Fall 1-8-2016

Insulin Dynamic Measures and Weight Change

Noreen Kloc

Noreen G. Kloc

ABSTRACT

Insulin Dynamic Measures and Weight Change

By

Noreen Kloc

B.S. Computer Information Technology, Purdue University

December 7, 2015

INTRODUCTION: Weight gain and obesity are risk factors for insulin resistance that can lead to type 2 diabetes and cardiovascular disease; however, there is a complicated interplay between insulin sensitivity (S_I), fasting insulin, acute insulin response (AIR), and disposition index (DI) and the relationship of these dynamic measures with weight change is not well understood.

AIM: The aim of this study was to investigate the relationships between insulin dynamic measures, S_I, fasting insulin, AIR, and DI, with weight change during a 5-years follow-up period in the multi-ethnic cohort of the Insulin Resistance Atherosclerosis Study (IRAS).

METHODS: Data on 879 men and women of Hispanic, non-Hispanic White, and African-American race/ethnicity aged 40-69 years were obtained at baseline (1992-1994) and at 5 year follow-up. Crude associations between the insulin dynamic measures and weight change were evaluated using Kruskal-Wallis test and the relationships between log-transformed insulin-related variables were examined using Spearman rank-order analysis. Multivariate regression models evaluated associations of interest adjusted for age, sex, ethnicity, and diabetes status in a time-dependent manner using mixed models.

RESULTS: Insulin sensitivity S_I inversely coevolves with weight, i.e. greater weight is predicted by lower S_I at any time point. To answer the question whether S_I is the cause or a consequence of weight change, we examined the associations with the baseline values and a change in S_I. In this model, both the baseline S_I and change in S_I were inversely correlated with weight gain. A similar approach showed that baseline values and change in fasting insulin were directly associated with weight gain. Weight change over time was associated with AIR, i.e. increases in AIR and greater AIR at baseline predicted weight gain. We did not find strong relationships between DI and weight change.

DISCUSSION: These results suggest that insulin sensitivity and insulin secretion can modulate weight in a non-diabetic population.

Insulin Dynamic Measures and Weight Change

by

Noreen Kloc

B.S. Computer Information Technology, Purdue University

A Thesis Submitted to the Graduate Faculty

of Georgia State University in Partial Fulfillment

of the

Requirements for the Degree

MASTER OF PUBLIC HEALTH

ATLANTA, GEORGIA

30303

APPROVAL PAGE

Insulin Dynamic Measures and Weight Change

by

Noreen Kloc

Approved:

Dora Il'yasova, Ph.D.

Committee Chair

Ruiyan Luo, Ph.D.

Committee Member

December 7, 2015

Date

Acknowledgments

With much gratitude, I recognize my thesis committee Dr. Dora Il'yasova and Dr. Ruiyan Luo who guided me through this research and kindly offered support.

Author's Statement Page

In presenting this thesis as a partial fulfillment of the requirements for an advanced degree from Georgia State University, I agree that the Library of the University shall make it available for inspection and circulation in accordance with its regulations governing materials of this type. I agree that permission to quote from, to copy from, or to publish this thesis may be granted by the author or, in his/her absence, by the professor under whose direction it was written, or in his/her absence, by the Associate Dean, School of Public Health. Such quoting, copying, or publishing must be solely for scholarly purposes and will not involve potential financial gain. It is understood that any copying from or publication of this dissertation which involves potential financial gain will not be allowed without written permission of the author.

Noreen Kloc

TABLE OF CONTENTS

List of Tables

Insulin Dynamic Measures and Weight Change

I. Introduction

Weight gain and obesity are risk factors for insulin resistance that can lead to type 2 diabetes and cardiovascular disease (CVD) (1). Physiologically, insulin is a hormone produced in the pancreas and moves into the blood helping glucose to be incorporated into cells. Muscle, fat and liver cells absorb glucose from the bloodstream which then lowers blood glucose levels. Insulin stimulates the liver and muscle tissue to incorporate the excess glucose. Insulin resistance is a syndrome in which insulin is produced but not used effectively causing the glucose to build up in the blood leading to impaired glucose status or type 2 diabetes (2). Other clinical diseases associated with insulin resistance syndrome are CVD, hypertension, polycystic ovary syndrome, nonalcoholic liver disease, sleep apnea, several types of cancer (3) and may be a risk for coronary heart disease and stroke (4).

There is a complicated interplay between weight gain, insulin sensitivity, and insulin secretion. Weight gain leads to a drop in insulin sensitivity (increase in insulin resistance). In non-diabetic individuals, change in insulin sensitivity is often compensated by an increase in insulin secretion and fasting insulin. Such compensation can produce a metabolic environment that promotes further weight gain. Insulin is known to promote weight gain in diabetic patients who take insulin as a part of their regimen. Thus, not only does weight gain promote insulin resistance but a compensatory increase in insulin can stimulate further weight increase, creating a vicious cycle. The aim of this study was to investigate how the insulin dynamic factors, insulin sensitivity (S_I), fasting insulin, acute insulin response (AIR), and disposition index (DI) influence weight change during a 5-year period in a cohort of 879 triethnic participants.

II. Review of the Literature

Research into insulin dynamics and weight change has been conducted for several decades; however the relationship is complicated. A higher S_I value expresses insulin sensitivity as a measure of insulin-stimulated glucose disposal. This is an inverse measure of insulin resistance. Another index of insulin resistance is higher fasting insulin. A higher AIR implies greater insulin secretion in response to glucose, which might be greater when insulin action is diminished. A product of S_I and AIR, DI offsets the influence of insulin resistance on AIR and is accepted as an index of pancreatic function (5).

The beneficial effect of weight loss on glucose tolerance has been documented in many research studies (6-9). However, the relationship of glucose regulation to changes in weight is not clear with studies documenting varying results. Early studies suggested insulin resistance may cause weight gain due to reduced thermic effects (10), increased appetite (11), or a genetic artifact for increased fat storage (12); but later studies have suggested insulin resistance might increase fat oxidation (13), or serve as a homeostatic mechanism protecting against weight gain (14, 15). A large population study showed that people who have been diagnosed with diabetes tend to not gain weight or lose excess weight (16). These studies provided weak evidence since biological tests and relevant confounders were not included.

The results of studies using clinical measures differ in their results due to different measures of insulin dynamics and weight, varying lengths of follow-up, and controlling for different confounders. Animal and human studies suggest that insulin dynamics including insulin sensitivity and insulin secretion are associated with weight change but the direction of that change (negative or positive) is inconsistent with different studies (17, 18). Age, sex, race/ethnicity, diabetic status, BMI, energy expenditure, smoking status, alcohol consumption and length of follow-up varied in study population parameters and the length of follow-up.

The studies examining the relationship of poor insulin dynamics and wait gain found that higher levels of fasting insulin at baseline predict visceral fat (19) or weight change (20, 21) during the follow-up. These studies did not include age or initial weight in the analysis, only non-diabetic adults were included, one study controlled for lifestyle variables (i.e. physical activity and diet fat intake), and the study follow-up period differed between 3 and 10 years.

Other studies documented a positive association of insulin dynamic measures to changes in weight with average plasma glucose predicting more weight gain (22-24) or higher insulin resistance at baseline predicted weight loss or no weight change during follow-up (15, 24-27). The studies that controlled for demographic variables included age, sex and race/ethnicity, four controlled for medication (22, 24, 26, 27) and some controlled for lifestyle behavior (15, 22, 27). The finding of these studies was that poor glucose was associated with lower weight gain but did not vary with age, initial weight, sex, and race/ethnicity while two studies found that insulin resistance and less weight gain were greater in participants not using insulin (24, 26).

Studies that documented complex relationships between glucose regulation and changes in weight suggest that age, sex, race/ethnicity, baseline weight, and specific measures of weight can affect the results. A five year longitudinal study controlling for age and BMI found results differed by race/ethnicity (28). In Chinese men, weight gain was predicted by insulin resistance which differed in Asian Indian and Creole adults where weight gain was predicted by better

insulin sensitivity. In addition, only body weight was associated with insulin resistance and no relationship was found in waist to hip ratio (28).

In reviewing the findings of the existing studies, the aim of this current study was to utilize a large study population of diverse race/ethnicity and demographic parameters, include relevant biological measures and control for relevant confounders including BMI, sex, age, and diabetes status.

III. Methods and Procedures

The Insulin Resistance Atherosclerosis Study (IRAS) was designed to assess the relation of insulin and insulin resistance to cardiovascular disease and its risk factors. Details of the IRAS study design have been previously published (29). The study protocols were approved by the institutional review boards of each clinical center located in Oakland, California; Los Angeles, California; San Antonio, Texas; and the San Luis Valley, Colorado (29). All participants provided written informed consent.

Sample Selection

The study recruited 1624 male and female participants aged 40 – 69 years from four geographic areas representing three ethnic groups (Hispanic, non-Hispanic white, and African-American) in 1992-1994. A follow-up period of approximately 5 years occurred between 1997 and 1998. Participants with existing diabetes status, missing weight at baseline or missing weight at follow-up were eliminated from the study population (n=730). Diabetic patients exhibit shifting insulin dynamics and insulin secretion in response to weight which differs between diabetics and non-diabetics and these patients often intentionally try to lose weight (1, 18). An additional four participants were eliminated due to a mismatch in weight and waist circumference and one participant with duplicate ID was removed. Eleven more participants with missing relevant data were eliminated with a final study population of 879.

Variable Measurement

During the first visit at each time point, a 75-g oral glucose tolerance test (OGTT) was used to assess glucose tolerance status based on the World Health Organization (WHO) criteria (30) and to determine fasting insulin concentration (26). The WHO diabetes status criteria using the OGTT : normal < 140 mg/dl, impaired 140 – 199 mg/dl, and diabetic ≥ 200 mg/dl (30). During the second visit at east time point, insulin sensitivity and first-phase insulin secretion were measured by FSIGTT with minimal model analysis (31). Insulin resistance, expressed as the Insulin Sensitivity Index (S_I) was calculated using mathematical modeling methods (MINMOD, version 3.0, Los Angeles, California, courtesy of Richard Bergman, PhD) (32). To assess

sensitivity of β–cell function, insulin secretion was measured by the AIR variable as the mean of plasma concentration from 2- and 4-minute time points after glucose administration (26). Disposition Index (DI) is an alternate insulin secretion variable based on the hyperbolic relation of insulin secretion to S_I and expresses the ability of the pancreatic β–cell to compensate for changes in S_I by increasing insulin secretion (33, 34). DI was calculated as the product of S_I and AIR. BMI was calculated as weight in kilograms divided by height in meters squared. Race/Ethnicity and other demographic data were assessed by self-report. Anthropometric measurements were obtained by trained personnel.

Statistical Analysis

All statistical analysis was performed using SAS statistical software (version 9.3, SAS Institute, Cary, NC). In multivariate correlations and regression models, log-transformed values of fasting insulin, AIR, S_I and DI were used to minimize the influence of extreme observations. Some individuals had an S_I value of zero so the natural logarithm of S_I was added to the contant 1 was used for transformation. DI was calculated as the sum of log-transformed S_I + 1 and log-transformed AIR. A weight change status variable grouped the difference in weight between baseline and follow-up into Increased Weight (≥5%), No Weight Change (<>5%) and Decreased Weight (≤5%).

The crude associations of weight change status and covariates were examined using chi-square test for the ordinal and categorical variables, and Kurskal-Wallis for all continuous variables including the main exposure variables S_I, Fasting Insulin, AIR and DI. Crude associations of the log-transformed insulin dynamic measures at baseline and at follow-up were evaluated using Spearman correlation coefficient as a nonparametric measure of association based on the rank order of the S_I, Fasting Insulin, AIR and DI values. Similarly, Spearman correlation coefficient was used to examine the associations between the log-transformed insulin dynamic measures at baseline and with the measures at follow-up.

Mixed effects models were created to examine the adjusted associations of weight and the insulin dynamic measure during the baseline and follow-up periods. The random effects included random intercepts and random slopes at the individual level and random intercepts at the clinic level. The fixed effects adjusted for baseline age, sex, race/ethnicity, baseline BMI and time-dependent diabetes status. S_I, fasting Insulin, AIR and DI were included separately in each model and were scaled to have unit variance. This analysis explained how weight coevolves with the insulin measures of interest.

In addition, this study analyzed a cross-sectional and prospective relationship between weight change and the insulin dynamic measures. In these models, time was presented as number of

months between the baseline and follow-up visits, whereas age at baseline was used as an adjustment variable. The insulin variables were presented as baseline value and change between follow-up and baseline. Interaction term between time and the baseline insulin measure presented a prospective relationship. We report three parameters for each insulin-related measure adjusted by age, sex, ethnicity, baseline BMI and time-dependent diabetes status: beta-coefficient for baseline variable presents cross-sectional association with weight at baseline, beta-coefficient for the interaction term between baseline values and time presents a prospective association between baseline and weight at follow-up, and beta-coefficient for change variable shows associations between change in the variable and weight during the follow-up period. The beta-coefficient and standard error values were scaled by the standard deviations of the corresponding predictors. These models answered the question of whether the dynamic measure of interest can be causal in relation to weight change.

IV. Results

Descriptive characteristics of the study population by weight change status (≥5% Increased Weight, <> 5% No Weight Change, and ≤5% Decreased Weight) are shown in Table 1. At the follow-up visit, 31% of the participants had increased weight, 58% had little weight change, and 12% had decreased weight. There was a significant difference in the proportions of females across weight groups: 61% females/39% males increased weight, 53% females/48% males had little weight change, and 66% females/34% males decreased weight ($p<0.008$). The results suggest BMI at baseline was significantly associated with weight change: participants with greater BMI were more likely to change weight in either direction whereas participants with lower BMI tended to have little weight change ($p<0.02$). Race/ethnicity was not associated with weight change. Participants with normal glucose tolerance (NGT) at baseline showed a greater tendency to increased weight ($p=0.06$).The overall test for the association between glucose tolerance/diabetes status and weight change showed no association, participants who developed diabetes also had a tendency to increase weight. Insulin sensitivity at baseline was similar among all three weight-change groups. During the follow-up, S_I decreases on average at follow-up with the greatest change among those who gained weight (-1.1 mean difference) as compared to participants with stable weight (-0.8 mean difference) and a no change among those with weight decrease $p<0.001$). As expected, relationship with Fasting insulin mirror those with S_I: participants with Increased Weight experienced the greatest increase in fasting insulin (+6.4 mean change) as compared to participants with No Weight Change(+2.5 mean change), whereas participants with Decreased Weight showed no meaningful changes in fasting insulin ($p<0.001$). Baseline acute insulin response showed a tendency toward inverse association with weight change with the greatest values among those who gained weight and lowest among those who lost weight ($p=0.2$). In all three weight change groups, AIR increased

over time (Increased Weight + 23.4 mean difference, No Weight Change +16.7 mean difference, Decreased Weight +2.7 mean difference) and these changes amplified the differences at the follow-up ($p<0.001$). Disposition Index at baseline showed a clear tendency of inverse association with weight change with the greatest values among those who gained weight and lowest among those who lost weight ($p<0.01$). However, the changes in DI were different among the three groups: participants with increased weight experienced the greatest drop in DI followed by those with relatively stable weight, whereas those who lost weight showed increase in DI at follow-up. The opposite tendencies in DI change between the weight loss and weight gain groups narrowed the gap in DI at follow-up as compared to baseline (p value for the difference between the groups at follow-up = 0.1).

Table 1. Characteristics of study population by weight change status

N=879	Increased Weight (≥5%) n=268	No Weight Change (<> 5%) n=510	Decreased Weight (≤5%) n=101	P
Age (years)	52.3±8.2	55.7±8.3	55.6±8.9	<0.001
Male (%)	104 (39)	242 (47.5)	34 (33.7)	0.008
Female (%)	164 (61)	268 (52.6)	67 (66.3)	0.008
Ethnicity				0.4
White	106 (39.6)	205 (40.2)	41 (40.6)	
African American	79 (29.5)	125 (24.5)	31 (30.7)	
Hispanic	83 (31)	180 (35.3)	29 (28.7)	
BMI (kg/m^2) at baseline	28.6±5.8	27.9±5.3	29.5 (5.3)	0.02
Glucose Tolerance (Diabetes Status) at baseline				0.06
Normal	189 (72.5)	342 (67.1)	58 (57.4)	
Impaired	79 (29.5)	168 (33)	43 (42.6)	
Glucose Tolerance (Diabetes Status) at follow-up				0.4
Normal	140 (52.2)	301 (59)	55 (54.5)	
Impaired	80 (29.9)	128 (25.1)	31 (30.7)	
Diabetic	48 (17.9)	81 (15.9)	15 (14.9)	
Insulin Sensitivity (S_I) (S_I, $x10^{-4}minutes^{-1}/\mu Uml$) at baseline	2.2±1.9	2.2±1.9	1.9±1.6	0.2
Insulin Sensitivity (S_I) (S_I, $x10^{-4}minutes^{-1}/\mu Uml$) at follow-up	1.1±1.4	1.4±1.4	1.9±1.4	<0.001
Fasting Insulin (uU/mL) at baseline	15.0±10.9	15.8±17.4	16.2±9.5	0.3
Fasting Insulin (uU/mL) at follow-up	21.4±13.7	18.3±13.2	16.1±9.1	<0.001
Acute Insulin Response (AIR) (μU/ml X minutes) at baseline	68.8±51.6	65.0±61.2	59.4±44.4	0.2

Acute Insulin Response (AIR) (μU/ml X minutes) at follow-up	92.2±72.3	81.7±79.0	62.1±44.8	<0.001
Disposition Index (S_I X AIR) at baseline	131.2±125.4	111.1±112.9	93.7±92.0	<0.001
Disposition Index (S_I X AIR) at follow-up	91.0±103.3	96.9±110.9	97.3±82.6	0.1

Data are n (%) and means ± SD. Categorical variables and age were assessed using Chi-square test. Continuous variables were assessed using Kruskal-Wallis test. AIR is the mean of 2,4 minute insulin injection.

To assess the association between the insulin dynamic measures at baseline, Spearman correlation coefficient test was used to rank-order pairs of S_I, fasting insulin, AIR and DI as shown in Table 2. As expected, there is a strong inverse association between fasting insulin and S_I ($r = -0.66$, $p<0.001$). Fasting insulin was positively correlated with AIR ($r = 0.33$, $p<0.001$) and negatively correlated with DI ($r = -0.10$, $p<0.005$). AIR was correlated with S_I ($r = -0.30$, $p<0.001$). Strongly associated AIR and DI is determined by the mathematical relationship between AIR and DI. DI was also correlated with S_I ($r = 0.34$, $p<0.001$).

Table 2. Correlation between insulin dynamic measures at baseline

N=879	Log Insulin Sensitivity	Log Fasting Insulin	Log Acute Insulin Response	Log Disposition Index
Log Insulin Sensitivity				
Spearman Corr.	.	-0.66	-0.30	0.34
Sig. (2-tailed)	.	<.0001	<.0001	<.0001
N	.	817	818	818
Log Fasting Insulin				
Spearman Corr.	-0.66	.	0.33	-0.10
Sig. (2-tailed)	<.0001	.	<.0001	0.005
N	817	.	840	817
Log Acute Insulin Response				
Spearman Corr.	-0.30	0.33	.	0.76
Sig. (2-tailed)	<.0001	<.0001	.	<.0001
N	818	840	.	818

Spearman correlation coefficient rho [r], Prob >[r]. Log-transformed S_I, fasting insulin, AIR and DI.

Next, the association of insulin dynamic measures between baseline and follow-up periods are shown in Table 3 to assess the correlation of the insulin variables between visits. As expected all predictors at baseline have high correlation with the follow-up period. Similar to Table 2, the correlations remain significant with the exception of the correlation between baseline DI and fasting insulin at follow-up which changes to not significant (r = -0.06, p = 0.11). Fasting insulin and S_I are inversely correlated which was also found in previous studies examining the IRAS cohort (26, 35).

Table 3. Correlation of insulin dynamic measures between baseline and at follow-up

N=879	Log Insulin Sensitivity Follow-up	Log Fasting Insulin Follow-up	Log Acute Insulin Response Follow-up	Log Disposition Index Follow-up
Log Insulin Sensitivity baseline				
Spearman Corr.	0.64	-0.56	-0.11	0.22
Sig. (2-tailed)	<.0001	<.0001	0.002	<.0001
N	737	813	756	736
Log Fasting Insulin Baseline				
Spearman Corr.	-0.51	0.60	0.14	-0.12
Sig. (2-tailed)	<.0001	<.0001	<.0001	0.0006
N	780	872	802	779
Log Acute Insulin Response Baseline				
Spearman Corr.				
Sig. (2-tailed)	-0.20	0.31	0.69	0.53
N	<.0001	<.0001	<.0001	<.0001
	759	836	778	758
Log Disposition Index Baseline				
Spearman Corr.	0.22	-0.06	0.61	0.69
Sig. (2-tailed)	<.0001	0.11	<.0001	<.0001
N	737	813	756	736

Spearman correlation coefficient rho [r], Prob >[r]. Log-transformed S_I, fasting insulin, AIR and DI.

The next analysis used a mixed-effects model approach to examine S_I, fasting insulin, AIR, DI that predicted weight. Table 4 shows time-dependent relationships between each insulin dynamic measure and weight during the follow-up period adjusting for baseline age, sex, race/ethnicity, central adiposity (baseline BMI) and glucose tolerance (diabetes status). The

strongest associations with weight in time were found for the variables related with insulin resistance. S_I shows an inverse association with weight in time: β = -0.91, 95% CI=(-1.27,-0.56), and fasting insulin positively correlates with weight β = 0.96, 95% CI=(0.64, 1.27). Response of the pancreases to glucose challenge showed weaker relationships with weight in time: AIR positively correlates with weight β = 0.38, 95% CI=(0.05, 0.73) and there is a weak tendency for inverse relationship between DI and weight.

Table 4. Weight and insulin dynamics during the follow-up period adjusted for age, sex, race/ethnicity, baseline BMI, and diabetes status and clinic included as a cluster variable

	Beta-coefficient (SE)	95% CI	P-value
Log S_I	-0.91 (0.18)	-1.27, -0.56	<.0001
Log Fasting insulin	0.96 (0.16)	0.64, 1.27	<.0001
Log AIR	0.38 (0.17)	0.05, 0.73	0.02
Log DI	-0.22 (0.18)	-0.56, -0.13	0.22

Beta-coefficient and standard error values are scaled to one standard deviation.

In Table 5, the relationships between each insulin dynamic predictor and weight is presented in three ways – cross-sectional association at baseline, association with change in the insulin measures, and a prospective association between baseline insulin measures and weight at the end of follow-up. This approach did not reveal any meaningful cross-sectional associations between insulin measures and weight at baseline. The strongest relationships were found between changes in the examined insulin measures and weight. Baseline values predicted weight change in a similar direction (except DI), but these associations were weaker. This approach showed that the change in S_I was inversely associated with weight: β = -2.43, 95% CI=(-2.99, -1.87). Also, greater insulin sensitivity at baseline predicted loss of weight when time elapsed for a long duration (t>0.123, β = -0.17, 95% CI=(-0.27,-0.08). Increase in fasting insulin implied weight gain: β = 2.10, 95% CI= (1.61, 2.60). Greater baseline fasting insulin also predicted increase of weight: β = 0.13, 95% CI=(0.04, 0.22). Similarly, increase in AIR had a positive association with weight: β = 1.11, 95% CI=(0.67, 1.55). Baseline AIR predicted weight gain: β = 0.11, 95% CI=(0.03, 0.19). DI did not show strong relationships with weight in this model.

Table 5. Associations of weight with baseline and change of insulin-related variables adjusted for age, sex, race/ethnicity, baseline BMI, and diabetes status and clinic included as a cluster variable

	Cross-sectional Assoc.	Beta-coefficient scaled to SD Association with Change	Prospective Association
Log SI			
β (SE)	0.30 (0.25)	-2.43 (0.28)	- 0.17 (0.05)
95% CI	-0.19, 0.80	-2.99, - 1.87	-0.27, -0.08
P	0.23	<.0001	0.0002
Log Fasting insulin			
β (SE)	0.001 (0.24)	2.10 (0.25)	0.13 (0.04)
95% CI	-0.46, 0.47	1.61, 2.60	0.04, 0.22
P	1.00	<.0001	0.003
Log AIR		.	
β (SE)	-0.02 (0.22)	1.11 (0.22)	0.11 (0.04)
95% CI	-0.46, 0.41	0.67, 1.55	0.03, 0.19
P	0.91	<.0001	0.008
Log DI			
β (SE)	0.10 (0.23)	-0.48 (0.29)	0.06 (0.05)
95% CI	-0.35, 0.55	-1.05, - 0.08	-0.03, 0.15
P	0.66	0.09	0.18

Beta-coefficient and standard error values are scaled to one standard deviation.

V. Discussion and Conclusion

The aim of this study was to investigate the insulin dynamic factors: insulin sensitivity (S_I), fasting insulin, acute insulin response (AIR), and disposition index (DI) associated with weight change in a cohort of multiethnic participants. The hyperbolic law of glucose tolerance states that DI should remain constant as long as changes in the insulin action are compensated for by the changes in insulin secretion to maintain glucose homeostasis (1, 36). Although it is possible that one of the insulin measures would play a dominant role, the pathways that determine observed levels of these metabolic predictors are interdependent as a function of biologic feedback systems (26, 37). We hypothesized that insulin resistance measures will increase but the insulin secretion measures will decrease with weight gain as the body compensates for energy imbalance.

Our study showed that all insulin dynamic measures are interrelated. Fasting insulin and AIR increase to compensate for lower insulin sensitivity, whereas DI shows pancreatic beta-cell function with the offset for insulin resistance (Tables 2 & 3). The crude associations show that

greater insulin secretion (AIR and DI) at baseline predict a risk of weight gain. However, weight gain leads to a decline in beta-cell function and therefore a decrease in DI (Table 1), whereas weight loss improves beta-cell function leading to an increase in DI (Table1). As insulin resistance is known to be associated with weight gain, time-dependent associations of weight with insulin measures show an inverse association with S_I and positive association with fasting insulin. Weight increase was also associated with insulin secretion probably as a compensation for increased insulin resistance (Table 4). When insulin measures were presented as baseline values, changes and the interaction between baseline and time, the cross-sectional associations were not important. Their change was mainly associated with weight dynamics and the baseline values showed associations with weight at follow-up in the expected direction. These results imply that insulin measures are mostly a consequence of weight change (strong correlation with change) and to a lesser degree a cause of weight changes (interaction between baseline and time).

A strength of this study design as identified in the review article by Chiu et al. was that few recent studies have examined weight as an outcome variable and also include laboratory tests to evaluate the insulin dynamic variables (17). Additionally, the study population was a large sample with even representation of men and women from a diverse race/ethnic background which were followed for a 5 year period. Few current studies have a large sample size or ethnic diversity. The statistical approach provided analysis of the insulin parameter of interest at baseline, and the change in value over time related to predicting weight change.

Although the range of laboratory tests and anthropometric measures were comprehensive in this study, selection of participants for a clinical study may reflect a different variability than the general population.

Future directions for research could investigate the diabetic status of individuals and relationship with weight change. Participants with impaired glucose status may have different associations than what we found in the current study. A better understanding of insulin dynamics may lead to earlier diagnosis of an imbalanced metabolic state and provide additional prevention programs to reduce morbidity associated with any negative impact of weight change.

VI. References

1. Weyer C, Hanson K, Bogardus C, Pratley RE. Long-term changes in insulin action and insulin secretion associated with gain, loss, regain and maintenance of body weight. Diabetologia. 2000;43(1):36-46.
2. National Institute of Diabetes and Digestive Kidney Diseases. Insulin Resistance and Prediabetes Bethesda, MD: U.S. Department of Health and Human Services; 2014 [updated June 2014; cited 2015 August 15, 2015]. Available from: http://www.niddk.nih.gov/health-information/health-topics/Diabetes/insulin-resistance-prediabetes/Pages/index.aspx.
3. Cheal KL, Abbasi F, Lamendola C, McLaughlin T, Reaven GM, Ford ES. Relationship to insulin resistance of the adult treatment panel III diagnostic criteria for identification of the metabolic syndrome. Diabetes. 2004;53(5):1195-200.
4. Gutch M, Kumar S, Razi SM, Gupta KK, Gupta A. Assessment of insulin sensitivity/resistance. Indian journal of endocrinology and metabolism. 2015;19(1):160-4.
5. Liese AD, Schulz M, Fang F, Wolever TM, D'Agostino RB, Jr., Sparks KC, et al. Dietary glycemic index and glycemic load, carbohydrate and fiber intake, and measures of insulin sensitivity, secretion, and adiposity in the Insulin Resistance Atherosclerosis Study. Diabetes care. 2005;28(12):2832-8.
6. Markovic TP, Jenkins AB, Campbell LV, Furler SM, Kraegen EW, Chisholm DJ. The determinants of glycemic responses to diet restriction and weight loss in obesity and NIDDM. Diabetes care. 1998;21(5):687-94.
7. Goodpaster BH, Kelley DE, Wing RR, Meier A, Thaete FL. Effects of weight loss on regional fat distribution and insulin sensitivity in obesity. Diabetes. 1999;48(4):839-47.
8. Ahmad F, Considine RV, Bauer TL, Ohannesian JP, Marco CC, Goldstein BJ. Improved sensitivity to insulin in obese subjects following weight loss is accompanied by reduced protein-tyrosine phosphatases in adipose tissue. Metabolism: clinical and experimental. 1997;46(10):1140-5.
9. Webber J, Donaldson M, Allison SP, Fukagawa NK, Macdonald IA. The effects of weight loss in obese subjects on the thermogenic, metabolic and haemodynamic responses to the glucose clamp. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity. 1994;18(11):725-30.
10. Felig P. Insulin is the mediator of feeding-related thermogenesis: insulin resistance and/or deficiency results in a thermogenic defect which contributes to the pathogenesis of obesity. Clinical physiology (Oxford, England). 1984;4(4):267-73.
11. Rodin J. Insulin levels, hunger, and food intake: an example of feedback loops in body weight regulation. Health psychology : official journal of the Division of Health Psychology, American Psychological Association. 1985;4(1):1-24.
12. Neel JV. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? American journal of human genetics. 1962;14:353-62.
13. Eckel RH. Insulin resistance: an adaptation for weight maintenance. Lancet (London, England). 1992;340(8833):1452-3.
14. Schwartz MW, Niswender KD. Adiposity signaling and biological defense against weight gain: absence of protection or central hormone resistance? The Journal of clinical endocrinology and metabolism. 2004;89(12):5889-97.
15. Swinburn BA, Nyomba BL, Saad MF, Zurlo F, Raz I, Knowler WC, et al. Insulin resistance associated with lower rates of weight gain in Pima Indians. The Journal of clinical investigation. 1991;88(1):168-73.

16. Nafziger AN, Lindvall K, Norberg M, Stenlund H, Wall S, Jenkins PL, et al. Who is maintaining weight in a middle-aged population in Sweden? A longitudinal analysis over 10 years. BMC public health. 2007;7:108.
17. Chiu CJ, Wray LA, Beverly EA. Relationship of glucose regulation to changes in weight: a systematic review and guide to future research. Diabetes/metabolism research and reviews. 2010;26(5):323-35.
18. Pittas AG, Roberts SB. Dietary composition and weight loss: can we individualize dietary prescriptions according to insulin sensitivity or secretion status? Nutrition reviews. 2006;64(10 Pt 1):435-48.
19. Tong J, Fujimoto WY, Kahn SE, Weigle DS, McNeely MJ, Leonetti DL, et al. Insulin, C-peptide, and leptin concentrations predict increased visceral adiposity at 5- and 10-year follow-ups in nondiabetic Japanese Americans. Diabetes. 2005;54(4):985-90.
20. Lazarus R, Sparrow D, Weiss S. Temporal relations between obesity and insulin: longitudinal data from the Normative Aging Study. American journal of epidemiology. 1998;147(2):173-9.
21. Mosca CL, Marshall JA, Grunwald GK, Cornier MA, Baxter J. Insulin resistance as a modifier of the relationship between dietary fat intake and weight gain. International journal of obesity and related metabolic disorders : journal of the International Association for the Study of Obesity. 2004;28(6):803-12.
22. Jacob AN, Salinas K, Adams-Huet B, Raskin P. Weight gain in type 2 diabetes mellitus. Diabetes, obesity & metabolism. 2007;9(3):386-93.
23. Ferriss JB, Webb D, Chaturvedi N, Fuller JH, Idzior-Walus B. Weight gain is associated with improved glycaemic control but with adverse changes in plasma lipids and blood pressure isn Type 1 diabetes. Diabetic medicine : a journal of the British Diabetic Association. 2006;23(5):557-64.
24. Shoff SM, Klein R, Moss SE, Klein BE, Cruickshanks KJ. Weight change and glycemic control in a population-based sample of adults with older-onset diabetes. The journals of gerontology Series A, Biological sciences and medical sciences. 1998;53(1):M27-32.
25. Sigal RJ, El-Hashimy M, Martin BC, Soeldner JS, Krolewski AS, Warram JH. Acute postchallenge hyperinsulinemia predicts weight gain: a prospective study. Diabetes. 1997;46(6):1025-9.
26. Mayer-Davis EJ, Kirkner GJ, Karter AJ, Zaccaro DJ. Metabolic predictors of 5-year change in weight and waist circumference in a triethnic population: the insulin resistance atherosclerosis study. American journal of epidemiology. 2003;157(7):592-601.
27. Wedick NM, Mayer-Davis EJ, Wingard DL, Addy CL, Barrett-Connor E. Insulin resistance precedes weight loss in adults without diabetes : the Rancho Bernardo Study. American journal of epidemiology. 2001;153(12):1199-205.
28. Hodge AM, Dowse GK, Alberti KG, Tuomilehto J, Gareeboo H, Zimmet PZ. Relationship of insulin resistance to weight gain in nondiabetic Asian Indian, Creole, and Chinese Mauritians. Mauritius Non-communicable Disease Study Group. Metabolism: clinical and experimental. 1996;45(5):627-33.
29. Wagenknecht LE, Mayer EJ, Rewers M, Haffner S, Selby J, Borok GM, et al. The insulin resistance atherosclerosis study (IRAS) objectives, design, and recruitment results. Annals of epidemiology. 1995;5(6):464-72.
30. Alberti K, Zimmet,PZ, Aschner, P, Assal, JP, Bennett, PH, Groop, L, Jervell, J, Y Kanazawa, H Keen, R Klein, JC Mbanya, D McCarty, A Motala, XR Pan, A Ramachandran, N Samad, N Unwin, P Vardi. Definition, Diagnoisis and Classification of Diabetes Mellitus and its Complications. Geneva Switzerland: World Health Organization, 1999 1999. Report No.: WHO/NCD/NCS/99.2.
31. Pacini G, Bergman RN. MINMOD: a computer program to calculate insulin sensitivity and pancreatic responsivity from the frequently sampled intravenous glucose tolerance test. Computer methods and programs in biomedicine. 1986;23(2):113-22.

32. Welch S, Gebhart SS, Bergman RN, Phillips LS. Minimal model analysis of intravenous glucose tolerance test-derived insulin sensitivity in diabetic subjects. The Journal of clinical endocrinology and metabolism. 1990;71(6):1508-18.
33. Bergman RN, Phillips LS, Cobelli C. Physiologic evaluation of factors controlling glucose tolerance in man: measurement of insulin sensitivity and beta-cell glucose sensitivity from the response to intravenous glucose. The Journal of clinical investigation. 1981;68(6):1456-67.
34. Kahn SE, Prigeon RL, McCulloch DK, Boyko EJ, Bergman RN, Schwartz MW, et al. Quantification of the relationship between insulin sensitivity and beta-cell function in human subjects. Evidence for a hyperbolic function. Diabetes. 1993;42(11):1663-72.
35. Anderson RL, Hamman RF, Savage PJ, Saad MF, Laws A, Kades WW, et al. Exploration of simple insulin sensitivity measures derived from frequently sampled intravenous glucose tolerance (FSIGT) tests. The Insulin Resistance Atherosclerosis Study. American journal of epidemiology. 1995;142(7):724-32.
36. Bergman RN. Lilly lecture 1989. Toward physiological understanding of glucose tolerance. Minimal-model approach. Diabetes. 1989;38(12):1512-27.
37. Qatanani M, Lazar MA. Mechanisms of obesity-associated insulin resistance: many choices on the menu. Genes & development. 2007;21(12):1443-55.