Diet-Induced Changes in Intra-Abdominal Adipose Tissue and Cardiovascular Disease Risk in African American and European American Women

Konstantina Katsoulis
University of Alabama at Birmingham

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DIET-INDUCED CHANGES IN INTRA-ABDOMINAL ADIPOSE TISSUE AND CARDIOVASCULAR DISEASE RISK IN AFRICAN AMERICAN AND EUROPEAN AMERICAN WOMEN

By

KONSTANTINA KATSOULIS

GARY R. HUNTER, COMMITTEE CHAIR
TAMI E. BLAUDEAU
JANE P. ROY

A THESIS

Submitted to the graduate faculty of The University of Alabama at Birmingham, in partial fulfillment of the requirements for the degree of Master of Arts in Education

BIRMINGHAM, ALABAMA

2008
DIET-INDUCED CHANGES IN INTRA-ABDOMINAL ADIPOSE TISSUE AND CARDIOVASCULAR DISEASE RISK IN AFRICAN AMERICAN AND EUROPEAN AMERICAN WOMEN

KONSTANTINA KATSOULIS

PHYSICAL EDUCATION

ABSTRACT

The purpose of this study was to determine what effect weight loss (WL) had on intra-abdominal adipose tissue (IAAT) and cardiovascular disease risk factors (CVD) in 135 premenopausal overweight African American (AA) and European American (EA) women. Blood lipids, blood pressure, and IAAT (CT determined) were examined prior to and after administration of an 800 kcal/day diet designed to reduce subjects to a BMI below 25 (average WL = 12 kg). AA women had lower IAAT (64 cm²) than EA women (94 cm²). Following WL and after one month of energy balance IAAT decreased significantly (~38%). Significant decreases in total cholesterol (TC; 3%), low-density lipoproteins (LDL: 6%), triglycerides (TG: 27%), cholesterol/high-density lipoprotein ratio (C/HDL ratio: 18%), systolic blood pressure (SBP: 3%), and diastolic blood pressure (DBP: 3%) occurred while HDL increased (16%). AA women had significantly lower TG and C/HDL but higher HDL, SBP, and DBP. Significant interactions between time and race show that AA women decreased TG and increased HDL proportionately more than EA women. After adjusting for ∆IAAT none of the CVD variables significantly changed after WL with the exception of HDL and C/HDL ratio. After adjusting for ∆LF, TC, TG, LDL, and C/HDL ratio were still significant. Pearson product correlations showed significantly positive relationships between ∆CVD risk factor and ∆IAAT with the exception of ∆HDL and ∆DPB. CVD risk factor changes were
negatively associated with ΔLF (except for BP) but only ΔTC and ΔTG were significantly related. Multiple regression showed that ΔIAAT and ΔLF were both independently and significantly related to ΔTC and ΔTG, but in opposite directions. IAAT changes with WL explained the majority of improvement in CVD risk while AA women improved their blood lipids and reduced IAAT proportionately similarly compared to EA women even though they had a relatively lower CVD risk prior to WL.
DEDICATION

I would like to dedicate this project to Dr. Gary Hunter, Dr. Tami Blaudeau, and Dr. Jane Roy for their patience and mentorship. I would also like to thank my parents Nick and Christine and sisters Debbie and Esther, and Gus and John, for their loving support and kindness. Without them, this project would not have been possible.
ACKNOWLEDGEMENTS

I wish to acknowledge committee members Dr. Gary Hunter, Dr. Tami Blaudeau, and Dr. Jane Roy, program coordinator Paul A Zuckerman, research assistants David Bryan, Amy Thomas, Dr. Paul McCarthy, the wonderful graduate assistants involved, and participants who volunteered, for their contribution to this project.

This research was supported by National Institute of Diabetes and Digestive and Kidney Diseases grants R01 DK-49779 and R01 DK-51684, DRR General Clinical Research Center Grant M01 RR-00032 from the National Center for Research Resources, and Clinical Nutrition Research Unit Grant P30-DK 56336. Stouffer’s Lean Cuisine entrees, Nestle Food, Solon, OH and Weight Watchers Smart Ones, HJ Heinz Foods, Pittsburgh, PA kindly provided food for dietary control.
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<table>
<thead>
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<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>African American</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>BP</td>
<td>blood pressure</td>
</tr>
<tr>
<td>C/HDL</td>
<td>cholesterol/high-density lipoprotein</td>
</tr>
<tr>
<td>CVD</td>
<td>cardiovascular disease</td>
</tr>
<tr>
<td>DBP</td>
<td>diastolic blood pressure</td>
</tr>
<tr>
<td>EA</td>
<td>European American</td>
</tr>
<tr>
<td>HDL</td>
<td>high-density lipoprotein</td>
</tr>
<tr>
<td>IAAT</td>
<td>intra-abdominal adipose tissue</td>
</tr>
<tr>
<td>LDL</td>
<td>low-density lipoprotein</td>
</tr>
<tr>
<td>LF</td>
<td>leg fat</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
</tr>
<tr>
<td>TC</td>
<td>total cholesterol</td>
</tr>
<tr>
<td>TG</td>
<td>triglyceride</td>
</tr>
<tr>
<td>UAB</td>
<td>University of Alabama at Birmingham</td>
</tr>
<tr>
<td>WL</td>
<td>weight loss</td>
</tr>
<tr>
<td>Δ</td>
<td>change</td>
</tr>
</tbody>
</table>
Introduction

According to the 2008 American Heart Association's Heart and Stroke Statistical Update, cardiovascular disease (CVD) remains the top reason for deaths in the United States (1). Obesity is known to increase CVD risk (2). Unfortunately despite its known deleterious impact on health, overweight and obesity continue to increase in western society.

It is now known that not all body fat regions affect risk of disease equally (3,4). Intra-abdominal adipose tissue (IAAT) confers much more risk for CVD than fat in other parts of the body (3-8). In fact, a number of studies have shown that while IAAT is positively related to increased blood pressure (BP) and an impaired blood lipid profile (3,8), increased leg fat (LF) is negatively related to CVD risk if differences in IAAT are accounted for (3,5,9). Although caution must be used in hypothesizing cause and effect in correlational studies, i.e. elevated LF somehow causes a decreased risk of CVD, these data do strongly suggest that large amounts of IAAT may be harmful while large amounts of LF, in the absence of large amounts of IAAT is relatively benign (5).

Both overweight/obesity and CVD are higher in African American (AA) women compared to European American women (EA) (1,2,10). Conversely, AA women have around 30% less IAAT than EA women of similar Body Mass Index (BMI: 11,12). In
addition, AA women have better blood lipid profiles compared to EA women of a similar BMI (1,13). For example, AA women have triglyceride (TG) levels that are over 35% lower than EA women with a similar BMI (11).

When compared to men (6,14) and post-menopausal women (15), premenopausal women have relatively low IAAT. For example, premenopausal slightly overweight EA women (~26% body fat) reportedly have IAAT levels that are around 50% below that for post-menopausal women of a similar BMI, and these IAAT amounts were about 40% below the established IAAT cut-points for CVD risk (16). However, it is not known how much of an improvement in CVD risk will occur following WL for moderately overweight premenopausal women, especially AA women.

Aerobic exercise training has been shown to be associated with loss of body fat and improvement in CVD risk (17,18). It has been difficult to separate the independent effects of exercise training on blood lipids from the effects of concomitant fat loss on blood lipids since many studies combine diet and exercise intervention to promote WL (19,20). It is well-established that resistance training is a successful mode of exercise for increasing strength and muscle mass (21,22) but it is not clear what effects it has on CVD risk.

Few studies have compared the losses in IAAT and improvements in CVD risk between AA and EA women following diet-induced WL (11,12,23). The few that have been conducted have either been on a relatively small sample size (23), studied obese women, or have not included exercise training during diet-induced WL (11,12). Therefore the purpose of this study is to determine what impact combined exercise training (either aerobic or resistance) and diet-induced WL (800 kcal/day) has on fat
mass, IAAT, and CVD risk in AA and EA premenopausal overweight women. A second objective is to determine whether losses in IAAT or LF best explain the improved CVD risk.

Methods

Study Participants

Participants were 135 sedentary premenopausal women (69 AA, 66 EA) aged 20-41 years with a BMI between 27-30 kg/m². Women were matched for age and BMI. Requirements for entry into study included a family history of obesity in at least one first-degree relative (BMI > 27 kg/m²), normal glucose tolerance, non-smoker, and not taking medications that may interfere with energy expenditure, blood insulin, heart rate, and thyroid function. Both parents/grandparents were of the reported race of participant. Women were recruited through newspaper advertisements and campus flyers. The Institutional Review Board for Human Use at The University of Alabama at Birmingham (UAB) approved the study and informed consent was obtained from all participants.

Study Design

To ensure weight stability before evaluations (< 1% variation), women entered a 4-week weight-maintenance phase before and after WL. During weeks 3 and 4 of the first weight-maintenance phase, participants were provided meals through the General Clinical Research Center at UAB and continued consuming only these meals for the remainder of the study. Women were weighed 3 times during the first 2 weeks and 5 times during the last 2 weeks of weight-maintenance, and energy content was adjusted accordingly to achieve a stable weight. Upon completion of the weight-maintenance
phases, women were admitted as inpatients for 4-day evaluations during the follicular phase of their menstrual cycle. Metabolic testing took place only during these evaluations. After being discharged from the 1st evaluation, women began the WL phase and were provided an 800 kcal/day diet designed to reduce body weight by > 10 kg and to reach a target ideal weight (BMI < 25 kg/m²).

**Body Composition**

Body composition (total fat and LF) was evaluated using dual-energy X-ray absorptiometry (Lunar DPX-L densitometer: LUNAR Radiation Corp., Madison WI) at UAB’s Nutrition Sciences building using Adult Software Version 1.33. IAAT was measured at L4-L5 using computed tomography scans in the University Hospital Radiology Department (GE HiLight/Advantage scanner, Milwaukee, WI). All scans were analyzed by the same investigator.

**Blood Pressure**

BP was measured with automatic auscultation while lying in the supine position. Readings were taken in the morning after a 12-hour fast, and were reported as an average of three successive measurements.

**Blood Lipids**

Blood lipids were drawn in the morning after a 12-hour fast and were analyzed using the Ektachem DT II system (TC, HDL, TG). LDLs were estimated using the Friedewald Formula (24).

**Exercise Intervention**

Women were randomized to 1 of 3 groups: Aerobic training (40 min, 3X/week, n = 45), resistance training (80% IRM, 2x10, 3X/week, n = 58), and controls (no exercise
intervention, n = 32). Training sessions were supervised at a training facility dedicated to research on UAB’s campus and lasted approximately 50 minutes. Exercisers began with a 3 minute warm up followed by 3-5 minutes of stretching. By the 15th week of training, aerobic trainers were exercising for 40 minutes at 75-80% of their maximum heart rate. Exercise modalities included cycle ergometry, stair stepping, walking, and running. Resistance trainers performed 2 sets of 10 repetitions of resistance training exercises at 80% of their 1-repetition maximum. Every 3 weeks, the women’s 1-repetition maximum was evaluated and adjustments for workouts were made accordingly. Workouts persisted throughout the WL phase as well as during the 2nd energy balance phase and immediately before the 4-day hospital admission for evaluation.

Statistics

A 2 (time) by 2 (race) ANOVA with repeated measures on time was used to observe the effect of time (WL) and race on all variables of interest. Risk factors were also evaluated with two separate ANCOVA analyses with one using ∆IAAT as an adjusting variable, and a second using ∆LF as an adjusting variable. Pearson Product correlations were used to observe relationships between ΔCVD risk factors and ΔIAAT and ΔLF. Multiple regression was used to determine whether ΔIAAT and ΔLF were independently related to the two CVD risk factors that were significantly correlated with both ΔIAAT and ΔLF in the simple correlations (ΔTC and ΔTG).
Results

A 2 (race) x 3 (group) x 2 (time) ANOVA with repeated measures on time was used to compare CVD risk before and after WL. Since there were no differences between the exercisers and non-exercisers, the groups were collapsed and all subsequent analyses were done using a time by race ANOVA with repeated measures on time. Descriptive values are contained in Table 1. There were no significant differences in age, weight, and BMI at baseline. Despite similar WL for AA and EA women (-11.7 kg vs. -12.6 kg, respectively), EA women lost slightly more weight. Despite comparable BMIs, EA women had more total fat at baseline compared to AA women, but both races lost the same amount of fat. EA women had significantly higher IAAT at baseline and lost significantly more after the intervention (-35.3cm² vs. -25.2cm² for EA and AA women, respectively). There was no difference in amount of LF at baseline and degree of loss after the intervention.

Blood lipids (Table 2) and BP (Table 3) changed significantly with WL. No race effect or time by race interaction was found for either TC or LDL. EA women had significantly higher TG and the significant time by race interaction shows that they lost significantly more TG after WL than the AA women. HDL were significantly higher in AA women at baseline and after WL, but the time by race interaction indicates the EA women increased HDL significantly more than AA women. C/HDL ratio was higher in EA women at baseline with the significant time by race interaction showing that the EA women decreased C/HDL ratio more than the AA women. SBP and DBP were higher in AA women but both races decreased BP similarly.
After adjusting for changes in IAAT, the time effect was no longer significant for TC, TG, and LDL, suggesting the WL effect on these variables was mediated by changes in IAAT (Table 2). When ∆LF was used as a covariate, the time effect for HDL was no longer significant suggesting the increase in HDL with WL was mediated by changes in LF (Table 2). The ∆SBP and ∆DBP was no longer significant after adjusting for both IAAT and LF changes suggesting that both fat depots may be contributing to the decrease in BP following WL.

IAAT was positively related to all CVD risk factors except HDL and DBP which were unrelated to IAAT (Table 4). LF was negatively related to TC and TG but was unrelated to the other CVD risk factors (Table 4). Multiple regression results show that both IAAT and LF were independently related to TC and TG after adjusting for each other (Table 5).

Discussion

Our results indicate that moderately overweight AA and EA women benefitted in terms of CVD risk from a moderate WL. Both races significantly decreased overall fat and IAAT as well as improved all CVD risk factors measured. This was particularly surprising in the AA women who had IAAT well below the 110 cm² set point previously proposed for identification of CVD risk (16) and had a relatively benign blood lipid profile prior to WL. Consistent with cross-sectional studies in which IAAT is clearly strongly related to CVD risk (3-8), IAAT changes with WL explained reductions in TC,
TG, and LDL. However, it is not clear which fat depot change mediated changes in other CVD risk factors.

EA women had higher absolute amounts IAAT and lost more IAAT than AA women. However, proportional decreases in IAAT were similar between the races (AAs = -39.3%, EAs = -37.4%). In addition, the losses in IAAT in the two races fit recently developed models for predicting the well known preferential loss of IAAT that occurs during interventions that induce WL (25,26). It appears that the amount of IAAT lost was appropriate for the amount of IAAT that was present prior to WL in both races.

It is well established that IAAT is related to increased CVD risk while LF is not (3,5,9). In fact, LF has been associated with decreased CVD risk, at least in studies that have had individuals with relatively similar percent body fat or studies in which statistical adjustments have been made for either total fat or IAAT (5,9). In the present study, IAAT changes were positively related to changes to all CVD risk variables with the exception of ∆HDL and ∆DBP. LF changes correlated negatively with changes in TC and TG. Multiple regression modeling shows that the respective positive and negative relationships for change in IAAT and LF with change in TC and TG are independent of each other. Consistent to cross-sectional data the results of this study suggest that losses in IAAT may be beneficial and losses in LF may be detrimental at least concerning changes in TC and TG (9). Taken together the results of previous studies showing a negative relationship between CVD risk and LF and this study showing a positive relationship between ∆LF and ∆CVD risk make it attractive to hypothesize that having LF might actually be beneficial for CVD risk. However other hypotheses are possible. One such hypothesis is that some other variable or variables that cause individuals to
preferentially deposit fat in the viscera, such as parity (27) and catecholamines (28) may be the mediating factor in reducing CVD risk. This would mean of course that this variable or variables would have to be decreasing during WL.

Since exercise appeared to offer no enhanced benefit to CVD risk factors over WL, it seems plausible to conclude that loss of fat, especially IAAT was the driving force for metabolic profile-improvements in this study. Confusion exists whether exercise training has an effect on causing a preferential loss of IAAT with some studies suggesting preferential loss of IAAT (17, 18, 21, 22) and others showing no preferential loss in IAAT (29,30,31). The effects of WL from restricting calories may be masking the independent effects of exercise on fat distribution and CVD risk factors. These results should not be interpreted to mean that exercise has no benefit during diet induced WL. Exercise has been previously shown to have positive effects on other factors, such as insulin sensitivity (30), energy expenditure and maintenance of muscle (31), and bone density (32) during diet induced WL. The average amount of time for exercise having taken place before metabolic testing was 60 hours in the present study, and there may have been acute effects of exercise confounding the blood analyses since some studies have reported temporary changes in blood lipids after 24-48 hours (33,34,35). The present study did not control for the acute effects of exercise, and it may have been a limitation in our results.

Conclusion

Both overweight, premenopausal, AA and EA women benefitted from WL by decreasing IAAT, and improving CVD risk. This finding occurred even in AA women,
who had little IAAT, and relatively low CVD risk before WL. The changes in IAAT were significantly related to blood lipids. A loss of LF seems to be related to reduced improvement in TC and TG. Based on these results, interventions should focus on changes on IAAT.
Table 1
Descriptive Characteristics of AA and EA women at Baseline and After WL

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AA (n = 69) Before WL</th>
<th>After WL</th>
<th>EA (n = 66) Before WL</th>
<th>After WL</th>
<th>p* (t, r, t x r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>34.9±6.2</td>
<td>35.1±6.6</td>
<td>0.807, 0.807</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.0±5.8</td>
<td>65.2±5.1</td>
<td>78.6±8.2</td>
<td>66.0±7.4</td>
<td>&lt;0.001*, 0.270, 0.049*</td>
</tr>
<tr>
<td>Body fat %</td>
<td>44.4±3.6</td>
<td>34.0±4.5</td>
<td>45.7±3.7</td>
<td>35.7±4.7</td>
<td>0.001*, 0.025*, 0.468</td>
</tr>
<tr>
<td>IAAT (cm²)</td>
<td>64.2±24.9</td>
<td>39.0±18.2</td>
<td>94.5±28.4</td>
<td>59.1±21.2</td>
<td>0.001*, 0.001*, 0.001*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.3±1.3</td>
<td>24.0±9.0</td>
<td>28.3±1.4</td>
<td>23.8±1.2</td>
<td>0.001*, 0.578, 0.211</td>
</tr>
<tr>
<td>LF (kg)</td>
<td>13.6±2.3</td>
<td>9.1±1.9</td>
<td>13.3±2.9</td>
<td>9.1±2.1</td>
<td>0.001*, 0.767, 0.324</td>
</tr>
</tbody>
</table>

* significance at p < 0.05
Table 2
Blood Lipids of AA and EA women at Baseline and After WL: Unadjusted, adjusted for $\Delta$IAAT**, and adjusted for $\Delta$LF***

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>AA Before WL</th>
<th>AA After WL</th>
<th>EA Before WL</th>
<th>EA After WL</th>
<th>p* (t, r, t x r)(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>156.3±32.5</td>
<td>150.7±28.1</td>
<td>159.9±29.5</td>
<td>155.1±28.7</td>
<td>&lt;0.001*, 0.410, 0.835</td>
</tr>
<tr>
<td>TC**</td>
<td>160.2</td>
<td>152.8</td>
<td>156.5</td>
<td>154.0</td>
<td>0.372, 0.812, 0.243</td>
</tr>
<tr>
<td>TC***</td>
<td>158.3</td>
<td>152.1</td>
<td>158.4</td>
<td>154.6</td>
<td>0.007*, 0.801, 0.534</td>
</tr>
<tr>
<td>LDL</td>
<td>98.9±30.9</td>
<td>91.9±23.7</td>
<td>101.6±26.2</td>
<td>95.9±23.8</td>
<td>&lt;0.001*, 0.433, 0.691</td>
</tr>
<tr>
<td>LDL**</td>
<td>103.1</td>
<td>94.0</td>
<td>98.0</td>
<td>94.0</td>
<td>0.513, 0.592, 0.115</td>
</tr>
<tr>
<td>LDL***</td>
<td>101.0</td>
<td>93.2</td>
<td>100.3</td>
<td>94.9</td>
<td>0.014*, 0.917, 0.451</td>
</tr>
<tr>
<td>HDL</td>
<td>43.1±11.4</td>
<td>47.9±11.5</td>
<td>35.2±9.3</td>
<td>42.8±12.3</td>
<td>&lt;0.001*, &lt;0.001*, 0.048*</td>
</tr>
<tr>
<td>HDL**</td>
<td>42.5</td>
<td>48.1</td>
<td>35.6</td>
<td>43.1</td>
<td>0.008*, 0.004*, 0.238</td>
</tr>
<tr>
<td>HDL***</td>
<td>42.9</td>
<td>48.0</td>
<td>35.2</td>
<td>43.2</td>
<td>0.201, 0.002*, 0.064</td>
</tr>
<tr>
<td>TG</td>
<td>71.9±28.3</td>
<td>54.7±15.9</td>
<td>115.4±53.7</td>
<td>82.1±34.2</td>
<td>&lt;0.001*, &lt;0.001*, 0.009*</td>
</tr>
<tr>
<td>TG**</td>
<td>72.6</td>
<td>53.4</td>
<td>114.3</td>
<td>84.3</td>
<td>0.059, &lt;0.001*, 0.122</td>
</tr>
<tr>
<td>TG***</td>
<td>72.5</td>
<td>54.7</td>
<td>114.4</td>
<td>82.9</td>
<td>&lt;0.001*, &lt;0.001*, 0.037*</td>
</tr>
<tr>
<td>C/HDL ratio</td>
<td>3.8±1.2</td>
<td>3.2±71</td>
<td>4.8±1.4</td>
<td>3.8±98</td>
<td>&lt;0.001*, &lt;0.001*, 0.005*</td>
</tr>
<tr>
<td>C/HDL ratio**</td>
<td>4.0</td>
<td>3.3</td>
<td>4.7</td>
<td>3.8</td>
<td>0.013*, 0.002*, 0.143</td>
</tr>
<tr>
<td>C/HDL ratio***</td>
<td>3.9</td>
<td>3.3</td>
<td>4.8</td>
<td>3.8</td>
<td>&lt;0.001*, &lt;0.001*, 0.019*</td>
</tr>
</tbody>
</table>

\(^1\)t = time, r = race, t x r = interaction \(^*\)significance at p < 0.05

12
Table 3
Supine Blood Pressures for AA and EA women Before and After WL: Unadjusted, adjusted for ∆IAAT**, adjusted for ∆LF***

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>AA Before WL</th>
<th>AA After WL</th>
<th>EA Before WL</th>
<th>EA After WL</th>
<th>p* (t, r, t x r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP</td>
<td>115.2±10.1</td>
<td>111.3±9.1</td>
<td>112.5±8.3</td>
<td>108.6±7.2</td>
<td>&lt;0.001*, 0.049*, 0.924</td>
</tr>
<tr>
<td>SBP**</td>
<td>115.8</td>
<td>111.8</td>
<td>111.5</td>
<td>108.0</td>
<td>0.448, 0.009*, 0.719</td>
</tr>
<tr>
<td>SBP***</td>
<td>114.9</td>
<td>111.3</td>
<td>112.5</td>
<td>108.4</td>
<td>0.594, 0.072, 0.728</td>
</tr>
<tr>
<td>DBP</td>
<td>65.9±8.5</td>
<td>63.4±8.2</td>
<td>61.8±6.2</td>
<td>60.1±6.2</td>
<td>&lt;0.001*, 0.002*, 0.361</td>
</tr>
<tr>
<td>DBP**</td>
<td>66.9</td>
<td>64.5</td>
<td>61.5</td>
<td>59.8</td>
<td>0.139, &lt;0.001*, 0.539</td>
</tr>
<tr>
<td>DBP***</td>
<td>66.3</td>
<td>64.1</td>
<td>62.1</td>
<td>60.2</td>
<td>0.474, 0.001*, 0.695</td>
</tr>
</tbody>
</table>

*significance at p < 0.05

1 t = time, r = race, t x r = interaction

Table 4
Correlations Between ∆CVD Risk Factors with ∆IAAT/∆LF

<table>
<thead>
<tr>
<th>∆CVD risk factor</th>
<th>r with ∆IAAT (p*)</th>
<th>r with ∆LF (p*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>∆TC</td>
<td>0.188* (0.037)</td>
<td>-0.194* (.025)</td>
</tr>
<tr>
<td>∆TG</td>
<td>0.214* (0.017)</td>
<td>-0.210* (.015)</td>
</tr>
<tr>
<td>∆HDL</td>
<td>-0.140 (0.121)</td>
<td>-0.072 (0.407)</td>
</tr>
<tr>
<td>∆LDL</td>
<td>0.215* (0.016)</td>
<td>-0.122 (0.161)</td>
</tr>
<tr>
<td>∆C/HDL ratio</td>
<td>0.280** (0.002)</td>
<td>-0.160 (0.065)</td>
</tr>
<tr>
<td>∆SBP</td>
<td>0.199* (0.026)</td>
<td>0.087 (0.311)</td>
</tr>
<tr>
<td>∆DBP</td>
<td>0.036 (0.689)</td>
<td>0.164 (0.055)</td>
</tr>
</tbody>
</table>

*significance at p < 0.05
Table 5
Multiple Regression for Estimating $\Delta TC$ and $\Delta TG$ from $\Delta IAAT$ and $\Delta LF$

<table>
<thead>
<tr>
<th></th>
<th>Intercept</th>
<th>Slope</th>
<th>Adjusted $\beta$</th>
<th>$p^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>13.922</td>
<td></td>
<td></td>
<td>0.014</td>
</tr>
<tr>
<td>(R = 0.262)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta IAAT$</td>
<td>0.235</td>
<td>0.178</td>
<td></td>
<td>0.045</td>
</tr>
<tr>
<td>$\Delta LF$</td>
<td>-3.660</td>
<td>-0.186</td>
<td></td>
<td>0.037</td>
</tr>
<tr>
<td>TG</td>
<td>36.654</td>
<td></td>
<td></td>
<td>0.006</td>
</tr>
<tr>
<td>(R = 0.286)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\Delta IAAT$</td>
<td>0.466</td>
<td>0.213</td>
<td></td>
<td>0.016</td>
</tr>
<tr>
<td>$\Delta LF$</td>
<td>-5.999</td>
<td>-0.184</td>
<td></td>
<td>0.038</td>
</tr>
</tbody>
</table>

*$significance at p < 0.05
References

   Web site: http://www.americanheart.org/presenter.jhtml?identifier=3000090


LITERATURE REVIEW

Introduction

According to the most recent American Heart Association Heart and Stroke Statistical Update, cardiovascular disease (CVD) remains the top reason for deaths in the United States (1). Obesity, high blood pressure, and an adverse blood lipid profile are known to increase CVD risk (2). Not all body fat affects health and risk for heart disease equally (3,4). Body fat distribution has been receiving a great deal of attention since much of the cross-sectional data implies an increased detrimental effect from intra-abdominal adipose tissue (IAAT: 3-8), although contradictory data also exists in the literature (9,10). Fat-patterns are different across ethnicities. IAAT in pre-menopausal women is relatively lower when compared to post-menopausal women (11) and men (6,9).

Interventions to improve metabolic profiles and decrease the risk for CVD and related co-morbidities, such as WL and exercise, use of supplements (12) and surgery (13), have been studied in different populations. Diet and/or exercise studies have been very common, and findings are discordant, i.e., certain studies find decreased CVD risk after WL (14-24), whereas other studies report no decrease in risk (25,26).

Differences in CVD risk have been reported in African American (AA) and European American (EA) women, with AA women having lower IAAT (27,28) and
better metabolic profiles (29,30). AA women also are known to have higher blood pressure (1) relative to EA women. With WL, it has been reported that EA women of similar BMI to AA women lose more IAAT and less abdominal subcutaneous adipose tissue (SAT) with similar WL (27,28).

Several main theories have emerged concerning the mechanism of increased CVD risk from elevated IAAT. The traditional ‘portal hypothesis’, which has been extensively studied and reviewed by Per Björntorp (31,32) as well as other researchers (33,34), revolves around the theory that IAAT is a larger contributor of free fatty acids (FFA) into circulation compared to SAT. As reviewed by Björntorp (31,32), steroid hormones (cortisol, estrogen, testosterone, progesterone) play a role in the accumulation and mobilization of fat. People with Cushing’s syndrome reflect this since they deposit fat centrally and have abnormally high amounts of cortisol. Other factors are also considered such as genetics, environment, lipoprotein lipase activity (important for storing and mobilizing FFA in adipose tissue) and having android obesity, which add to the evidence of this theory. However, other studies have shown that when lipolysis rates were compared between IAAT and SAT, SAT was the fat depot that was liberating FFA at a higher rate (10), or there was no difference between fat depots (35) therefore the portal theory has not been shown to be the major mechanism for IAAT deposition.

The adipocytokine theory is more recent (34). Researchers have found that adipose tissue is not an inert mass, but rather secretes its own substances, termed adipocytokines, into the systemic circulation (36). Examples of reported markers that increase atherosclerotic plaques in arteries and serve as inflammatory markers are tumor necroses factor-α, interleukin-6, plasminogen activator inhibitor 1 (37), intercellular
adhesion molecule-1 (38). Not all adipocytokines are considered harmful; Adiponectin is negatively related to CVD risk, and has been associated with less risk for diabetes (37).

Several studies have shown that lower body obesity does not yield the same detriments as other body fat depots, and could actually be beneficial in terms of CVD risk (3,5). However, cause-and-effect cannot be interpreted from correlational studies, although the findings are interesting. Kahn (39) has suggested possible theories. Kahn’s first theory was that body fat distribution reflects dietary fat ingested, and the second theory surrounds cell proliferation at gestation. The first theory suggesting a dietary fat relationship to IAAT deposition was refuted by Larson et al (40) where a cross-sectional analysis of 135 EA men and 214 EA women showed that dietary fat had only a very minor role in overall adiposity and did not express preferential fat deposition towards IAAT. Jones et al (41) proposed that the lower body fat predominating in women is linked to the lower sympathetic neural activity as well as the lower IAAT found in women compared to men. Although the relationship between sympathetic neural activity and fat distribution may help explain why some people gain greater amounts of fat in the viscera while others gain more in the legs, it does not explain why leg fat tends to be independently related to an improved blood lipid profile independent of visceral fat. Better studies that directly measure sympathetic neural activity such as Jones’ are needed to further validate these results.

Björntorp proposed a link between abdominal obesity and endocrine activity involving catecholamines (32). Higher IAAT has been linked to elevated sympathetic neural activity (42,43). After showing that EA parous women had higher IAAT than their nulliparous counterparts (42), Blaudeau et al (45) tested the link between IAAT and
parity and the possible mediating effects of catecholamines (dopamine, epinephrine, norepinephrine, and total catecholamines) and the IAAT-parity relationship in 47 AA women and 44 EA women who were premenopausal and BMI between 27 and 30 kg/m². Blaudeau found the same increased IAAT in parous AA women compared to their nulliparous matches, and only dopamine was lower in parous women and higher in AA women. Dopamine, however, did not mediate the IAAT relationship with parity.

This review serves to provide a background to the major issues and findings concerning IAAT and CVD risk, CVD risk interventions, and CVD risk and race (AA and EA women).

IAAT, Health, and CVD Risk

IAAT has been linked to many health problems and conditions related to inflammation (38,44), cancer (45), increased sympathetic nervous system activation (41,42,43), and endothelial dysfunction (38). There have been many cross-sectional studies which have examined body fat distribution with a focus on IAAT and its relationship with CVD risk. It is well established that people with higher amounts of IAAT tend to have a higher risk for CVD (3-8). Though direct effects cannot be assumed with correlations, the argument of detrimental IAAT can be strengthened by showing a weaker association between CVD risk and other body fat depots, such as abdominal SAT (7) or LF (4,48). Fox et al (7) conducted a study among men and women, with an average age of 50, from the Framingham Heart Study (n = 3001). They found that the strongest correlations with CVD risk (blood pressure, blood glucose, blood lipids) were with
IAAT, and these associations were stronger than with CVD risk and SAT or any other body fat depots. The participants’ body fat distribution was measured by computed tomography (CT) and Pearson correlation coefficients were used for statistical analysis. The investigators concluded that their study was consistent with others in that IAAT appears to be a unique, pathogenic fat depot. Williams et al (5) studied 224 women (pre and post-menopausal) and found that IAAT (CT determined) and trunk fat were both consistently positively correlated to CVD risk (blood pressures and blood lipids), rather than IAAT alone. Also reported by Williams was a negative association between leg fat and CVD risk, which has been reported in other studies (3,48). These researchers have advised to carefully interpret the negative correlation of relationship between leg fat and CVD risk, and that other analyses were needed to further understand those results. The idea that leg fat may be harmless or is protective further reflects the diversity in possible varying roles in body fat distribution.

Non-traditional methods of measuring IAAT-relation to direct risk are also being found in the literature, and a common example is measuring plaque formation in arteries using ultrasound. Kawamoto et al (49) studied men and women (n = 1458) and found significant associations between IAAT (measured by ultrasound) and the interaction of IAAT and BMI (for overall adiposity) with carotid atherosclerosis. These participants were Japanese and were over 50 years old. Those with higher IAAT amounts also had greater carotid intima-media thickness (IMT: a precursor to preclinical atherosclerosis). Another study measuring carotid atherosclerosis via IMT was done by Lear et al (6). Lear found that in men and women (n = 794) with similar BMI (of aboriginal, Chinese, European and South Asian descent), men had IAAT levels that were independently
associated with atherosclerosis, but this was not the case in women. Conway et al (9) studied diabetic men and women (n = 315, mean age = 42) and the relationship between IAAT and coronary artery calcification (CAC: a subclinical precursor to coronary vascular disease) and found a significant trend between adiposity and CAC. However, IAAT was no different in its contribution compared to other body fat depots. In fact, when Conway limited the analysis to only those participants with measurable amounts of CAC, a negative relationship between IAAT and CAC was found, i.e. people with lower IAAT had higher CAC scores.

WL/Exercise, and IAAT

It has constantly been found that WL has resulted in decreased risk for CVD (14-24). Studies have looked at obese (BMI > 30 kg/m²) people (20,22), both overweight and obese together (14-16,18,21,23) or lean participants (17,24) when exploring the effects of WL on physiologic indices. Traditionally, factors measured for CVD risk are fat distribution (3), blood pressure (21), blood lipids (23), insulin (20), and inflammatory markers (eg. C-reactive protein (CRP), E-selectin, intercellular adhesion molecule (ICAM): 25). Rector et al (21) examined overweight/obese (BMI = 33.0 +0.8) men (n = 8) and women (n = 17) in a diet and WL study. After a 9 kg WL, participants had significant decreases in weight, body fat, blood pressure, total cholesterol, triglycerides, and low-density lipoproteins, but reported no significant changes in high-density lipoproteins after 4-7 months of treatment. The diet intervention consisted of a 500 kcal deficit, and the exercise protocol was 45min/day of aerobic training (walking, slow
jogging) at 60% of the participants’ VO$_{2\text{max}}$. Race and age were not reported. Santosa et al (23) studied 35 overweight/obese women (BMI = 31.4 ± 2.8, aged 35-58 years) in a diet and exercise study. The women were counseled to decrease energy intake by 20% and increase energy expenditure by 10%. Participants showed the same results as Rector, except that there was a significant increase in high-density lipoproteins after WL. Blood pressure changes and race were not reported. The women in Santosa’s study were tested after 2 weeks of energy balance at baseline and post WL, and lost about 3 more kg compared to Rector’s participants. These factors may have played a role in the differences reported. These studies represent the number of reports of a diet and exercise intervention designed to induce WL, but do not allow independent distinctions of the effects of either factor alone, and have not compared similar body types.

In an attempt to see an enhanced effect from exercise, Redman et al (50) conducted a study in 35 men and women (premenopausal) who were put into one of three groups: caloric restriction (25% deficit), caloric restriction and exercise (12.5% each, for a combined deficit of 25%), and controls (maintained weight with a healthy diet). Redman only looked at body composition and reported that with a moderate amount of WL (-10%), there was no difference in the diet alone or diet plus exercise groups in either IAAT or SAT losses after 6 months treatment. Both groups lost the same amount of weight, and both groups lost significant amounts of IAAT. A similar study to compare diet and exercise roles was carried out by Ryan et al (22), but used post-menopausal obese women (n = 33, BMI = 32 kg/m$^2$) who were randomly assigned to a diet group, or a diet and exercise group intervention. Specific percentages for allocating deficits in energy balance were not reported, however, Ryan confirmed Redman’s results in that
exercise did not enhance the removal of fat from the IAAT. Ryan did measure insulin sensitivity and glucose utilization, and did see an improvement in the exercisers compared to the non-exercisers, implying an enhanced benefit of diabetes-protection from exercise. Ross et al (51) studied 33 obese (BMI > 27 kg/m²) men in a WL study and randomized participants to either diet only (n = 11), diet and aerobics (n = 11), or diet and resistance training (n = 11). All the men reduced caloric intake by 1000kcal/day for 16 weeks, and were weight stable for 1 week before and after the caloric restriction phase. At the end of the study, all groups significantly reduced body weight (10%), abdominal SAT (25%), IAAT (35%). There was a uniform preferential reduction in VAT across groups, however, diet and aerobics/diet and resistance training groups saw a larger increase in abdominal SAT (27%) compared to gluteal-femoral region (20%). The diet only group significantly decreased lean tissue, whereas the exercisers better preserved lean tissue. Ross demonstrated that even though all interventions decreased IAAT, exercise offered additional benefits of maintaining lean tissue and skeletal muscle in the appendicular regions.

Many studies (15,17,18) used exercise only as the intervention to observe regional body distribution changes. Aerobics exercise training was used in a study (18) with 24 men who were lean (n = 8, BMI < 25 kg/m²), obese (n = 8, BMI > 27 kg/m²), and obese with type II diabetes (n = 8, BMI > 27 kg/m²). Men were fed a weight-maintenance diet, and calories were provided to compensate for the energy burned during exercise. After 3 months of aerobics at 60 minutes, 5 times a week, body weight did not change. There were, however, significant increases in muscle mass and significant decreases in total body fat and IAAT in all groups. The obese and obese with type II diabetes group lost
significantly more IAAT compared to the lean men. Donnelly et al (15) performed a study with men and women where the participants were randomized to either the exercise intervention (n = 16 men, 25 women) or control group without exercise (n = 15 men, 18 women). The participants were aged 17-35 years, and were overweight/moderately obese. Subjects increased exercise duration and frequency to 45 minutes of aerobic training at 75% VO$_{2\text{max}}$, 5 days a week. Exercising men decreased body weight (-5.2 kg) and IAAT significantly (23% loss in exercisers, 7% loss in controls). Female exercisers lost significant amounts of IAAT (5% loss in exercisers, 5% gain in controls) and maintained weight while the control group gained weight (+3.5%).

Treuth et al (24) studied resistance training in 14 healthy, relatively lean (BMI = 25.1 ± 1) post-menopausal women (aged 67 ± 1 years). The women performed resistance training exercises 3 times a week for 4 months, and progressed to 2 sets of 12 repetitions at 67% of their one repetition-maximum. After the treatment, there was no overall loss of weight from baseline, but the women did see significant decreases in IAAT with concomitant increases in strength. There were no changes in blood lipids and blood glucose after resistance training. Hunter et al (17) studied men (n = 14) and post-menopausal women (n = 12) of normal BMI (< 25 kg/m$^2$) aged 61 – 77 years, in a 6-month resistance-training program. There were no main effects in either IAAT or SAT, but post-hoc analyses revealed that significant decreases in IAAT and SAT were observed in the women, but not for the men. Again, Hunter confirmed IAAT-losses with resistance training, even without an overall WL. Also, these benefits were observed in a lean population, displaying that even normal-weight people can benefit from exercise training through reducing their CVD risk.
Acute effects of exercise should also be considered when analyzing blood lipids and blood pressure. Studies have reported acute changes in metabolic variables with exercise (52,53) and other studies have not (54,55). Exercise intensity is a factor to be considered, and some studies have reported intensity to mediate changes in TC and HDL (56,57) Crouse et al (58) conducted a study to separate the acute effects of exercise from the chronic effects on blood lipids. Hypercholesterolemic men (n = 26) trained 3 times/week at either 80% intensity or 50% intensity on a cycle ergometer until the required caloric expenditure was achieved. Blood lipids were measured at baseline, and then 8, 16, and 24 weeks from baseline. Testing as conducted 60-72 hours after the participants’ last exercise session for the pre-exercise blood draw (5 minutes before exercise), and then immediately after assigned exercise (within 10 minutes) for a post exercise blood draw. Blood samples were then measured 24 hours later as well as 48 hours later where no exercise was permitted in this testing period. TC, TG, HDL, and HDL₃ were analyzed from blood samples, and HDL₂ and LDL were estimated. At the end of the study, the men experienced a small but significant WL (-1.4 kg) but no changes in caloric intake/diet composition were observed. Changes were seen in LDL immediately after exercise, but rose back to pre-exercise levels 24 and 48 hours after exercise when examined prior to any exercise and after 24 weeks of exercise. After 48 hours, TC and HDL were approximately 0.4% and 6% higher, respectively, and TG were approximately 5% lower. These data imply that exercise training may have an acute and a chronic effect on at least some blood lipids after 48 hours of an exercise bout. This suggests that improvements in blood lipids may be enhanced if exercise is replicated every 24-48 hours. Even though TC was higher 48 hours after exercise, this would not be
considered to be a negative effect of exercise since an increase in TC. was entirely
Crouse proposed that exercise should be avoided at least 60 hours before blood testing to
eliminate the potential acute effects of training.

Race, IAAT, and CVD Risk

Differences in body composition and metabolic profiles have been reported
between AA and EA women. AA women deposit fat differently from EA women, with
AA women having much lower IAAT compared to EA women of similar body weight in
an overweight state (27,28). In studies where highly obese women at the L4-L5 regions,
there were no statistically significant differences in IAAT levels between AA and EA
women (29,59). Weinsier et al (28) conducted a diet-induced WL study with AA and EA
premenopausal women (23 of each). In these overweight women, where there were no
significant differences in age, body weight, BMI, body fat %, and fat free mass. IAAT at
baseline was ~40% higher in EA compared to AA women. After these women lost the
weight (~13 kg), EA women lost more IAAT compared to AA women, but proportional
changes were similar. Gower et al (27) reported around 44% higher IAAT levels in EA
women (n = 18) compared to AA women (n = 19) at baseline in a slightly smaller,
overweight sample. The changes persisted after a WL intervention, with similar
proportional losses in IAAT from baseline. Conway et al (29) compared similar obese
women and found higher IAAT in EA women at the L4-L5 site compared to AA women
(21%), though not statistically significant, it was borderline (p = 0.054). Conway found
that after WL (approx. 17 kg), there was no difference in fat liberation from IAAT and
SAT. Conway used a much smaller sample size (AA = 8, EA = 10) and studied obese women, which may account for differences. In cross sectional data of lean and obese, premenopausal women in one study (60), there were no significant difference in IAAT between AA and EA women. AA women had lower values of IAAT, but p-values were above 0.25.

AA women also have better blood lipid profiles (29,30) overall and higher blood (1) pressure relative to EA women. Gower et al (27) reported blood lipids in BMI-matched premenopausal women in a WL study. At baseline, AA women had lower triglycerides than EA women. After WL, both races reported decreases in triglycerides and low-density lipoproteins, as well as an increase in high-density lipoproteins. There was no change in total cholesterol after WL. When Conway et al (29) looked at obese women at baseline, AA women had lower triglycerides and higher high-density lipoproteins. There were no changes in blood lipids after WL.

Conclusion

A great deal of the literature is presenting IAAT as a unique pathogenic fat depot (3,7), whereas other studies are making this association less clear (6,9). Since CVD is a major problem in the western world and other countries (1,2), it is important to know the harmful body fat depots. Doing so will make it easier for health professionals to target areas where interventions are needed, and to improve these interventions. WL is an effective method for decreasing CVD risk (21,27,28), but is not easy to achieve by most populations in American culture, which is reflective of obesity problem. Exercise has
been shown to decrease CVD risk (14-24), but not in all parameters measured (25) and enhanced effects are not always clear (50). Even where studies have shown that exercise offered no direct benefit for CVD risk, one must not overlook the benefits that others have shown from exercise, such as maintaining muscle mass (51), preventing bone-density losses (61), and studies that have reported lower CVD risk in smokers who exercise regularly compared to non-exercising smokers (19). AA women are at a greater risk for CVD than EA women despite their better blood lipid profile. Interestingly, AA women may benefit as much as EA women from WL even though they have lower IAAT (27,28). As research continues, results are validated, and methods improve, i.e. drawing blood samples at the proper time to avoid the acute effects of exercise training (58), targeting the harmful fat depots in attempts to improve CVD risk and measurements may help decrease CVD incidences and improve quality of life in those that are currently at risk.
References


APPENDIX A

Institutional Review Board Approval Form

DATE: 1/3/07

MEMORANDUM

TO: Konstantina Katsoulis
   Principal Investigator

FROM: Sheila Moore, CIP
   Director, IRB

RE: Request for Determination—Exempt Research
IBB Protocol # N971320003—Diet-Induced Change in Intraabdominal
Adipose Tissue and CVD Risk in African American and European American
Women

The Office of the IRB has received the above referenced exemption application. The application
has been reviewed according to the IRB Policies and Procedures and it has been determined that
your project qualifies as Not Human Subjects Research. Should your research change you will
need to resubmit to the IRB for further review and determination.

SM/cw