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Title

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**Assessing associations of cardiorespiratory fitness (CRF)
and degree of obesity with insulin-resistance**

Independent Study Project Report

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Abstract:

Background: Obesity and poor cardiorespiratory fitness (CRF) are strong predictors of insulin resistance. The mechanisms underpinning the beneficial effects of CRF on insulin action, however, are not fully understood. Several weight loss intervention trials have suggested that while improving CRF is associated with better insulin sensitivity in adolescents and adults, this association is no longer significant with correction for indices of adiposity. A growing body of literature in the last decade also indicates that CRF with or without changes in BMI/waist circumference enhances insulin sensitivity and that overweight/obese individuals with an adequate level of CRF may consequently be at a reduced risk of diseases associated with insulin resistance. In this project, we investigate whether CRF and degree of obesity have independent associations with insulin resistance in overweight/obese women enrolled in a weight loss trial.

Methods: The data are from the MENU Study (Diet Composition and Genetics: Effects on Weight, Inflammation and Biomarkers), a randomized clinical trial funded as part of the TREC initiative at UCSD (Trans-disciplinary Research on Energetics and Cancer (TREC) - NCI U54CA155435). The main objective of the MENU trial is to examine if different macronutrient compositions in the diet affect a differential weight loss response in 234 healthy obese women, depending on insulin resistance status. The current paper utilizes baseline data on the 98 women who are enrolled in the first cohort. The variables used for the current analysis include BMI and waist circumference (WC), as well as insulin sensitivity by HOMA (homeostasis model assessment) approach. CRF was assessed by measuring heart rate during recovery after a 3-minute stepping test. Linear

regression models were used to examine associations between CRF, BMI and insulin sensitivity.

Results: The findings indicated that CRF was associated with less insulin resistance, independent of BMI and WC. The present study, along with others in recent literature, suggests that CRF may attenuate insulin resistance apart from its known impact on BMI/WC and may be an important determinant of cardiometabolic disease risk particularly in populations of obese women.

Background:

Insulin resistance has become a major health challenge worldwide over the past few decades and is a central feature in type 2 diabetes (DM 2), stroke and coronary artery disease (CAD). Obesity and central body fat distribution, along with poor cardio-respiratory fitness (CRF) are strong predictors of insulin resistance (1-3).

Cardiorespiratory fitness is a measure of the strength of one's aerobic energy system-one's circulatory and respiratory systems to provide oxygen during physical activity. While a person's level of physical activity generally varies from day to day, CRF remains relatively static, and reflects habitual physical activity.

The weight of evidence from epidemiological studies of fitness and body fatness indicates that a moderately high level of fitness can significantly reduce the risk of CVD/CHD in the overweight and obese. This reduction can be to the extent that an active or fit overweight or obese individual is likely to exhibit lower CVD risk than an inactive or unfit individual of normal weight (33-34). However, a fit/active person who is overweight or obese will likely still be at an increased CVD risk compared with a fit/active person whose BMI is in the normal range. Several investigations (4-6) have demonstrated that improving CRF enhances insulin sensitivity in previously sedentary adults, which likely accounts for some of the protective effects of CRF. The specific mechanisms underpinning the beneficial effects of CRF on insulin action at present, however, are not fully understood.

It has long been established that exercise improves glucose metabolism acutely (7). One moderate-intensity exercise session can cause a 40% improvement in glucose uptake, but these effects diminish within 48 to 72 hours of an exercise session (8).

Cessation of exercise, even in trained persons, is associated with a marked and rapid decrease in insulin sensitivity (9). The impact on glucose metabolism of chronic exercise, and specifically, improved cardiorespiratory fitness, remains unclear. On the other hand, there is a clear relationship between abdominal adiposity and level of insulin resistance (10). Even though the acute effects of an exercise session on insulin sensitivity occur too rapidly to be mediated by decreased abdominal adiposity, research suggests that the latter probably accounts for the long-term effects of exercise on insulin sensitivity. Many exercise intervention trials have suggested that while improving CRF is associated with better insulin sensitivity in adolescents and adults, the association is no longer significant after correction for BMI/WC (11-12). Furthermore, data suggests that it is decreasing visceral adiposity in particular, that most improves insulin sensitivity following an exercise intervention (13-14).

In this study, we evaluate the associations between CRF, waist circumference and insulin sensitivity in healthy overweight or obese women. A growing body of literature proposes that CRF with or without changes in BMI/WC improves insulin sensitivity and its associated cardiometabolic disease risk. In a multivariate analysis of a cross-sectional study of 407 adults aged 50–95 years, Racette et al. (19) reported that both waist circumference and maximal oxygen uptake in a treadmill test were significant independent predictors of insulin sensitivity. In the study, abdominal obesity (assessed by dual-energy X-ray absorptiometry or hydrodensitometry) was found to be a stronger predictor, however. In a cross-sectional study of two hundred Japanese patients with impaired glucose tolerance (IGT) and type 2 diabetes mellitus, Nagano et al. reported that the prevalence of hyperinsulinemia was significantly lower in “mid-fitness” and “high-

fitness” level groups of men and women compared with the “low-fitness” group (classified by testing on a cycle ergometer), independent of visceral fat accumulation, as measured by computed tomography scan (15). Gerson et al. assessed insulin sensitivity in 10 overweight women with high CRF, 9 lean women with high CRF, and 10 overweight women with low CRF and found that compared with lean fit women, insulin sensitivity was only slightly lower and plasma triacylglycerols were almost identical in overweight women with equally high CRF despite a twofold elevation in body fat percentage. Overall, these studies suggest that overweight and obese individuals with an adequate level of CRF may have improved insulin sensitivity, apart from changes in degree of fatness. Improvements in insulin sensitivity may also be the key to why those who are “fat and fit” experience a lower incidence of cardiometabolic disease compared to those with low CRF (15-18).

The present study evaluates whether cardiorespiratory fitness (CRF) and degree of obesity are independently associated with insulin-resistance in 98 otherwise healthy obese women, ages 21 years and older. Our specific hypothesis was that better physical fitness would be associated with less insulin resistance independently of BMI/WC. The data used were collected as part of the MENU (Metabolism, Exercise, and Nutrition at the University of California, San Diego) Study, which is an ongoing randomized clinical trial that examines if different macronutrient compositions in the diet affect a differential weight loss response in 234 healthy obese women, depending on insulin resistance status.

Methods:

The analysis in this study was performed utilizing baseline data from the MENU study.

Participants: Participants included non-diabetic obese women (n=98) living in San Diego, CA. Recruitment procedures included community outreach through email and posting flyers. Other strategies included conducting large scale direct marketing mailings. Inclusion criteria for the study were: female gender, aged 21 years and older, with initial BMI ≥ 30.0 kg/m² and ≤ 40 kg/m², willingness to participate in clinic visits, willingness to undergo blood collections, and ability to perform a simple step test for assessing cardiopulmonary fitness. Exclusion criteria were inability to participate in physical activity because of severe disability (e.g., severe arthritic conditions) and a history or presence of comorbid diseases for which increased physical activity may be contraindicated. Women found to have a fasting glucose concentration >125 mg/dL at the baseline measurement point were excluded, as this level is indicative of diabetes.

Measurements: Anthropometric measurements (height, weight, and waist and hip circumferences) were collected at baseline using standard procedures.

A 30 mL blood sample was collected from each participant for measurement of fasting insulin and glucose. Following centrifugation and separation, plasma or serum was stored at -80 degrees Celsius until analyses were conducted.

Physical fitness data were collected with a stepping test. CRF in this test was measured as the heart rate during the first 15 seconds of recovery from three minutes of stepping on a step bench. While measurement of VO_{2max} is the gold standard for measuring CRF, the step test has been shown to have high reliability (0.92), sensitivity to change, and been widely used to assess CRF (37, 42).

Statistical Analysis

Summary statistics (means, SD, ranges) of age, ethnicity, BMI, waist

circumference, CRF, and insulin resistance were computed to examine all relevant demographic and clinical characteristics of the sample. We conducted homeostasis model assessment (HOMA) of insulin resistance, determined by the following formula: fasting serum insulin (mUL) X fasting serum glucose (mmol/L)/22.5 (49). Using the HOMA approach, insulin resistance was defined as having a HOMA-IR value >3.0, as this is an observed and/or applied cut-point in numerous clinical studies (50-54). Pearson correlations were performed to detect associations among CRF, BMI, and insulin resistance. Linear regression models were employed to further examine relationships between waist circumference, BMI, and CRF as potential predictors, and insulin resistance (dependent variable). An alpha value ≤ 0.05 was considered statistically significant. All statistical analyses were executed using SAS Version 9.2 (Cary, NC).

Results

Demographic and clinical characteristics of the participants are reported in Tables 1 and 2. Participants ranged from 22 to 70 years of age, with a mean of 49. There was a wide range in the post-step test heart rate values (primary indicator of CRF), ranging from 74 - 168. The mean value from this test was 121, which is a slightly below average CRF score, for a female with the mean age of the participants. BMI of the participants ranged from around 30 to 40, with a mean BMI around 34 kg/m². In our population, about 63% of women were classified as insulin resistant.

Of the 98 participants, the majority was white non-Hispanic (66%) and 21% were Hispanic. Among Hispanic participants, about 67% were found to be insulin resistant as compared to 55% in white non-Hispanic participants. Asian-Americans, although barely represented in our sample, had the highest HOMA and waist circumference values among

the groups (except the “other” category) while having the lowest mean age and BMI values of all groups. Comparative analyses between racial/ethnic groups were not performed due to low numbers of participants in the sample.

Associations among all participants characteristics, CRF, BMI, waist circumference and insulin resistance (HOMA), are presented in Table 3. Pearson correlations revealed that post-step test heart rate (CRF) and insulin resistance were significantly and inversely correlated ($r = 0.24$, $P < 0.05$), and post-step test heart rate (CRF) and BMI were significantly and positively correlated ($r = 0.25$, $P < 0.05$). BMI and insulin resistance had a direct relationship that was nearly significant.

Table 4 displays the results of a regression analysis for insulin resistance, controlling for CRF, BMI, and waist circumference. Only CRF was detected to have a significant predictive relationship with insulin resistance ($P < 0.05$). Waist circumference had a near-significant association with HOMA values ($P = 0.055$), while BMI and age were not significantly associated with CRF in this regression analysis in our sample.

Discussion:

In this study, CRF was found to be a significant predictor of insulin resistance in obese women independent of BMI and waist circumference. This result is somewhat different than previous research that suggested that a reduction in weight or abdominal obesity typically attenuates the effects of CRF on insulin resistance (11-12). There are various mechanisms described in the recent literature for how CRF could mitigate insulin resistance separately, such as by enhancing GLUT4-dependent and hypoxia-dependent glucose transport in skeletal muscle and attenuating inflammation (20-25, 30-32, 48).

While CRF was found to be significantly associated with insulin resistance in our correlation and regression analyses, WC, BMI, and age were neither significantly associated with nor independently predictive of insulin resistance. Previous cross-sectional studies, however, have reported strong correlations between these other variables and insulin resistance [11-15, 43-45]. It is perhaps noteworthy to mention that waist circumference had a near-significant association with insulin resistance and was a stronger predictor of insulin resistance than BMI. This finding agrees with the current understanding that in contrast to BMI, which is a reflection of overall fat distribution, waist girth, which reflects visceral fat, is a better predictor of insulin resistance. There are at least a few of plausible explanations for why no significant associations were found between variables other than CRF with insulin resistance.

One reason could be the narrower ranges of BMI and WC values in our data compared to variation in CRF values. During recruitment, we only included participants with an initial BMI ≥ 30.0 kg/m² and ≤ 40 kg/m². The majority of participants (~95%, within two SDs) had WC values of 36-48. Secondly, while participants were obese, mean CRF was found to be slightly below the “average” fitness cutoff of 116 for a female with the mean participant age. Half of the participants were of average or above-average fitness level. There are several studies to suggest that in the obese population, a moderate to high level of CRF significantly enhances insulin sensitivity and is more important as a cardio-protective factor than low adiposity (15-18, 50-51). It is plausible that our population of obese women was fitter than some other study populations, perhaps in part because of being recruited from San Diego, California, which is consistently rated as one

of the “fittest cities” in the nation according to the annual American College of Sports Medicine’s American Fitness Index report.

Another reason that could account for differences between our study findings and others is that we excluded individuals with diabetes. Because this condition is strongly related to the variables tested, exclusion of such potential participants is likely to have shifted the observed correlations between age, BMI, WC, and insulin resistance downward.

Our exclusion criteria may have also left us with a “metabolically healthier” sub-population of the obese. As part of the EPIC-InterAct Case-Cohort Study, European researchers looked at data on 340,234 people who were tracked for a total of nearly 4 million person-years. They found that among women, those who were obese were 11.6 times more likely than non-obese women to develop diabetes. The relative risk for women with WC greater than 35 inches was 11.6 (53). The average age of onset for type 2 diabetes in the United States has been found to be around 46 years (46). Our study population consisted of obese women with a mean WC value of 42 inches and a mean age of 48 years; we studied a group of non-diabetic women who would be considered at significant risk of type 2 diabetes. It is possible our sample was biased towards including “metabolically healthier obese women,” a subset of obese individuals who recent research shows have specific, identifiable anatomic, cellular and molecular features such as lower liver fat content and adipose tissue dysfunction, separating them from the majority of “metabolically unhealthy” obese patients (47-49). Other contributors to this heterogeneity in the obese population that have been cited are CRF and fat distribution (49).

The current study sample represents only two of five cohorts in the five-year MENU study. We did not have adequate representation of different ethnic sub-groups in our current data to make between-group comparisons. Nonetheless, our summary statistics show that while BMI and CRF do not appear to differ significantly between Hispanics and non-Hispanic whites, Hispanics may have significantly higher insulin resistance as a group when our data expands. The same may be true of Asian-American women, who currently have the highest insulin resistance values, while having the lowest mean age and mean BMI values.

Conclusions:

The present study, along with other recent investigations, suggest that CRF may attenuate insulin resistance apart from its known impact on BMI/WC and may be an important determinant of cardiometabolic disease risk, particularly in obese women. Currently, evidence suggests that the likelihood of an obese individual sustaining substantial long-term weight loss may be low (35-36). Thus, while being fit and having normal BMI may maximize one's cardiometabolic disease risk reduction, increasing fitness may be beneficial to participants who lose some weight, but still do not fall into the "normal" BMI range. Several recent studies have also shown convincing evidence that cardiorespiratory fitness is a much stronger predictor of longevity and reduced risk of cardiovascular mortality and all-cause mortality than BMI. Rather than the exclusive focus on BMI and weight loss, focusing on maintaining an adequate level of physical activity and fitness throughout life may be the most effective way to counter the deposition of abdominal fat and the adverse metabolic changes that accompany it.

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Table 1. Clinical characteristics of study participants (N=98)

Variable	N	Mean (SD)	Range
Age (years)	98	48.8 (11.1)	22.0-70.0
BMI (kg/m ²)	98	34.4 (2.7)	29.9- 39.7
WC (in)	98	42.4 (3.2)	35.5- 50.0
Step test (heart rate during recovery)	98	121.1 (8.4)	74. 0-168.0
HOMA	98	4.2 (2.7)	1.1-14.94

Table 2. Clinical characteristics of study participants by race/ethnicity (N=98)

Ethnicity	N	Step test*	BMI [kg/m ²]	Age [years]	Waist circ. [in]	HOMA	Insulin Resistance
Non-Hispanic white	65	120.8 (7.3)	34.1 (7.8)	51.0 (2.6)	42.4 (3.3)	3.8 (2.3)	0.6 (0.5)
Hispanic	21	119.0 (9.5)	34.8 (2.4)	45.1 (13.2)	42.2 (3.4)	4.7 (2.8)	0.7 (0.5)
African-American	6	123.3(10.7)	36.7 (2.2)	49.8 (8.4)	42.3 (2.5)	3.0 (1.3)	0.5 (0.6)
Asian-American	3	136.7 (8.4)	33.0 (4.9)	31.3 (8.3)	43.2 (6.0)	8.0 (3.7)	1.0
Other ^a	3	123.3 (11.2)	35.3 (3.1)	44.0 (21.0)	43.7 (0.23)	6.6 (7.3)	0.3 (0.6)

* Step test [heart rate 15s after completing step test]

^a Polish German/ Hispanic, Filipino, Hispanic/Black

Table 3. Pearson correlation matrix: age, BMI, cardio-respiratory fitness (heart rate 15 seconds after completing step test), HOMA

	BMI (kg/m ²)	Waist Circ. (in)	Step test (heart rate)	HOMA
BMI (kg/m ²)	1.00	0.63900 (p<0.001)*	0.24708 (p <0.05)*	0.05016 (p = 0.62)
Waist Circ. (in)		1.00	0.69070 (p = 0.09)	0.16000 (p = 0.11)
Step test (heart rate)			1.00	0.23759 (p< 0.05)*

Table 4. Regression model for insulin resistance (HOMA) controlling for waist circumference, BMI, Step test, and age

Classification	N	P	Beta
Waist circumference (in)	98	0.0554	0.2128
BMI (kg/m ²)	98	0.2238	-0.1646
Step test (heart rate)	98	0.0230*	0.0765
Age (years)	98	0.3733	0.0231
	$R^2 = 0.11$		

* P < 0.05