength of comparisons. Still, the increase in total lean mass seen in the exercise cohort was similar to that reported by Reynolds et al[Reynolds 04] in their examination of resistance training in adult hypertensives. Again, a more homogenous group of subjects may have been the

key difference between that study and the current investigation. The standard deviation of their sample at baseline was approximately 7% as compared to the nearly 20% value seen in the exercise subjects in this work.

The increase in lean mass in the exercise subjects was well below the nearly 20% increase reported by Park et al[Park 03], but the trend towards increased muscle mass in the current subjects is nonetheless encouraging. Several other studies report implied lean mass gains by reporting decreases in fat mass with a stable or increasing total body mass.[Maiorana 02, Cuff 03, Hayase 02, Ibanez 05] At least one combined strength and aerobic training study reported decreases in weight, BMI and fat mass without significant alteration in lean body mass but clearly the focus of the intervention in this study was on the aerobic component, the opposite of that in the current work.[Hayase 02]

Lean body mass is frequently ignored or at least not specifically addressed in exercise studies examining subjects with a particular disease or health risk factor such as senescence. This is likely the byproduct of the focus on fat- and weight-reduction in disease intervention or obesity reduction/prevention, generally leading to a focus on aerobic exercise. While this is an understandable focus, the importance of lean mass in glycemic control should not be overlooked. As such, many of the studies surveyed that addressed treatment of insulin resistance or diabetes, particularly Type 2 Diabetes, addressed lean mass at least in passing. The variability of the results in the present study, particularly with regard to anthropometry and body composition, are a confounding condition with regards to the analysis of exercise impact on glycemic control if it is exclusively through impact on body composition. The heterogeneity of both the exercise

and control cohorts is significant, and while that perhaps enhances the generalizability of the results to the population it does decrease the statistical power of the study. Because of the small sample size the magnitude of changes reported in this work, while similar in magnitude to significant findings in other studies, do not achieve statistical significance.

INSULIN RESISTANCE

Glucose

Glucose is a vital fuel source for muscle, brain and organ function in humans and is primarily stored in the body as glycogen, a glucose polysaccharide. It is derived in one of three methods: from intestinal absorption following digestion of carbohydrate; from the formation of glucose via gluconeogenesis from pyruvate or other substances in the liver; or from glycogenolysis, the lysing of stored glycogen. In the fasted non-exercising condition, plasma glucose is generally stable in a range from 70-100 mg/dL, indicating a match between utilization and supply. Following meals in non-diabetic, otherwise healthy individual's plasma glucose should be expected to fall between 70-145 mg/dL. Diabetes, the most profound and common disease of glucose disregulation, is diagnosed based on the criteria of fasting blood glucose consistently $\geq$ 126 mg/dL or a 2-hour postprandial blood glucose consistently $\geq$ 200 mg/dL.[(Giugliano 08)]

Significant regulation of glucose levels within the body is required to prevent or limit incidence of hypo- or hyperglycemia. The interaction between counter-regulatory hormones such as insulin and glucagon strives to maintain blood sugar levels by, for instance, reducing endogenous production of glucose following meals or increasing production when plasma glucose levels fall during fasting or exercise. Hypoglycemia can lead to nausea, anxiety, cognitive dysfunction or in extreme cases coma and

death.[Clarke 08] Hyperglycemia symptoms include excessive thirst, headache, frequent urination and fatigue. Chronic hyperglycemia is associated with neural dysfunction, stomach and digestive distress and delayed healing of injury as well as the risk of diabetes. In addition to the host of health issues attendant with diabetes, prolonged hyperglycemia has been associated with independent cardiovascular disease risk.[Guigliano, 08]

Maiorana et al[Maiorana 2002] and Ibanez et al[Ibanez 2005] both reported decreased plasma glucose in subjects following intensive resistance training, leading to increased insulin sensitivity and improved glycemic control. Other investigators, however, have reported improved insulin action and glycemic control without significant decrease in fasting plasma glucose.[Cuff 2003, DiPietro 2006, Fenicchia 2004] As insulin-mediated glucose disposal is a dynamic mechanism, perhaps fasting glucose is not as strong an indicator of glycemic control as might be desired. Insulin sensitivity, when measured indirectly via fasting plasma glucose and/or insulin levels, is an index based on the ratio of those variables. An improvement in sensitivity could be the result of a reduction in plasma glucose, plasma insulin, or both. Similarly, if a reduction in plasma insulin was accompanied by an increase in plasma glucose the combined effect might yet be an improvement in insulin sensitivity. As such, while fasting plasma glucose values are important they do not always provide a complete understanding of glycemic control or insulin sensitivity in a subject.

In the pooled subjects at baseline, fasting glucose was significantly positively correlated with percent fat ($r = 0.47$, $p < 0.05$) and was found to be significantly higher (p

< 0.05) in women (94.09 ± 24.50 mg/dL) than men (60.38 ± 18.93 mg/dL). Though the correlation was not statistically significant, baseline glucose was inversely correlated with both total lean mass and trunk lean mass (r = -0.31 and -0.32 respectively). This may explain some of the difference in fasting plasma glucose between gender groups as the men had a decidedly higher amount of lean tissue at baseline as compared to the women. There were no significant relationships between fasting glucose and weight or BMI at the onset of the current study.

In contrast to the findings in some other published studies[Maiorana 02, Ibanez 05], plasma glucose increased significantly ($p < 0.05$) in the intervention cohort in this study, but without a concomitant increase in insulin. Subjects in the control group evidenced a high-magnitude increase in plasma glucose levels (25.37 ± 16.94 mg/dL, $p = 0.058$) that approached, but did not achieve significance. In the exercise cohort, change in fasting glucose was strongly inversely correlated ($r = -0.80$, $p < 0.01$) with change in trunk lean mass, while the association between change in glucose and change in total lean mass was of high magnitude ($r = -0.58$) it did not reach statistical significance. In either case it is indicated that an increase in lean mass is associated with a decrease in plasma glucose, as would be expected given the dominance of skeletal muscle in glucose clearance in both the postprandial or fasting and exercise state.[Meyer 02, Hamada 03] Given the near-significant increase in trunk lean mass and the trend to increase total lean mass in the exercise cohort, the significant increase in average fasting plasma glucose in this group seems to be at odds with the correlative results. This may be the result of subject attrition skewing

data or the decrease of glucose in those greatly increasing lean mass being outstripped by the increase of glucose levels in those that did not gain lean mass.

Insulin

Insulin is the primary hormone involved in the regulation of blood glucose. Secreted from the beta cells of the pancreas, insulin acts in two avenues to maintain normoglycemia: on the liver to decrease gluconeogenesis, particularly during fasting conditions without energy demand, and on peripheral tissues to stimulate glucose clearance from the blood. Insulin release is stimulated by elevated plasma glucose and is opposed by stress hormones such as epinephrine or cortisol. Insulin signaling is opposed by glucagon, a counter-regulatory hormone.(Giugliano 08, Trout 07) The mean fasting plasma insulin level in healthy individuals is approximately 5 uU/mL, though some sources indicate a range of 5-20 uU/mL as normal.(Sonksen 00) A surfeit or deficit of insulin can result in hypo- or hyperglycemia with the attendant consequences as detailed previously in this work. Hyperinsulinemia is frequently seen in pre-diabetic patients, appearing in 70-85% of patients before diagnosis, as well as those with early Type 2 diabetes, as the pancreas struggles to secrete sufficient insulin to overcome peripheral resistance. Prolonged elevated insulin levels may also contribute to hypertension in the absence of diabetes.(Cornier 08) Later stage Type 2 diabetes and, of course, Type 1 diabetes are associated with decreased insulin secretion leading to hyperglycemia in the absence of pharmacologic intervention.

Baseline fasting insulin levels in the combined control and exercise cohort exhibited a wide range of values (0.51 to 13.71 uU/mL), indicating the presence of both

"normal" and modestly hyperinsulinemic subjects in the initial sample. The mean value (3.56 ± 3.62 uU/mL) falls within the expected normal range, though the small sample size and spread of values result in a high standard deviation. While not statistically significant, there is a gender difference in fasting insulin levels of high magnitude, with the average female value (3.21 ± 3.35 uU/mL) well below the average male value (5.55 ± 5.28 uU/mL). The randomized control and exercise groups were very nearly identical in value and deviation, limiting the impact of baseline values on subsequent findings. Baseline fasting insulin values were not significantly correlated with any measure of body composition, but the r-values for the correlation between insulin and waist circumference ($r = 0.41$) and insulin and trunk fat mass ($r = 0.41$) were of some magnitude. It has been proposed that the link between increasing weight or obesity and increased plasma insulin levels requires or is linked to the onset of insulin resistance. If the insulin resistant state has not yet been reached, there is not yet a metabolic drive to increase insulin secretion, thus the progression from obesity to insulin resistance to hyperinsulinemia.(Hsu 07) The high magnitude of the correlation between waist circumference or trunk fat and insulin level, while not significant, may indicate progress on the track from obesity to hyperinsulinemia.

Fasting plasma insulin was relatively static from baseline to post-intervention in both the control and exercise cohorts. There was a strong negative correlation ($r = -0.74$, $p < 0.05$) between change in fasting insulin and change in lean trunk mass, suggesting that as subjects gained muscle their insulin levels decreased. This is a logical conclusion as skeletal muscle is a prime depot for storage of glucose and an increase in storage

capacity reduces the level of insulin required to maintain euglycemia. The correlation between change in insulin and change in total lean mass was less vigorous (r = -0.45) and did not achieve significance, but the magnitude again suggests that sample size was the limiting factor. There was no link between change in insulin and any measure of fat mass.

That insulin levels remained unchanged following this resistance exercise intervention is in agreement with the majority of surveyed literature[Dunstan 2002, Kang 2002, Fenicchia 2004, DiPietro 2005], while the improved glycemic control reported by these authors and others[Maiorana 2002, Ibanez 2005, Cuff 2003] suggests an increased response to insulin as opposed to a change in secretion. That a reduction in insulin was correlated with an increase in lean mass, yet exercise interventions fail to consistently elicit a change in fasting insulin levels presents a conundrum. A possible explanation is that the increase in lean mass was not universally large enough to consistently reduce fasting plasma insulin levels, particularly given the large variability in insulin values across the sample.

HOMA-IR

The measurement of insulin resistance in this study is a modified product of fasting plasma glucose (expressed in mmol/L instead of the clinical standard of mg/dL, divided by 22.5) and fasting plasma insulin. As the glucose component is reduced by division and the insulin component is unmodified, fasting plasma insulin dominates the calculation. The use of a model such as HOMA-IR provides an efficient and affordable vehicle for the estimation of insulin resistance, particularly important for studies where a frequently-sampled oral glucose tolerance test or clamp experiment might not be tenable.

An accepted limitation of this model is that it represents only a momentary snapshot and estimate of the glycemic control of the patient. On the other hand, a measure such as glycosylated hemoglobin (HbA1C) provides the best assessment of glycemic control over the recent 2 to 3 months, but may not provide the best information on recent changes in glycemic control. Thus, assessment of glycemic control via HbA1C would require several months to accurately gauge change from an intervention.

Stern et al.[Stern 05] compiled clinical data and examined a number of variables to determine appropriate diagnostic cut-points for determination of insulin resistance via routine clinical measures. The guidelines suggested by the authors indicate that subjects with a HOMA-IR $\geq$ 4.65, or subjects with a HOMA-IR $\geq$ 3.60 and BMI $\geq$ 27.5 should be considered insulin resistant. A large sample cross-sectional study found that healthy subjects had a mean HOMA-IR of 2.1 compared to 4.3 in subjects with impaired glucose tolerance and 8.3 in diabetic subjects.[Trout 07]

In the current study the pooled subjects mean HOMA-IR was 0.85 $\pm$ 1.07 (no units), with negligible differences between gender or intervention randomization groups. The range of initial values was broad as indicated by the standard deviation, but on the whole the study participants were insulin sensitive. The two subjects who approached insulin resistance (HOMA-IR scores of 2.84, still insulin sensitive, and 4.69, insulin resistant) unfortunately did not complete all aspects of the study. Given the links between RA and IR discussed previously in this work it may have been expected that the subjects in the current study would exhibit elevated HOMA-IR scores, approaching if not exceeding the benchmark of 4.65 for insulin resistance. The subpopulation of RA

patients selected for this study, however, were necessarily very well-controlled, highly functional rheumatoid arthritics. Given these criteria, the subjects were generally otherwise healthy, non-obese and as active as many non-exercisers, all qualities which would be expected to reduce the likelihood of insulin resistance. Furthermore, potential subjects were required to have been on a stable infliximab regimen. As documented previously, several studies have found a significant improvement in insulin sensitivity among RA or similar autoimmune disorder patients when treated with anti-TNFα agents such as infliximab.[Gonzalez-Gay 06, Kiortsis 06, Rosenvinge 07, Tam 07]

As previously indicated, insulin dominates the calculation of the HOMA-IR value. Thus, at every time point and for each cohort, gender or experimental condition, one would expect insulin and HOMA-IR to be significantly positively correlated. This is borne out in the current study, with correlation values in excess of 0.900 for both fasting values and change in fasting values. Fasting plasma glucose was significantly correlated with HOMA-IR in the pooled baseline cohort ($r = 0.50$, $p < 0.01$) as well. Though not significant, the correlation between these measures in the control cohort post-intervention was of high magnitude ($r = 0.69$), even greater than that seen in the pooled subjects at baseline. The magnitude of the correlation in the exercise cohort following intervention was much lower ($r = 0.35$).

In the pooled subjects at baseline, HOMA-IR was positively correlated with waist circumference ($r = 0.44$) and trunk fat mass ($r = 0.52$), both significant ($p < 0.05$). While not statistically significant, the magnitude of the correlative values for comparisons of HOMA-IR and BMI ($r = 0.35$) and HOMA-IR and total fat mass ($r = 0.43$) were near

significance. Given the well established links between insulin resistance and obesity these relationships are not surprising.

An examination of the formula for HOMA-IR calculation and the attendant correlations thus suggests that a very large change in fasting glucose or a smaller change in insulin is required to significantly alter the measure of insulin resistance. As neither criterion was met in the present study there were no significant changes in mean HOMA-IR in either the exercise or control groups. There was, however, a significant correlation between change in trunk lean mass and HOMA-IR ($r = 0.78$, $p < 0.05$), suggesting at first approximation that in the exercise cohort a gain in trunk lean tissue is associated with an increase in whole body insulin resistance. This finding is in opposition to the overwhelming majority of published literature and is counterintuitive, but may be related to the near-significant positive correlation between increase in lean trunk mass and increase in TNF-α ($r = 0.616$, $p = 0.084$), given the known impact of the cytokine on insulin resistance. These data may have also been impacted by two exercise subjects whose baseline HOMA-IR scores were exceedingly and perhaps artificially low. The scores for these subjects at the post intervention time point were still near the bottom of the range (ranking 3rd and 4th lowest). Removal of these two subjects from the correlation presents a drastically different relationship ($r = -0.67$, $p = 0.150$), but does reduce the sample size to 9 for correlation with weight, BMI and waist circumference and 7 for the remaining variables. While not statistically significant, the magnitude of the r-value is very high.

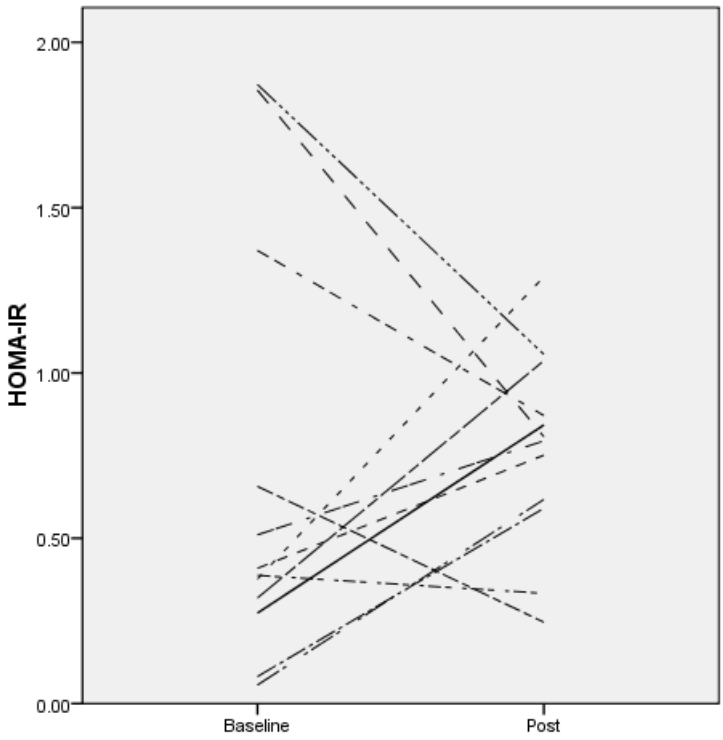
Discussion Table I – Revised Δ HOMA-IR Correlates in Exercise Subjects (r-value)

	ΔWeight	ΔBMI	ΔWaist	ΔFat Total	ΔFat Trunk	ΔFat Abd	Δ% Fat	ΔLean Total	ΔLean Trunk
ΔHOMA-IR	-0.35	-0.07	0.35	0.20	0.01	-0.04	-0.07	-0.01	-0.67
p-value	0.33	0.85	0.39	0.71	0.98	0.93	0.89	0.99	0.15

Furthermore, the direction of the relationship now reflects the expected and accepted link between increased lean mass and decreased insulin resistance. Table 1 displays the HOMA-IR related correlations following the removal of those data points. An increase in BMI being associated with a decrease in HOMA-IR might at first approximation appear to be counterintuitive, as increased weight is associated with insulin resistance in the literature. It must be remembered in this case, however, that the subjects in the exercise cohort of this study were not expected to lose weight but to, in fact, gain lean mass over the course of the intervention. As such, the BMI increases in the exercise cohort are expected to be the result of the addition of lean mass, not fat mass. If that is the case, the relationship between Δ HOMA-IR and Δ BMI is understandable and appropriate. The direction of the relationships between Δ HOMA-IR and Δ waist circumference and Δ total fat mass, both measures of adiposity, are positive, indicating concomitant increase of insulin resistance with adiposity. The magnitudes of the remaining correlations are so small as to preclude assessment.

Although there was no significant change in mean HOMA-IR in the exercise cohort, the impact of exercise on insulin resistance shouldn't be discounted out of hand. As shown in Figure 1, there may well be a relationship between resistance exercise and reduction of insulin resistance. Four of the five subjects with the highest HOMA-IR scores reduced their value from baseline to post intervention, and the only one of those five who did not decrease the value had an exceedingly modest increase. It is further noteworthy that none of the subjects that completed this study had a clinically significant elevated HOMA-IR.

Figure 1 - Change in HOMA-IR in Exercise Group Subjects



It may well be that resistance training does not improve the insulin sensitivity of those subjects who are already normally sensitive, but may offer improvement for those that have elevated resistance indices.

Indeed, this is similar to the findings of Yazdani-Biuki et al.[(Yazdani-Biuki 04)] in a study of insulin resistance subjects during prolonged treatment with infliximab. A small cohort of subjects with appropriate auto-immune disorders was examined retrospectively before and after onset of a regular infliximab regimen. The investigators in that study found that those subjects with the greatest HOMA-IR scores (far in excess of the insulin resistance cutoff of 4.65) saw significant improvement in insulin sensitivity while the subjects who were nearest to insulin sensitive did not improve noticeably. Body weight was maintained during the time course of the retrospective data, indicating the infliximab therapy might be likely candidate for improving insulin sensitivity in these patients. The impact of these findings is that perhaps the infliximab therapy of the subjects in this study has already normalized the insulin sensitivity of those who might have otherwise been insulin resistant and that any additive effect of the exercise regimen might only be seen in those in the upper range of HOMA-IR scores.

CYTOKINES AND ADIPOKINES

Adiponectin

One of several adipokines, adiponectin is synthesized by white adipose tissue and in serum concentrations between 2 – 20 μg/mL. In the current study, pooled subject baseline mean adiponectin was 6.97 ± 5.10 μg/mL, with a range of data from 0.64 to 18.80 μg/mL. Women tended to have higher circulating adiponectin than men, but the

difference was non-significant, and the two experimental conditions were very similar in adiponectin value to one another.

Adiponectin levels have been shown by other investigators to correlate inversely with BMI and insulin resistance in human and mouse models.[Vettor 2005, Matsuzawa 2005] The subjects examined in this study did display a significant inverse correlation at baseline between measures of weight or fatness and adiponectin although the correlation between adiponectin and HOMA-IR was not significant. Ruan et al[Ruan 2004] report that administration of adiponectin can be therapeutic in obese mice models by reducing the triglyceride content of the muscle and liver, potentially contributing to increased insulin sensitivity by reduction of substrate that reduces signaling. Given that significant deleterious health issues excluding conditions related to RA was exclusionary to, and that normal weight/fatness was required for participation in this study, the subjects were not impacted by triglyceride-modulated insulin resistance and were thus unlikely to see an impact of adiponectin in this venue. Interestingly, in the pooled subjects at baseline total lean mass and trunk lean mass were both significantly negatively correlated with adiponectin. Given the significant difference in muscle mass between the genders and the noteworthy but not statistically significantly ($p = 0.14$) difference in adiponectin, the negative correlative value may be in part the result of the gender differences. Use of partial correlations controlling for body weight renders the relationship between adiponectin and total lean or trunk lean mass inconsequential ($r = -0.08$ and $r = 0.01$ respectively), suggesting the initial correlative finding to be an artifact of the subject demographic.

Adiponectin levels did not significantly increase from baseline to post-intervention in exercise subjects in the current study. Conflicting evidence is available in the literature with regards to the effects of resistance exercise on adiponectin levels. Marcell et al[(Marcell 2005)], Boudou et al[(Boudou 2003)] and Hara et al[(Hara 2005)] all reported that adiponectin levels were not influenced by resistance exercise training, despite changes in insulin sensitivity. Furthermore, Hara et al[(Hara 2005)] indicate that changes in adiponectin levels are related to changes in body composition and not necessarily the method of training leading to the changes in body composition.

In contrast, Fatouros et al[(Fatouros 2005)], Blüher et al[(Blüher, 2006)] and Oberbach et al[(Oberbach 2006)] all reported increases in plasma adiponectin following intensive resistance training regimens. Exercise intensity, body composition and baseline health all seem implicated in this relationship, however, as opposed to a simple training effect. In a report published by Fatouros et al[(Fatouros 2005)], the authors report that only those subjects participating in the highest intensity training displayed a significant increase in adiponectin levels, despite all levels of training intensity reducing BMI and having beneficial effects on body composition in their study. Blüher et al[(Blüher, 2006)] indicate a correlation between body composition and adiponectin in their subjects both prior to and after intervention, perhaps indicating that change in composition contributes more to the change in adiponectin levels than training alone. This supports the findings discussed by Oberbach et al[(Oberbach 2006)], where subjects with impaired glucose tolerance or Type II diabetes underwent a training intervention and after 4 weeks had increased plasma

adiponectin levels. Significant decreases in body fat and total weight were also found, again providing a possible confounder for the exercise effect.

In the present study mean plasma adiponectin in the exercise cohort did not increase following the intervention, but change in adiponectin levels was significantly correlated with change in trunk lean body mass ($r = 0.75$, $p < 0.05$) and approached significance with change in trunk region lean mass ($r = 0.70$, $p = 0.051$), agreeing with the findings of the authors previously cited. It seems likely that the small sample size is again masking significance, given the magnitude of the Pearson correlation value. Correlation values between change in adiponectin and change in body fat (whole and trunk region) were much smaller in magnitude but did show the negative vector.

Resistin

Resistin, first highlighted in 2001, was originally described as an adipokine that provided a link between obesity and insulin resistance. Subsequently it has been found that resistin is expressed at low levels in human adipocytes, while monocytes, macrophages and bone marrow cells exhibit high levels of expression. Several factors have been suggested which may up-regulate synthesis and secretion of resistin, including corticosteroids, testosterone, growth hormone, pro-inflammatory cytokines such as IL-6 and TNF-α, obesity, particularly abdominal obesity, and rheumatoid arthritis.(Bokarewa 05) Mean resistin values in reasonably healthy subjects in a large heterogeneous cohort study were 4.1 ± 2.4 ng/mL (interquartile range) and indicated no significant differences between men and women or young and old.(Vilarrasa 05) Azuma et al(Azuma 03) found a significantly higher mean in their healthy control cohort of 12.83 ± 8.30 ng/mL in a

comparison between lean and obese subjects, indicating some variability in the standard. An examination of patients with systemic lupus erythematosus (SLE) and controls found a higher mean serum resistin value of 6.24 ng/mL with a range from 0.47 to 17.12 ng/mL, with no differences found between control and SLE patients.(Almehed 08) An examination of resistin levels in RA patients found a significant increase in serum resistin compared to healthy controls (6.72 ± 4.59 vs. 3.15 ± 1.66 ng/mL) with a much greater range of values in the RA patients. That study also indicates a significant correlation with TNF-α levels, suggesting a role in the rheumatoid inflammation process.(Migita 06)

The mean serum resistin for the pooled subjects at baseline in the present study were 15.23 ± 3.96 ng/mL. This value is much higher than that reported by Migita(Migitia 06) above, but the range in the current study (9.64 – 23.00 ng/mL) was very similar in magnitude to that work. It is worth mention that Bokarewa et al(Bokarewa 05) indicated a significant accumulation of resistin in the synovial fluid and inflamed joints of RA patients exceeding 20 ng/mL, suggesting a local peripheral effect on resistin levels. There were no significant differences in resistin values between genders or between subjects randomized to exercise vs. control conditions in the current study.

Baseline resistin was significantly positively correlated with insulin and HOMA-IR, adding evidence to the link between this adipokine and insulin resistance that generated its name. Interestingly, resistin was not found to be significantly correlated with TNF-α in the current study, perhaps due to the infliximab regimen. Again according to expectations, resistin was positively correlated with waist circumference ($r = 0.44$, $p = 0.037$, $n = 23$) and trunk fat ($r = 0.45$, $p = 0.046$, $n = 20$) while being very nearly

significantly correlated with total fat mass ($r = 0.41$, $p = 0.070$, $n = 20$). Interestingly, percent fat was not significantly correlated with resistin in the current study.

Resistin levels after training tended to be higher in exercise subjects in the current study, nearing significance ($p = 0.100$) via paired samples t-test, despite a significant decrease in trunk fat and a downward trend in total body fat. This was somewhat surprising given the links between adiposity/obesity and resistin put forth by other investigators[Azuma 2003, Matsuzawa 2005], but the answer to this increase may lie outside body composition changes. Resistin is produced in the peripheral tissues, and not solely in adipose tissue, and this may be the source of the modest increase in the "adipokine" seen in this study. This may also help explain the significant correlation between change in resistin and change in TNF-α following intervention. Jamurtas et al[Jamurtas 2006] reported no transitory increases in resistin levels following acute bouts of aerobic exercise. Similarly, Giannopoulou et al[Giannopoulou 2005] reported no significant changes in resistin following a 14-week walking exercise intervention in type 2 diabetics. These findings do not, however, conclusively eliminate resistance training as a stimulus for increased resistin levels. Furthermore, the evidence put forth that resistin accumulated in inflamed joints in RA patients and the link between resistance training and inflammation may account for the increase seen in the exercise cohort of the current study.

Change in resistin was not significantly correlated with any measure of blood chemistry or weight and body composition over the course of the study, but this may be due in large part to the sample size. The magnitude of the r-values of the correlations between change in resistin and change in insulin ($r = 0.44$, $p = 0.155$) or HOMA-IR ($r =$

0.39, p = 0.213) were both relatively high, and change in adiponectin (r = -0.35, p = 0.240) was not much reduced. It is worth mention that the direction of all three relationships is in line with expectations given the links between these elements that have been previously mentioned. Correlations among change in resistin and change in total fat mass (r = 0.36), change in trunk fat mass (r = 0.48) and change in percent fat (r = 0.44) were of similar magnitude and also exhibited the anticipated direction but failed to achieve significance. Though none of these correlations were proven statistically significant, they all correspond to the expected relationship – increases in resistin are associated with increases in insulin resistance and by extension insulin, while increases in adiposity are associated with increases in insulin. Conversely, as fat masses decrease, resistin decreases, and as resistin decreases measures of insulin resistance decrease.

An additional finding that was considered novel is that the duration of infliximab treatment was positively correlated with baseline plasma levels of resistin. This association has not been previously reported in studies of this sort and may indicate an interesting side-effect of treatment. It is conceivable that this represents an avenue for the attenuation of the drug's theorized ability to reduce insulin resistance via reduction of inflammatory factors that inhibit insulin action and may explain some of the increase in mean resistin over that reported in other studies.

TNF-α

In the pooled subjects at baseline, mean TNF-α was 12.79 ± 12.74 pg/mL. This is much higher than anticipated based on the work of Petrovic-Rackov et al[(Petrovic-Rackov 2005)] who reported means up to 7.5 ± 3.4 pg/mL in RA patients in their study. A review of the

data for the current study finds that one patient had serum TNF-α in excess of 50 pg/mL, certainly having a substantial impact on the mean in the current study. Assessment of the cohort without that subject finds a mean TNF-α of 10.69 ± 8.57 pg/mL, still above that previously cited by much closer in magnitude. The range in values following this correction was similar to that seen in the previous study, though clearly skewed slightly higher.

Baseline blood TNF-α was not significantly correlated with any other measure of blood chemistry in the current study, nor was it found to be significantly correlated with any measure of weight or body composition. This lack of relationship may be the result of the anti-TNF-α therapy. Though blood samples were to be obtained as close to immediately before infliximab dosing as possible it may well be that the effect of the drug is sufficient to alter TNF-α throughout the time course of the therapy. Change in TNF-α was significantly negatively correlated with change in total lean mass ($r = -0.67$, $p = 0.049$) and nearly significantly correlated with change in trunk lean mass ($r = -0.61$, $p = 0.084$), indicating that those that gained lean mass reduced circulating TNF-α levels. Change in TNF-α was not significantly correlated with any other change variable, but the direction indicated by the r-values was generally consistent with expectations. Change in measures of adiposity generally related to increases in TNF-α, while change in weight or BMI was associated with a decrease in TNF-α. Recall that as weight change was generally lean tissue, this second result is as expected.

TNF-α levels were relatively unchanged following the exercise intervention (10.15 ± 8.67 pg/mL at baseline, 9.76 ± 5.79 pg/mL post intervention, $p = 0.914$). This

result is aligned with published literature, which suggests that resistance training can impact insulin sensitivity measures without alteration of TNF-α levels.[Conraads 2002, Reynolds 2004] In addition to plasma TNF-α levels, Reynolds et al[Reynolds 2004] examined levels of soluble TNF-α receptors 1 and 2 (sTNFR1 and sTNFR2), again finding no significant change but a clear and significant improvement in insulin sensitivity as assessed by hyperinsulinemic, euglycemic clamp. Conraads et al[Conraads 2002] examined receptor levels in coronary heart failure (CHF) and coronary artery disease (CAD) patients, and found that, while TNF-α levels were unchanged, sTNFR1 decreased following training in both disease states and sTNFR2 decreased in the CAD group. One study has even reported a tendency for TNF-α levels to increase following resistance training. Hayase et al[Hayase 2002] found a non-significant but interesting increase in TNF-α in 6 of their 9 exercise subjects, while 2 remained unchanged and 1 decreased. Given the small sample examined and wide inter-individual differences in magnitude, however, the results were not sufficient to achieve significance.

Studies examining TNF-α following aerobic training have presented more varied results. Reynolds et al[Reynolds 2002] again reported improved insulin sensitivity as well as a decrease in body fat mass without any alteration in TNF-α in an aerobic exercise study in hypertensive women. A study on the impact of a walking regimen in type 2 diabetics found no significant change in TNF-α despite decreases in body fat and other inflammatory cytokines.[Giannopoulou 2005] Strackowski et al[Strackowski 2001], however, report a significant decrease in TNF-α and sTNFR2 levels following a bicycle ergometer exercise regimen in obese women, while sTNFR1 levels remained unchanged, and the authors

report that the changes remained significant after adjustment for body composition changes. Other reviewers continue to propose that TNF-α levels should decline, or at least be attenuated by decreased receptor levels following aerobic or resistance exercise training, but the primary literature remains varied.(Petersen 2005)

The wide variance in the literature serves to underscore the need to further examine the mechanisms driving TNF-α synthesis, release and action. This cytokine has been linked with decreased insulin action and has been positively correlated with body fat, BMI and obesity. A more complete understanding of exercise impact on TNF-α may allow clinicians to better tailor treatment regimens for patients with impaired insulin sensitivity.

Much like resistin, TNF-α may be synthesized and released from multiple sites and from multiple stimuli. Without the ability to assess the source of TNF-α circulating in the blood it is not possible to be certain that a change in synthesis in tissues beside fat did not accompany a change in body composition. As such, it is not outside the bounds of possibility that the trend to reduction in body fat would normally have been accompanied by a reduction in adipose-synthesized TNF-α but the increase in strenuous physical activity induced an increase in peripheral synthesis, counteracting the change in body composition effect. This is, of course, speculative, but is included to illustrate the potential confounding effects that the dynamics of inflammatory agents could have on analysis. Furthermore, the large variance in change in the current study is a significant detraction to the strength of any analysis relating to this cytokine.

REGRESSION ANALYSES

Prediction of Insulin Resistance

Regression analysis was employed in the current study to provide better understanding of the impact of variables and their roles in insulin resistance. A cross-sectional analysis of the baseline data from all subjects was employed to maximize the sample size and generate the most applicable and generalizable findings. Despite the small sample size, significant predictive power was found in regression modeling. As expected, Remicade treatment over time was predictive of a lessened HOMA-IR, while body fat in the trunk was found to be associated with increased HOMA-IR. The predictive power of this regression was substantial with an adjusted R^2 of 0.342, and a significance level of $p = 0.014$ as derived from ANOVA.

A thought-provoking finding was that the duration of Remicade treatment was a "negative" predictor of HOMA-IR while being positively correlated with plasma levels of resistin. Resistin is known to interfere with insulin action and was positively correlated with HOMA-IR in this study as well, even if it did not play a significant role in the regression analysis.(Vettor 2005, Matsuzawa 2005) This correlation has not been previously reported in studies of this sort and may indicate an avenue for attenuation of Remicade's potency in reducing insulin resistance.

A large group of investigators have independently verified the impact of TNF-α on insulin sensitivity, agreeing in principal that increasing plasma levels are detrimental to insulin action.(Csehi 05, Valverde 98, Hotamisligil 03, Plomgaard 05) As such, it stands to reason that infliximab, an anti-TNF drug would attenuate the impact of the cytokine on insulin action, thus improving signaling in the treated subjects. Several investigators have

examined the efficacy of Remicade in improving insulin resistance in subjects already being treated with the drug.[Yazdani-Biuki 2004, Kiortsis 2005] Yazdani-Biuki et al[Yazdani-Biuki, 2004] report that obese patients with a pronounced insulin resistance showed significant improvement over the course of several months of infliximab treatment, while those more healthy subjects did not change their insulin sensitivity during the regimen.

Similarly, Kiortsis et al[Kiortsis 05] reported that the RA patients in their study with the greatest degree of insulin resistance saw an improvement in insulin signaling, as assessed by HOMA-IR or QUICKI over a year-long infliximab treatment. HOMA values were reduced from 3.01 to 1.89 ± standard deviation without significant changes in BMI or waist-to-hip ratio, suggesting that the infliximab treatment was the primary impetus for change, but only in those most insulin resistant at the onset of treatment.

Why, then, does decreasing active TNF-α not improve insulin sensitivity in the modestly insulin resistant? Resistin, a protein found to be generated in fat tissue as well as human immune cells is known to decrease insulin sensitivity when injected into mice[Vettor 2005, Matsuzawa 2005], as well as being positively correlated with HOMA-IR in the present study.

Though not a significant predictor in the regression model presented herein, resistin may be playing a modest role in decreasing the efficacy of the Remicade treatment on insulin signaling. Patients in this study displayed a positive correlation between months of Remicade and resistin levels that persevered when controlling for patient age and disease duration. It may also be hypothesized that the higher mean resistin levels found in subjects of the current study compared to those of the Migitia[Migita

06) and Bokarewa(Bokarewa 05) studies may conceivably be linked to the infliximab regimen of the patients in the current study. If this relationship holds true in other RA populations it may help explain the diminished effect of anti-TNF-α treatments on insulin sensitivity in the moderately resistant. The mechanisms by which Remicade duration and resistin levels are linked are unclear, but if this relationship persists it may well hold interest for future investigators.

Prediction of Change in Insulin Resistance

Although no significant differences in HOMA-IR were found in exercise participants post-intervention it is valuable to assess factors which may improve insulin sensitivity following exercise. To this end, regression analysis was employed to assess the predictors of change in HOMA-IR in the current study. The initial model included change in variables suggested by the published literature or those that were most associated with HOMA-IR in the current study as well as baseline HOMA-IR. It was discovered that inclusion of baseline HOMA-IR dominated assessment of change in HOMA-IR to such an extent that no other variable or combination of variables could improve predictive strength. To allow for examination of other factors it was subsequently removed from analysis. However, it does seem to add additional weight to the possibility that only those subjects with elevated HOMA-IR are likely to see improvement from anti-TNF-α drugs or exercise interventions. After removal of baseline HOMA-IR, other variables were removed one at a time based on significance. The final regression included the variables change in lean mass, change in resistin and change in

TNF-α. Although the final model only approaches significance (P = 0.063) it does have an adjusted R^2 value of 0.464, suggesting some predictive strength.

COMMENTARY

The use of infliximab and other anti-TNF-α drugs have been approved for the treatment of diseases outside RA, and investigators have begun assessing the impact of these pharmaceuticals on conditions secondary to arthritis. Dr. Kenneth Warrington[(Warrington 04)] suggests that given the association of RA and atherogenesis and the common mechanisms between the two that anti-TNF-α treatment is deserving of serious examination as a potential therapeutic in this arena as well. Another investigative group recommends continued examination of autoimmune disease treatment with infliximab beyond those currently approved.[(Atzeni 04)] There are published reports that indicate anti-TNF-α therapy does not provide efficacious treatment for non-autoimmune diseases, including insulin resistance. Dominguez et al[(Dominguez 2005)] examined the impact of etanercept on insulin resistance and found acute reduction of inflammatory markers but did not find any impact on insulin sensitivity. Di Rocco et al[(Di Rocco 04)] reports a similar finding, indicating that morbidly obese subjects did not see an improvement in insulin sensitivity following infliximab treatment. This seems contrary to previously mentioned reports showing improvement of sensitivity in RA patients.[(Kiortsis 05, Yazdani-Biuki)] The key, however, may be in the course of treatment. In the studies above, the time course for intervention was very short – 4 weeks for the etanercept regimen and a single dosing for the infliximab treatment. RA patients treated with infliximab are not expected to see improvement in symptoms for at least 6 weeks[(Channual 09, Harriman 99, Lipsky 00, Markham 00)]

and the present study indicates that insulin signaling was best correlated with duration of infliximab treatment. As such, it might well be appropriate to examine the impacts of a lengthy course of treatment on insulin signaling in non-RA patients prior to disregarding it as therapeutic.

The results of the present study confirm that body composition and the adipokine resistin are correlated with insulin resistance measured by HOMA-IR. The direction and magnitude of correlations between measures of body fat and hormones/adipokines measured were appropriate and were similar to what has been previously reported. The present study has also found significant correlation between infliximab treatment duration and insulin resistance as assessed by HOMA-IR, and that time of treatment was a significant predictor of HOMA-IR in a regression model. Interestingly, infliximab treatment duration was also seen to be correlated with plasma resistin levels, an adipokine known to decrease insulin sensitivity. Further investigation may shed light on this relationship and provide further insight into the efficacy of infliximab treatment as an insulin sensitivity enhancement.

LIMITATIONS

Sample Size

A significant limitation of the present study was the relatively small sample size. As a result of the limited subject pool, and by extension study sample, correlations of moderately high magnitude could not be shown to be statistically significant. Nevertheless, their magnitude compared favorably with the magnitude of correlations reported in the literature that were found to be significant.

The state of disease control, existing infliximab regimen, absence of confounding conditions, time availability sufficient to engage in the exercise training program, ability to participate in the wide variety of assessments and the wherewithal to accommodate the time and transportation burden imposed by this study greatly limited the available pool of subjects available for inclusion. These issues were further exacerbated by the number of seasonal residents of the area and travel interruptions that occur over a four-month period, further excluding those who may have otherwise been willing to participate.

The limited success of initial recruitment due to the above criteria and obstacles indicated that a broader age range would have to be allowed in an effort to generate a sufficient number of volunteers to form the sample for this study. While this widening of the subject pool provided the opportunity to make a valid investigation of the impact of weight training on disease state and control along with social and affective characteristics of the subjects, it led to perhaps a more heterogeneous sample and may have an adverse impact on the statistical strength of some assessments. The wide range of weights, body composition and blood variables, particularly at baseline, limits the ability to assess potentially small changes in values, as any such change is easily occluded by the large initial range of values. That being said, expanding the selection criteria did allow the study to be successfully completed.

Even with the sample size limitation, however, significant improvements in strength and body composition were found following intervention with modest or no change in weight. In agreement with surveyed literature, changes in adiponectin, resistin

and TNF-α correlated with changes in body composition variables as opposed to absolute changes following the exercise intervention.

The problem of the small sample size was in one sense attenuated by the use of a 2:1 randomization scheme (intervention to control) to maximize the likelihood of a significant number of participants successfully completing the intervention. An unfortunate consequence of this scheme was that the control group, reduced in number at baseline, was more threatened by subject attrition, missing data or increased variation in the acquired data.

Heterogeneity

An additional impact of the limited recruitment pool for the present study is the diverse nature of the subjects who volunteered to participate. The range of subject ages, from 29y to nearly 75y, is significant when considering the variations in weight and body composition, glucose metabolism and general health across such a spectrum of subject ages. The large number of female participants makes the age range particularly important as the menopausal status of the subject can have significant impact on body fat content and distribution. This was further exacerbated by an even greater variability in RA duration, where the standard deviation of the mean duration was nearly equal to the mean itself (13.67 ± 9.90 y). These two issues present a significant challenge to the ability to accurately assess change resultant from an intervention, as both age and disease duration can exert independent effects on the variables of interest.

The inclusion of a small number of male subjects in a predominantly female sample also impacts statistical analysis, particularly given the expected increase in body mass, particularly lean tissue mass, and muscle strength. At least one male subject was

already of a level of fitness that would suggest frequent physical labor or training, despite his RA-related pain and complications.

Self Selection

A requirement of recruitment into the study was that potential subjects already be undergoing an infliximab treatment regimen. The cost associated with this treatment, either direct or via insurance premiums, presents the potential for limiting the subject pool to those who are in a position to afford the infusion treatments. Furthermore, the possibility of randomization into an exercise intervention may have had the effect of encouraging those potential subjects who thought they would like to exercise or discouraging those who would not may have altered the composition of the volunteer pool. As this element of the intervention had to be disclosed early in the recruitment process it is possible that it was a significant incentive or, conversely, a significant dissuader to participation.

Self-selection bias is a concern in the majority of human research and in arguably all intervention-based research. The broad array of subjects included in this study, despite being a limitation in terms of statistical power, does seem to mollify some concerns about the self-selection bias limiting participants to a single demographic in this case. Still, it is an issue that has to be considered when generalizing findings from the study.

Wide Biological Variability

In several assessments the data reported for the current study displayed a significant degree of variability, with standard deviations equaling or even exceeding the

magnitude of the mean. While this is clearly linked to the issues raised with sample size and heterogeneity, there may be a component linked to other biological factors as well. In some cases the range of expected results is so broad that it is reasonable to expect to see values for one subject exceeding that of another by a factor of 2, 3 or even 5, such as is the case with insulin. Assessment of biological factors linked to metabolism, inflammation, and disease state can all be in a state of flux and the window of time in which the blood is drawn for the assay may not be indicative of "normal" levels of a given factor for a given subject. Combining this with the variability brought into the equation with age, gender and body composition results in a wide range of assay values. Sample size is the best solution to this issue, but in a study with a sample size limitation, it simply must be accepted that data ranges will not always lend themselves to strong statistical power or broad generalizability.

The impact of this wide biological variability might have been mitigated and experimental measurement error reduced if blood replicates drawn on additional visit days had been available for analysis. Given the fluctuations seen from day to day in some variables, particularly those linked to inflammation and disease state for Rheumatoid Arthritis, sampling at additional time points might have increased the accuracy and utility of the measurements.

SUMMARY AND CONCLUSION

The parent study of the present work was designed to test the primary hypothesis that a 16-week, progressive, individualized, intensive strength training program in RA patients taking Remicade^{TM} would improve strength, body composition, disease activity,

physical function, pain and quality of life outcomes as compared to RA patients on Remicade™ without the strength training program. The results of this study clearly indicate that RA patients on infliximab are able to tolerate a progressive and intensive strength training regimen, and that this individualized program resulted in significant strength gains in the overwhelming majority of exercise participants and in every movement assessed. Fat mass was generally reduced in exercise participants, though not always achieving the $p < 0.05$ significance criteria, while trunk lean mass was significantly increased, and total lean mass trended higher, approaching significance. Disease activity, physical function and quality of life outcomes are discussed in detail in another work.(Flint-Wagner, 05)

An additional objective of this investigation and the focus of this dissertation was to assess the degree of association of several factors implicated in IR on the level of systemic insulin resistance in RA patients currently undergoing a prescribed Remicade™ treatment regimen. Examination of subject data at baseline verified associations of weight and fatness as well as adipokines on insulin resistance in line with published literature, though the anticipated link between TNF-α and insulin resistance could not be confirmed. In support of the hypothesis that infliximab might improve insulin resistance, the duration of Remicade treatment was found to be inversely correlated with HOMA-IR, suggesting that those RA patients on a Remicade regimen might experience insulin-protective benefits. This benefit may be reduced, however, by the tendency for resistin to increase with Remicade treatment duration.

A further intent of this study was to examine the changes in body composition, adiponectin, resistin, TNF-α, glucose and insulin following a 16-week progressive resistance training regimen in rheumatoid arthritis patients treated with Remicade™, testing the hypothesis that lean mass will increase while weight and fat mass will decrease, leading to a concomitant increase in adiponectin with decreases in resistin, TNF-α and insulin, and by extension HOMA-IR. As indicated above, lean mass did tend to increase while adipose tissue mass did tend to decrease. Significant variability and the heterogeneity of the sample adversely impacted the statistical significance of the intervention effect on cytokine and adipokine measures. However, the directions of the relationships assessed were generally as expected and the magnitude of the associated r-values might well have achieved significance in an expanded study cohort. Increased lean mass and change in the cytokines known to act counter to insulin action was related to change in HOMA-IR as hypothesized, but perhaps only in those subjects with elevated insulin resistance.

FUTURE DIRECTIONS

The reduction of HOMA-IR values seen in the subjects initially expressing the worst insulin sensitivity suggests that TNF-α blockade may improve glycemic control for those subjects in most need. This is not conclusive, however, and additional directed effort must be made to verify the effect of anti-TNF-α agents on insulin signaling. Examination of more concrete or specific measures of insulin sensitivity such as oral glucose tolerance test data, clamp tests or glycosylated hemoglobin (in a study of extended duration) would provide further elucidation of this issue. Adiponectin and TNF-

α, both previously shown to have impact on insulin action, were relatively unchanged. Resistin, both an adipokine and inflammatory cytokine, trended higher following training, though not significantly. This may be related to increased peripheral production of resistin as it was not correlated with any changes in body composition factors. Further study, particularly with larger sample sizes, will be required to better elucidate the impact of resistance training on these adipokines and cytokines. Of particular interest is the location of resistin synthesis in these subjects. It is possible that peripheral accumulation of the cytokine secondary to the stress of resistance exercise may limit or reduce improvements in insulin action that may be derived fromthe anti-TNF-α action of infliximab or similar agents.

The potential therapeutic effects of infliximab on insulin resistance will remain a topic of debate until such time as a larger scale study is undertaken using randomization to treatment in RA patients for which the drug might be well suited. Comparison of this treatment group to an age, gender, weight and body composition and perhaps disease state matched control group would allow for a more conclusive statement on the ability of the drug to limit insulin resistance in RA patients.

An alternative approach would be to examine a group of RA patients as they transit the onset of infliximab therapy. Concrete analysis of the insulin sensitivity testing of these patients prior to the initial dosing of infliximab and then longitudinal examination of test results over the next several months to one year would provide a more conclusive picture of the impact of the drug therapy on insulin sensitivity. A proposed assessment schedule would involve OGTT and clamp testing, as well as

obtaining an HbA1C value, prior to the initial dosing. These tests would be replicated once optimal dosing has been reached, likely a minimum of 2 months after the initial battery of tests, and then a third or fourth iteration of the testing 6 months and a year down the line. Comparison against RA patients of similar demographic and physical characteristics who have not elected to begin anti-TNF-α therapy would provide the control.

By extension, a study using these groups with a further layer of exercise intervention randomization would allow the best possible assessment of the usefulness of Remicade in promoting tolerable resistance exercise in RA patients, leading to improvement in disease activity, physical function, general health and quality of life for this population.

APPENDIX A – QUESTIONNAIRES AND SURVEYS

The following questionnaires and surveys were used in the assessment portion of the current study.

- AIMS 2 (Arthritis Impact Measurement Scale 2): Assesses health status, health status satisfaction and patient-designated priorities for improvement. The AIMS 2 generates 12 scales covering different areas of health – mobility, walking and bending, hand and finger function, arm function, self-care, household tasks, social activity, support from family and friends, arthritis pain, work, level of tension and mood.
- HAQ (Health Assessment Questionnaire): Measures health and effects of disease in terms of disability, discomfort, side-effects of treatment and medical costs. Assessment is based on a 0 (no difficulty) to 3 (unable to perform) scale on responses to 20 questions. Questions regarding the use of assistive devices and their use were also included.
- Medical History – A comprehensive medical history was taken, including medications, disease duration, lifestyle habits, family history, past surgery or hospitalizations and any other salient information. This was supplemented by telephone interview providing the subjects opportunity to read from their medicine containers for accurate dosage information.
- Medical Outcomes Study Short Form 36 (MOS SF-36): Assesses health status and quality of life including physical function, pain, social function, vitality, general and mental health perceptions. Questions ask about views of personal

health and ability to perform usual or everyday activities.

- Aerobic Center Longitudinal Survey (ACLS) and 7-Day Physical Activity Recall: Assesses the subject's historic physical activity and recent physical activity, respectively. The ACLS is a self-administered recall questionnaire that is designed to provide information on activity performed at least once a week over the last 3 months. The 7-day recall is a greater-detail examination of sleep and activity over the past week and is taken in conjunction with an interviewer. Intensity and duration of activity were important components of the recall, allowing energy spent to be estimated.
- Arizona Food Frequency Questionnaire (AFFQ): A scanned form that assesses, based on subject recall, foods consumed. Subjects are asked about the frequency (times per day, week or month) of consumption and portion sizes (small, medium or large) they consumed for 159 different food items. Dietary supplementation such as vitamins or minerals was included as well. A number of diet-related calculations can be derived from the AFFQ including daily nutrient totals and food group analysis.
- Arthritis Self-Efficacy Scale (ASES): The ASES measures "self-efficacy", or the belief that a particular task or behavior can be performed, by asking the respondent to address 20 different tasks. This questionnaire was designed specifically for arthritis patients, and generates 3 scores – self-efficacy for physical function, pain management and controlling other arthritis symptoms.
    - Self-efficacy 1: Similar to the ASES, this questionnaire assesses how

confidant a subject was about their ability to exercise under a number of different conditions (such as fatigue, busy schedule and inclement weather)

  - Self-efficacy 2: Assesses how confidant the respondent was that they could complete a range of physical activities, related specifically to this trial/intervention.

- Exercise Stages of Change Short Form: This form is intended to help identify and predict which groups of patients might be most likely to participate in and see positive outcome from exercise interventions.
- Exercise Decisional Balance: Assesses cognitive and motivational/emotional aspects of decision making when considering exercise activity. This questionnaire consists of 10 questions assessing positive and negative aspects of exercise and weighs incentives and deterrents for the individual subject.
- Body-Image Cathexis Questionnaire: Assesses the feelings and opinions of a subject regarding their body. Respondents scale their feelings from strongly negative to strongly positive about their mood, confidence, intelligence, physical and sexual appeal, coordination, weight, hands and hips. It also scales satisfaction with the various parts or processes of the body in an effort to develop a clear representation of the subject's view of themselves. This questionnaire contains 40 items.
- Center for Epidemological Studies Depression Scale (CES-D): A self-reporting assessment of frequency of symptoms of depression (including guilt,

worthlessness, helplessness and hopelessness) over the past week.

- Multidimensional Assessment of Fatigue (MAF) and Sleep Questionnaire: Assesses the impact of weekly activity on fatigue by measuring 16 topics divided in 4 areas – Severity (2), Distress (1), Timing (2) and Interference with Activities of Daily Life (11). The sleep questionnaire consisted of 4 questions meant to asses regular sleeping patterns, times and state of rest achieved.

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