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Insulin Resistance Improves More in Women than In Men in Association with a Weight Loss Intervention

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Abstract

Background: Fasting glucose and homeostatic model assessment-insulin resistance (HOMA-IR) are important measures of the risk for metabolic syndrome and diabetes. Weight loss interventions are considered part of the first line of therapy for those who develop disease states associated with insulin resistance, such as pre-diabetes, diabetes, or metabolic syndrome. Sex differences in insulin resistance have been extensively reported, but sex differences in the ability to improve insulin sensitivity are not well-established. This study sought to identify factors that predict change in HOMA-IR in response to weight loss.

Methods: Non-diabetic subjects who were overweight/obese (n=100) were randomly assigned to a walnut-enriched reduced-energy diet or a standard reduced-energy-density diet in a 6-month weight loss intervention. There were no significant differences in weight change, glucose, insulin, or HOMA-IR between the two diet groups. These subjects were combined into a single cohort and analyzed with multivariate analysis.

Results: The combined groups lost an average of 8.7 kg ($p<0.0001$), decreased serum glucose by an average 0.2 mmol/L ($p<0.001$), and decreased HOMA-IR by an average of 1.4 ($p<0.0001$). Change in HOMA-IR ($R^2=0.69$) was positively associated with weight change ($p<0.0001$) and male sex ($p<0.01$), and negatively associated with baseline HOMA-IR ($p<0.0001$).

Conclusion: Findings from this study suggest that men may have a more difficult time improving insulin sensitivity as compared with women with an equivalent weight loss and baseline HOMA-IR. One hypothesis to explain the differences across sexes may be due to sex differences in visceral adipose fat (VAT). This may mean that insulin resistant men require more aggressive intervention than women to prevent progression to metabolic syndrome or diabetes.

Keywords: Walnuts; Insulin resistance; Weight loss; Diabetes; Metabolic syndrome; Sex

Abbreviations: BMI: Body Mass Index; CV: Coefficient of Variation; HOMA-IR: Homeostasis Model Assessment-Insulin Resistance; RBP4: Retinol Binding Protein 4; VAT: Visceral Adipose Tissue

Introduction

Insulin resistance is a strong independent risk factor for development of type 2 diabetes [1] and metabolic syndrome [2]. It is believed to be a key element in the pathophysiology of these syndromes [3]. Obesity is known to contribute to the development of insulin resistance. This likely occurs through excess energy intake relative to expenditure leading to hyperinsulinemia, and subsequent down regulation of overstimulated insulin receptors. There are other proposed mechanisms, including free fatty acids accumulating in skeletal muscle and interfering with mitochondrial function [4]. Inflammatory cytokines associated with excess white adipose tissue may also play a role in the development of insulin resistance, as shown in mouse models [5] and in humans [6].

Data on whether men show more insulin resistance than women are conflicting. There is some evidence for sex differences in insulin resistance in mice [7] and in humans [8,9]. For example, older obese men were found to be more insulin resistant than older obese women, though they had lower total body fat, less subcutaneous fat, and greater fat free mass [9]. However, if type 2 diabetes is considered a manifestation of insulin resistance, the evidence is less clear. The CDC shows overall diabetes incidence for adults aged 18-79 that does not differ between sexes beyond the standard error, with historical data that shows some years where men have higher incidence, and other years where women have higher incidence [10]. Incidence by sex also differs when stratified by age and race. For example, white non-Hispanic women aged 65-74 years had a lower incidence of diabetes compared to white non-Hispanic men (17.1 per 100 *vs.* 22.3 per 100), but African-American women in the same age range had a much higher incidence than African-American men (38.2 per 100 *vs.* 29.6 per 100). The same trend was found for Asian females vs. Asian males in this age range (29.4 per 100 *vs.* 22.5 per 100). These comparisons do not hold true over all age ranges – African-American and Asian females have lower incidence than African-American and Asian men, respectively, in the >75 years age range. Incidence is much less dissimilar between sexes in all races aged <64 years [11], but it is clear the relationship between age, sex, and race is complicated. These

statistics do not differentiate type 2 diabetes from other types, but it is important to note that type 2 diabetes makes up about 95% of diabetes and the incidence of type 1 diabetes is primarily in children, which were not included in the figures tabulated [12]. Another interesting finding from the CDC is that while adult (aged ≥ 18 years) men and women in the US had similar prevalence of diabetes (15.3 million men, 14.9 million women), adult men had a much higher prevalence of pre-diabetes than adult women (44.5 million men, 39.5 million women) [13]. This higher prevalence of pre-diabetes in men might be explained by sex differences in insulin resistance.

Previous large studies have shown that insulin sensitivity increases in a dose dependent manner with weight loss [14-16]. However, the question of whether sex can predict the degree of insulin sensitivity improvement a ter weight loss has not been adequately answered. Only one previous study that examined this question has been reported, using linear regression to examine the connection between change in percent body mass index (BMI) and change in homeostasis model assessment-insulin resistance (HOMA-IR) in a one-year observational study with a Japanese population of 1199 women and 2014 men. While percent BMI was found to be a signi icant predictor of percent HOMA-IR change for both men and women, men had a higher beta coefficient than women (4.15 *vs.* 2.41) indicating men had a larger increase in percent HOMA-IR for each percent of BMI gained [17]. However, sex was not included as a coefficient in regression, so these indings are incomplete, and further study is warranted. The present study was designed to examine factors that are associated with changes in insulin resistance in response to a 6-month behavioral weight loss intervention in overweight and obese men and women. Factors that are associated with improvement in insulin resistance a ter a weight loss intervention are relevant to the treatment of metabolic syndrome, pre-diabetes, type 2 diabetes, and other diseases associated with insulin resistance.

Materials and Methods

The present study is a prospective observational cohort design that examined sex differences in the change in insulin resistance among participants in a trial comparing two different dietary strategies in a behavioral weight loss intervention [18]. There were no differences in baseline characteristics, changes in weight, glucose, or insulin measurements between the two diet groups, so they were combined for analysis as a cohort.

Study participants and intervention

The analytical sample consisted of 100 non-diabetic overweight or obese men or women enrolled in a weight loss trial over a six month period. Subjects whose fasting glucose by finger-stick test exceeded 125 mg/dl were excluded from the study. Additional eligibility inclusion and exclusion criteria are reported elsewhere [18]. The UCSD institutional review board approved the study protocol, and all participants provided written informed consent. Demographic data were obtained by questionnaire; weight, height, and waist circumference were measured, and BMI was calculated as weight (kg)/height (m^2) at baseline and 6-month clinic visits. At these visits, a fasting (>6 hours) blood sample was collected and blood pressure was measured. Systolic and diastolic blood pressure was averaged from two sitting blood pressure measurements. The participants were assigned to consume either a standard reduced-energy-density diet, or a walnut-enriched reduced-energy diet. Both diet groups were counseled to increase physical activity, with a goal of 1 hour of moderate to strenuous intensity physical activity daily.

Measurements

A fasting blood sample was collected at baseline and 6-month clinic visits. Following appropriate processing, cryovials were stored in -80 degree C freezers prior to analysis. Insulin was measured by Arup Laboratories (Salt Lake City, UT, USA) using the ADVIA Centaur assay, a double antibody immunoassay with chemiluminescent detection. The inter-batch and intra-batch coefficient of variation (CV) was 3.3% and 2.3%, respectively. Glucose was also measured by Arup Laboratories (Salt Lake City, UT, USA) using enzymatic methodology that formed NADPH from a catalytic reaction of glucose with hexokinase, and NADPH was measured photometrically. The method CV for 95.1 mg/dl and 137 mg/dl was 1.1% and 1.2%, respectively. HOMA-IR was computed from the measured levels of insulin and glucose, ([fasting glucose, mmol/L] × [insulin, mIU /l]/22.5) with HOMA-IR >3.0 considered indicative of insulin resistance. This approach to assess insulin resistance status has been validated in previous studies and is considered an acceptable indicator of insulin resistance [19].

Statistical analysis

Weight, percentage who were obese (de ined as a BMI of >30) glucose, insulin, HOMA-IR, and insulin resistance status (resistant or sensitive) were compared between baseline and 6 months using paired t tests for continuous measures, or chi-square tests for categorical variables. Any variables which were skewed (e.g., insulin, HOMA-IR) were log-transformed in analysis. A multivariate regression model for change in HOMA-IR was constructed using the following as possible associated factors: sex, age, and marital status, baseline level of HOMA-IR, change in weight, and change in physical activity. Analysis was performed in SAS version 9.4 (Cary, NC, USA), and alpha level was set at 0.05.

Results

Twenty-one male and 79 female subjects aged 27 to 74 years were enrolled in the study (Table 1).

Parameters	Female (N=79)	Male (N=21)
Age Category N (Percentage)		
27-39	13 (16.5)	3 (14.3)
40-49	10 (12.7)	4 (19.1)
50-59	32 (40.5)	7 (33.3)

60-74	24 (30.4)	7 (33.3)
Race/Ethnicity N (Percentage)		
Non-Hispanic White	59 (74.7)	14 (66.7)
Minority	20 (25.3)	7 (33.3)
Body Mass Index N (Percentage)		
27-29.99	27 (34.2)	5 (23.8)
30-34.99	36 (45.6)	12 (57.1)
35-39.99	16 (20.3)	4 (19.1)

Table 1: Characteristics of participants at enrollment in a weight loss intervention.

The participants were primarily white non-Hispanic (73%). There were no significant differences in baseline characteristics between the male and female participants.

Weight, obesity, biological and physiological measures

Weight loss, obesity, and biological measures at baseline and at 6 months are shown in (Table 2).

Parameters	Baseline	6 Months	p Value
Weight (kg)	91.0 (1.5)	82.3 (1.5)	<0.0001
(Percentage) Obese 68		44	<0.0001
Glucose mmol/l	5.54 (0.05)	5.34 (0.07)	0.0004
Insulin mU/mL	15.4 (0.8)	9.8 (0.6)	<0.0001
HOMA-IR	3.8 (0.2)	2.4 (0.2)	<0.0001
(Percentage) insulin Resistant	64	23	0.01

Table 2: Weight, obesity, and biological measures at baseline and after a 6-month weight loss intervention.

Overall, the participants lost an average of 8.7 kg, or 9.6% body weight (p<0.0001). The proportion of obese individuals declined during the study from 68% to 44% (p<0.0001). HOMA-IR decreased by an average of 1.4 (p<0.0001), resulting in an increase in insulin sensitive participants from 36% at baseline to 77% at 6 months (p=0.01). Among men, there was a smaller proportion of insulin sensitive participants at baseline than among women (19% vs. 39%) and also at 6 months (63% vs. 80%). Men had a higher systolic blood pressure at baseline than women (130 *vs.* 122) that was marginally significant (p=0.07). As noted above, there were no significant differences between diet groups in percent weight lost, glucose, insulin, or HOMA-IR at baseline and at 6 months.

Multivariate model for factors associated with HOMA-IR improvement

The multivariate model showed that weight change was strongly associated with change in HOMA-IR, with a 0.13 reduction in HOMA-IR for every 1 kg weight lost (Table 3). Baseline HOMA-IR was inversely related to change in HOMA-IR, where those with higher baseline levels had larger decreases. Age, marital status, and change in physical activity were not significantly associated with HOMA-IR change in the multivariate model. Women had larger changes in HOMA-IR (mean [SE] decrease 1.7 [0.2]) than men (decrease 0.7 [0.7]) when adjusted for weight change and baseline HOMA-IR. Despite this finding, men lost more weight than women (10.9 [1.3] kg *vs.* 7.5 [0.5] kg; p=0.03), and had higher baseline HOMA-IR (4.9 *vs.* 3.6; p=0.03). At study end, only 6 (4 women and 2 men) of the 94 subjects with blood samples at 6 months showed an increase in HOMA-IR.

Associated Factors	Change in HOMA-IR (R^2=0.69)	
	Beta (SE)	p Value
Male sex	0.750 (0.260)	0.005
Baseline HOMA-IR	-0.625 (0.052)	<0.0001
Change in Physical Activity hrs/wk	0.039 (0.033)	0.24
Age	0.001 (0.010)	0.93
Weight Change	0.127 (0.021)	<0.0001
Married or Living Together	0.188 (0.199)	0.35

Table 3: Multivariate model for factors associated with improvement in HOMA-IR after 6 months in a weight loss intervention.

Discussion

The lack of a difference in weight loss and improvement in insulin resistance between diet groups suggests that these goals can be achieved equally well with various dietary strategies that reduce energy intake relative to expenditure. The association between degree of weight loss and HOMA-IR change is consistent with previous studies that show a strong positive relationship between insulin resistance and body weight [14-16]. The finding of greatest interest in this study was that men had smaller decreases in HOMA-IR than women after the weight loss intervention, when adjusted for other factors known to be associated with improvement in insulin resistance, such as amount of weight lost and baseline HOMA-IR. Findings from this study are not in agreement with those in the previous Japanese study that found men to have greater change in insulin resistance status after a change in percent BMI than women [17]. The divergence from that study could be due to differences in the study populations. The present study had

73% non-Hispanic white subjects, while the Japanese study focused on a Japanese population. There are likely enough genetic differences across these study populations that could explain the different results, evidenced by the higher rate of diabetes in non-Hispanic white men than women aged 65-74 years, contrasted by the higher rate of diabetes in Asian women than Asian men in the same age group [11]. Also, the Japanese study did not involve a comprehensive lifestyle intervention, while the present study did. It is possible that men more readily acquire insulin resistance with weight gain, but exhibit less responsiveness in becoming more insulin sensitive with weight loss. If the bulk of the Japanese participants gained weight or remained the same weight, and the bulk of the participants in the present study lost weight, the divergent result might be explained.

There are several possible explanations for why the men in the present study were not able to improve insulin sensitivity as well as the women in response to a weight loss intervention. There were only 21 men included in the study, a number small enough that genetic differences between them could become clinically important. Type 2 diabetes is estimated to be 77% heritable [20], so if a higher proportion of men had genes that predisposed them to diabetes than women in the study, a reduced HOMA-IR response might be expected after equivalent weight loss. While no genetic data were collected or analyzed in this study, racial data were collected. A recent review found racial disparities of both genetic and environmental origin in insulin sensitivity, with African-Americans showing strong evidence of higher rates of insulin resistance than non-Hispanic whites [21].

A better hypothesis to explain the differences across sexes may be due to sex differences in body fat distribution. The ratio of subcutaneous fat to visceral adipose fat (VAT) appears to be sex- and age-linked, with a higher ratio in women than men, and in younger than older individuals [22]. The role of estrogen appears to be one reason for this sex difference, with subcutaneous fat having higher concentrations of estrogen receptors, and VAT having higher concentrations of androgen receptors [23]. This difference in VAT may explain the sexual differences in insulin sensitivity, as a recent study on healthy women found VAT to be associated with elevated retinol binding protein 4 (RBP4) [24], a factor that has been shown to contribute to insulin resistance in obesity and type 2 diabetes [25].

A year-long trial of healthy eating and lifestyle modification in viscerally obese men found that VAT loss was associated with improvement in HOMA-IR, and those who worsened their glucose tolerance lost less VAT [26]. Another study found that a higher prevalence of type 2 diabetes in older men vs. older women (14.6% *vs.* 9.1%) was associated with a larger amount of VAT in men [27]. If the male participants in the present study followed this trend and had higher amounts of VAT relative to the women, it could explain their reduced response in HOMA-IR to weight loss. The only measurement of abdominal obesity that was done in the present study was waist circumference, but no significant difference was found between the amount of waist circumference lost between men and women (10.0 cm vs. 10.6 cm; P=0.72). It should be noted, however, that a previous study found the correlation between waist circumference and VAT in adults to be only fair (r=0.73-0.77), and it may better reflect abdominal subcutaneous fat (r=0.82-0.92). Additionally, women with the same waist circumference as men in that study were found to have higher levels of subcutaneous fat [28].

Sex-specific risk factors might also be confounding the present findings. In a study that compared type 2 diabetes incidence in men and women aged 35 to 74 years, men had higher incidence (5.8 per 1000 person-years) than women (4.0 per 1000 person-years). That study found male-specific risk factors including higher systolic blood pressure, regular smoking, and high daily alcohol use, and female specific risk factors that included higher uric acid and more physical inactivity during leisure time [29]. Since risk factors differ between men and women, it is possible the men in the present study had more male-specific risk factors and the women had fewer female-specific risk factors, making it easier for the women to reduce their HOMA-IR with weight loss. Systolic blood pressure was measured in this study, and men were found to have a non-significantly higher systolic blood pressure at baseline than women, providing some evidence in support of this possibility.

An alternative explanation for the smaller decreases in HOMA-IR for men is differences in level of exercise. While all participants in the study were given the same guidance on physical activity as a component of the weight loss intervention, it is possible that men focused on different aspects of exercise than women, which may have impacted their HOMA-IR in a different way. This idea is supported by one small study that compared the effect of moderate intensity training with high intensity training on HOMA-IR in patients with chronic heart failure, and found that only high intensity training produced a significant decrease in HOMA-IR [30]. However, the men and women in the present study had no significant difference between their weekly minutes of strenuous activity at baseline, at six months, or in the overall increase in strenuous activity, and strenuous activity was not found to be a significant predictor of change in HOMA-IR in this population. Another aspect of physical activity that may affect change in HOMA-IR is exercise duration. A small Chinese study on patients with type 2 diabetes showed that patients randomized to a low intensity, extended duration exercise regimen sustained improvements in insulin sensitivity as measured by an oral glucose tolerance test longer than patients assigned to a high intensity, shorter duration exercise regimen that achieved the same total energy expenditure [31]. The men in the present study were found to have more total minutes of physical activity than women at baseline (208 *vs.* 108 minutes per week; $P<0.05$), and this difference was no longer significant at six months. The change in physical activity duration after six months was also not significantly different between the sexes. Men exercising more at baseline is interesting given there were proportionately more insulin resistant men at baseline than women, and the men had higher average baseline HOMA-IR. This suggests that even more exercise was not adequate to bridge the gap in insulin resistance between men and women.

The strengths of this study include the low rate of drop-out rate and missing data. This study included both sexes and a relatively representative racial sample of the population, which makes the results more generalizable. The study participants lost a substantial amount of weight as a result of the weight loss intervention. A limitation is that the proportion of men to women in the study was not equal, limiting the statistical power to test interactions. The sample population was free-living, which limits the collection of details on individual diets and exercise patterns and allows for variability in adherence. Nonetheless, the weight loss demonstrated by the overwhelming majority of participants suggests excellent adherence.

Conclusion

In conclusion, findings from this study suggest that men may have a more difficult time improving insulin sensitivity as compared with women with an equivalent weight loss and baseline HOMA-IR. This

may mean that insulin resistant men require more aggressive intervention than women to prevent progression to metabolic syndrome or diabetes. Future larger diet studies with more balanced male-to-female ratios are needed to better elucidate the underlying explanation for this difference between men and women, and to further investigate if it holds true across age ranges and between races.

Informed Consent

Written informed consent for data collection was obtained from all subjects at the point of recruitment and before any data collection.

Ethical Considerations

All procedures were in accordance with the ethical standards of the responsible committee on human experimentation.

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Clinical Trial Number

NCT02501889 on http://www.clinicaltrials.gov.

Conflict of Interest

The authors declare no conflict of interest.

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