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Relationship between insulin sensitivity and long-term weight change in adults

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Abstract

Objective—To understand if insulin resistance is associated with reduced risk of weight gain we related insulin action with respect to glucose metabolism with subsequent weight change.

Patients and Methods—We reviewed the medical records of volunteers who had undergone a euglycemic, hyperinsulinemic clamp in our research studies between October 20, 1986, and January 30, 2002, at Mayo Clinic. The data from 116 volunteers who had at least one year of follow up was analyzed.

Results—The average baseline BMI was 29.4 ± 5.3 kg/m² and the follow-up time averaged 8.1 ± 5.9 years. We found no significant correlation between baseline insulin action and annual weight change or overall weight change ($p = 0.60$ and $p = 0.11$) or between log-transformed insulin action and annual weight gain ($p = 0.61$).

Conclusion—These results suggest that in free living healthy Caucasian adults there is not a clinically meaningful relationship between insulin action and the subsequent weight change.

Keywords

insulin resistance; obesity; insulin clamp

INTRODUCTION

Dr. Eckel hypothesized that insulin resistance serves as a physiologic preventative measure against future weight gain(1) by allowing preferential fatty acid mobilization and oxidation. This model implies that with insulin resistance fatty acids are used as fuel rather than being stored in adipose tissue and ectopic depots. The first evidence for this relationship between insulin action and weight change was from a study of Pima Indians(2). Subsequent studies have provided evidence both in support and against this hypothesis(3–8).

We hypothesized that some of the inconsistent data may relate to the fact that only the Pima Indian study used the gold-standard euglycemic, hyperinsulinemic clamp to measure insulin sensitivity. Because our group has used the insulin clamp technique for many years as part

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of metabolic studies we decided to take advantage of the Mayo Clinic integrated medical records system to track the weight, medication use and medical conditions of volunteers who participated in insulin clamp studies. We hypothesized that after adjusting for baseline BMI those who were most insulin sensitive would gain the most weight over time.

METHODS AND MATERIALS

Participants

Data was collected from a total of 6 research protocols that involved 156 insulin clamp studies conducted at Mayo Clinic between 1986 and 2002 (Table 1). Each study was approved by the Mayo Institutional Review Board and informed, written consent was obtained. In order to be included in this study the volunteer must have also given permission to allow their individual medical records to be used for research purposes. Some volunteers participated in more than one study, in which case data from their first study was used for baseline insulin sensitivity purposes. There was no follow up data available beyond 1 year after the insulin clamp study for some volunteers and in that case their data was not included in the analysis. This left follow-up data for 116 participants with insulin sensitivity measurements.

Data collection

From the original research records the following data was abstracted: height, weight, date of birth, body composition (% body fat and kg of fat free mass), waist-to-hip ratio, date of insulin clamp, fasting plasma glucose and insulin, average plasma glucose and insulin concentrations during the final 30 min of each insulin clamp step, and average glucose infusion rate ($\mu\text{mol}\cdot\text{kg fat free mass}^{-1}\cdot\text{min}^{-1}$) during the final 30 min of each insulin clamp step. The initial weights were obtained using a calibrated scale in the Mayo General Clinical Research Unit. Volunteers were always weighed in the morning after an overnight fast, without shoes and with light clothing. The follow up weight data was collected from clinical measures done at Mayo Clinic Rochester, where the electronic scales are calibrated on a regular schedule. Height and weight measurements in the clinic are performed with patients clothed, but without shoes.

From the medical records we abstracted the following information (if available) for each medical encounter: date of visit, height, weight, diagnoses, procedures and medication use. For the purposes of statistical analysis the diagnoses, procedures and medications were then converted into CPT codes and National Drug Code (NDC). Diagnosis and procedure information was collected so that subjects undergoing potentially confounding interventions (i.e. bariatric surgery) could be excluded from the follow-up database as of the date of the procedure.

In attempts to account for the potential influence of medications associated with weight change, we grouped all medications that subjects were prescribed according to their potential effects on weight according to literature reports (see Appendix 1).

Statistical Analysis

Characteristics of the study population were calculated as means for continuous variables and percentages for categorical variables. Insulin action was calculated as the change in glucose infusion rate divided by the change in insulin concentration. For those participants who underwent a single step insulin clamp insulin action was calculated as:

$$(\text{glucose infusion rate during the clamp} - 0) \div (\text{insulin concentration during clamp} - \text{fasting insulin concentration})$$

For studies in which a two step insulin clamp was performed ($n = 36$) insulin action was calculated using mixed models with a random intercept and slope with insulin action as the fixed and random effect for slope measuring the change in glucose over the change in insulin concentration. The range of insulin action values was log-transformed in order to obtain a linear relationship between log insulin action and annual weight change.

All medications taken by study participants were recorded and grouped according to their potential effects on weight in an individual (see Appendix 1). Medications were dichotomized with weight gain medications coded as 'ever use' (yes/no) while weight loss medications were coded as 'last use' (yes/no).

Repeated measures analysis of covariance (ANCOVA) was used to assess the effect of insulin action of weight change. For these analyses, the dependent variable was the annual weight change calculated by taking the weight change for each participant divided by the total number of years of follow-up. Using this approach, the implicit assumption is that weight change is consistent over time. Although this is not the case, we believe that the duration of follow up for most volunteers is such that the average weight change over time represents a reasonable measure of weight gain/loss tendencies for the purpose of this analysis. The independent variable was log-transformed insulin action. Participant within study was included as a repeated measure, to adjust for the correlation between participants within a study. All models were adjusted for baseline tertiles of BMI ($18-24.9 \text{ kg/m}^2$, $25-29.9 \text{ kg/m}^2$, and greater than 30 kg/m^2) and the study of which the participants were a part. SAS Version 9.1 was used for all analyses (SAS Institute, Inc. Version 9.1 Cary, NC).

RESULTS

The sex distribution, age, and BMI at baseline, as well as information on duration of follow up are provided in Table 2. 57% of the study population were obese ($\text{BMI} \geq 30 \text{ kg/m}^2$) at baseline, 30% were of normal weight ($\text{BMI} < 25 \text{ kg/m}^2$), and 13% were overweight ($25 \text{ kg/m}^2 \leq \text{BMI} < 30 \text{ kg/m}^2$). As a result of the different purposes and recruiting goals for each of the original protocols, some subject characteristics, such as age ($P = 0.02$) were different between studies. There was not a significant difference in BMI ($p = 0.15$) by study. Follow-up time for the combined studies was 8.1 ± 5.9 years, with a median of 5.3 years and a range of 1 to 22.5 years.

Insulin action as assessed by the insulin clamp is plotted vs. WHR (Figure 1, panel A) and percent body fat (Figure 1, panel B). There was a significant negative relationship between WHR and log-transformed insulin action in women ($r = 0.28$, $P = 0.014$) and men ($r = 0.68$, $P < 0.0001$), as well as between percent body fat in women ($r = 0.36$, $P = 0.0006$) and men ($r = 0.51$, $P < 0.0001$).

There was no statistically significant interaction of ever use of a weight-gain medication modifying the relationship between log-transformed insulin action and annual weight change ($P = 0.27$). Similarly, there was no statistically significant interaction of last use of a weight-loss medication and the association of log-transformed insulin action and annual weight change ($P = 0.97$). Consequently, medication use was not included in the model as an effect modifier.

The average follow-up data available varied somewhat in those with different baseline insulin action with respect to glucose metabolism. Those individuals who were in the bottom, middle and top tertiles of insulin sensitivity (most to least insulin resistant) had average follow-up time of 6.6, 7.1 and 11.8 years, respectively ($p < 0.001$) by ANOVA. Thus, we had significantly longer follow up of the most insulin sensitive participants.

Pearson correlation between log-transformed insulin action and annual change in weight was small and not significant (Figure 2, $r = 0.05$, $P = 0.60$). Similarly, the correlation between insulin action and annual weight change adjusted for baseline tertile of BMI was not statistically significant (Figure 3; $r = 0.15$, $P = 0.11$). After adjusting for BMI and the study in which the volunteer was enrolled, the slope of the regression line was 0.099, which represents < 0.1 kg increase in weight per year for every unit change in log-transformed insulin action.

DISCUSSION

We took advantage of research records of insulin clamp studies and the integrated Mayo Clinic paper and electronic records to assess the relationship between insulin action and subsequent weight change. Our study population included over 100 adults from Rochester, MN some of whom had over 20 years of medical records data available for analysis. If insulin resistance is a mechanism to prevent further weight gain we would have expected those who were most insulin sensitive, adjusted for baseline BMI, to have gained the most weight. Instead, we found no significant relationship between weight change and insulin action as measured by the euglycemic, hyperinsulinemic clamp.

Evidence has been presented both in favor of (2–6) and against (4;7;8) the hypothesis that insulin resistance protects against weight gain. Some of the variability between studies may relate to the methods used to measure insulin sensitivity. Only the Pima Indian's were tested using the gold-standard euglycemic, hyperinsulinemic clamp and it is uncertain whether we can extrapolate results from this characteristically obese population (mean body mass index (BMI) = 34 ± 1 kg/m²)(2) to other groups. Other studies used related metrics for insulin sensitivity such as fasting plasma insulin concentrations (3;5;7) and the homeostasis model assessment (HOMA) (4;6). Several provide data for ethnic minority populations (2;4;6;9), but not Caucasians.

Sometimes no relationship between indices of insulin action and weight gain were found for the entire population, but sub-group analysis discovered associations (4;5;7). This could be because insulin action is a contributing factor to weight gain only in select groups or because Type 1 statistical errors may occur when multiple associations are tested for in large data sets.

The use of the insulin clamp to assess insulin action in this study should have greatly increased our statistical power to detect associations between insulin sensitivity and weight change. This is especially true given the wide range of insulin action observed in our population. Likewise, the long average follow up (~ 8 yrs.) of our volunteers also increases the accuracy of the weight change trend over time. A lengthy follow up period is crucial in research of this topic because weight fluctuations are common, especially in modern Western culture. For example, we observed some dramatic short-term weight changes, including a 9.8 kg weight loss in one year in one participant relating to a weight loss diet. Longer follow-up times, such as we report here, are helpful in “evening out” these yearly fluctuations in weight and allowing a better test of the insulin resistance/weight gain hypothesis. Finally, by using medical records to assess medication use we were able to test whether our results were confounded by pharmacologic interventions and medical diagnoses. A number of psychiatric, anti-diabetic and hormonal medications are recognized to have effects on weight that need to be controlled for in long-term studies of large populations. We believe our study is the first to take this issue into account. In addition, we were able to avoid including weight data from individuals after undergoing bariatric surgery, which would have created a major confounding effect if not addressed.

One concern about using data from studies conducted over a 15 year interval is that our measure of insulin action may lack consistency over time. If so, pooling of data from several studies might provide a less precise measure of baseline insulin sensitivity and make it more difficult to detect associations with weight change. The finding that our insulin action data correlated with both WHR and % body fat in the expected direction (Figure 1) in the pooled data set suggests this is not a major limitation. However, studies that employ an entirely consistent measure of insulin sensitivity combined with equally long follow-up data will provide further insight into the proposed relationship between insulin action and the tendency to weight gain. Our study population data appear similar to other studies (2) conducted over briefer periods of time.

Improvements to our study could be made by increasing the size of the study group and involving a more ethnically diverse population. The participants in our original research protocols were predominantly Caucasian and similar results might not be seen in other ethnic groups. We believe, however, that this information compliments existing data from other groups and provides strong evidence that insulin resistance in healthy, free living Caucasian adults does not uniquely protect from weight gain.

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Figure 1.
Panel A - Relationship between log transformed insulin sensitivity and waist-to-hip ratio (WHR). Panel B - Relationship between log transformed insulin sensitivity and percent body fat.

Figure 2.
Relationship between log transformed insulin sensitivity and observed annual weight change.

Figure 3. Relationship between log transformed insulin sensitivity and annual weight change adjusted for baseline BMI tertile (18–24.9 kg/m², 25 – 29.9 kg/m², and greater than 30 kg/m²) and study in which they participated.

Table 1

Characteristics of original studies from which participants were selected

Authors	N	BMI (recruiting characteristics)	Insulin infusion rate
(10)	22	14 obese women; 8 non-obese women	0.25 mU•kg LBM ⁻¹ •min ⁻¹ (obese); 0.15 mU•kg LBM ⁻¹ •min ⁻¹ (non-obese)
(11)	27	19 obese women (BMI 30–35; 8 non-obese women (BMI 19–25)	0.2 mU•kg LBM ⁻¹ •min ⁻¹
(12)	16	8 obese men; 8 non-obese men	0.25 and 1.0 mU•kg LBM ⁻¹ •min ⁻¹
(13)	28	7 non-obese women and 7 non-obese men, 7 obese women and 7 obese men,	0.25 and 2.5 mU•kg LBM ⁻¹ •min ⁻¹
(14)	63	35 women BMI 18–37.8; 28 men BMI 19.7–40.5	1.0 mU•kg LBM ⁻¹ •min ⁻¹

Table 2

Participant demographics

	Mean $\pm$ SD (range)
Male/ Female	35/81
Age (yrs)	36.1 $\pm$ 7.4 (20 – 50)
BMI (kg/m ²)	29.4 $\pm$ 5.3 (18.0 – 39.5)
Weight change (kg/yr)	0.33 $\pm$ 2.00 (–9.88 – 3.18)

BMI – body mass index.

Appendix 1

Medications taken by study participants and the effect on weight change

<u>Weight Gain</u>	<u>Weight Loss</u>	<u>No Net Weight Change</u>
PREDNISON	BUPROPION	VERAPAMIL
CITALOPRAM	APREPITANT	NIACIN
MEDROXYPROGESTERONE	AMLODIPINE	ZOLPIDEM
PAROXETINE	ORLISTAT	CYCLOBENZAPRINE
PROGESTERONE	THEOPHYLLINE	CHLORPHENIRAMINE POLISTIREX, HYDROCODONE POLISTIREX
AMITRIPTYLINE HCL	VENLAFAXINE	MEPERIDINE
INSULIN, HUMAN REGULAR	METFORMIN	CETIRIZINE
LEUPROLIDE	METHYLPHENIDATE	LORAZEPAM
DEXAMETHASONE	SERTRALINE	FEXOFENADINE
CLONIDINE	SIBUTRAMINE	DES Loratadine
GABAPENTIN		ATORVASTATIN
DIVALPROEX		HYDROCHLOROTHIAZIDE, LOSARTAN
LITHIUM CARBONATE		PROSED*
METHYLPREDNISOLONE		CHLORPROMAZINE
CLONAZEPAM		NIFEDIPINE
QUETIAPINE		CELECOXIB
OLANZAPINE		ALOSETRON
TRIAMCINOLONE		QUINAPRIL
TRAZODONE		NORTRIPTYLINE
FLUOXETINE		RIZATRIPTAN
GLIPIZIDE		HYDROCHLOROTHIAZIDE, LISINAPRIL
		TERBUTALINE
		DIAZEPAM
		ONDANSETRON
		CISAPRIDE
		ORPHENADRINE
		LISINAPRIL
		ATENOLOL
		ROFECOXIB
		GEMFIBROZIL
		GLIMEPIRIDE
		FENOFIBRATE
		NABUMETONE
		ACETAMINOPHEN, HYDROCODONE
		SALMETEROL
		CLOMIPHENE
		NARATRIPTAN
		PROPRANOLOL
		ZOLMITRIPTAN

<u>Weight Gain</u>	<u>Weight Loss</u>	<u>No Net Weight Change</u>
		IPRATROPIUM
		DESIPRAMINE
		FLUNISOLIDE
		NEFAZODONE
		IMIPRAMINE
		ISOSORBIDE
		RABEPRAZOLE
		CARBAMAZEPINE
		ZALEPLON
		BUSPIRONE
		CHLORPHENIRAMINE, METHSCOPOLAMINE, PHENYLEPHRINE
		PROMETHAZINE
		DOXYCYCLINE
		AZITHROMYCIN
		LEVOTHYROXINE
		BUDESONIDE
		BECLOMETHASONE (NASAL)
		ALBUTEROL (INHALED)
		CONJUGATED ESTROGENS
		METOPROLOL
		ESTRADIOL
		FLUTICASONE
		TRIAMCINOLONE (INHALED)
		FLUTICASONE (INHALED)
		TESTOSTERONE
		RALOXIFENE
		ETHINYL ESTRADIOL, LEVONORGESTREL
		LOSARTAN
		PRAMIPEXOLE
		NICOTINE
		TAMOXIFEN

* Atropine, benzoic acid, hyoscyamine, methenamine, phenyl salicylate