HHS Public Access

Author manuscript

Obesity (Silver Spring). Author manuscript; available in PMC 2016 May 18.

Published in final edited form as:

Obesity (Silver Spring). 2015 November ; 23(11): 2216–2222. doi:10.1002/oby.21213.

Relationship of Insulin Dynamics to Body Composition and Resting Energy Expenditure following Weight Loss

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Abstract

Objective—To examine associations of baseline insulin dynamics with changes in body composition and resting energy expenditure (REE) following weight loss.

Methods—Twenty-one participants with overweight or obesity achieved 10-15% weight loss and then received 3 weight-loss maintenance diets (high-carbohydrate, moderate-carbohydrate, low-carbohydrate) in random order, each for 4 weeks. Body composition was measured at baseline and after weight loss. Insulin 30 minutes after glucose consumption (insulin-30; insulin response), C-peptide deconvolution analysis, HOMA, hepatic insulin sensitivity (IS), and REE were assessed at baseline and after each maintenance diet.

Results—Insulin-30, but not maximal insulin secretion, hepatic IS or HOMA, predicted changes in fat mass (standardized β=0.385, 1.7 kg difference between 10^{th}-90^{th} centile of insulin-30, P=0.04) after weight loss. Insulin-30 (β=−0.341, −312 kcal/d, P=0.008), maximal insulin secretion (β=−0.216, −95 kcal/d, P=0.0002), HOMA (β=−0.394,−350 kcal/d, P=0.002) and hepatic IS (β=0.217, 225 kcal/d, P=0.0003) predicted change in REE during weight-loss maintenance,

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Disclosure: DSL received royalties from books about nutrition and obesity. The other authors have no competing interests.

Author contributions: CBE, HAF and DSL designed research; CBE and DSL conducted research; BMH and HAF analyzed data; BMH and DSL wrote the paper; DSL had primary responsibility for final content. All authors read and approved the final manuscript.

Clinical trial registration: NCT00315354

independent of changes in body composition. The inverse relationship between insulin-30 and REE was substantially attenuated when the low-carbohydrate diet was consumed first.

Conclusions—These findings distinguish a novel phenotype, characterized by high insulin response, at risk for weight regain, and identify a dietary approach to ameliorate this risk.

Keywords

Insulin; body composition and energy expenditure

Introduction

Individual physiological responses to weight loss may vary by phenotype, specifically by variations in insulin dynamics. Conventional measures of insulin sensitivity include the glucose and insulin response to oral glucose load and the homeostatic model assessment of insulin resistance (HOMA). While traditional models suggest that impaired insulin sensitivity leads to compensatory hyperinsulinemia, primary hypersecretion of insulin may also lead to development of obesity ([1]), insulin resistance ([2]) and type 2 diabetes ([3]).

The insulin concentration 30 minutes following oral glucose load (insulin-30) is a novel, reliable proxy measure of insulin secretion ([4–6]). In the Quebec Family Study, baseline insulin-30 strongly predicted changes in weight over a 6-year period, such that those with highest baseline insulin secretion gained the most weight ([7]). This effect was especially pronounced in the setting of a low-fat/high carbohydrate diet ([7]), which increases insulin secretion more than comparison diets controlled for total calories ([8]). In animal models, high insulin secretion is associated with increased weight gain when consuming a high, but not low, glycemic index diet ([9]). In human weight loss trials, subjects with high baseline insulin secretion lost more weight on a low-glycemic load diet ([10,11]).

As an anabolic hormone, insulin mediates post-prandial conversion of glucose and lipids into storage forms ([12]). Increased insulin action promotes body fat gain ([13]), as demonstrated by chronic insulin administration in animals ([14]), initiation of insulin treatment in type 2 diabetes ([15]) and excessive insulin treatment in type 1 diabetes ([16]) – an effect that appears to be at least partially independent of energy intake ([17]). Moreover, high endogenous insulin secretion arising from genetic variation ([18]), pancreatic tumor, hypothalamic damage, or other causes ([19]) is prospectively associated with weight gain, whereas drugs that inhibit insulin secretion attenuate weight gain ([20]). Indeed, among patients with type 2 diabetes receiving standard treatment, high insulin action may adversely affect energy expenditure ([21]).

Therefore, we aimed to examine the associations of baseline insulin dynamics with changes in body composition during weight loss, and changes in resting energy expenditure (REE) during weight loss maintenance. In addition, we hypothesized that dietary composition may be an effect modifier of these relationships.

Methods

Study design

Participants with overweight or obesity, and otherwise healthy, consumed a reduced-calorie Run In diet (60% of estimated caloric needs) designed to produce 10-15% weight loss over 12 weeks. Following a 4-week weight stabilization period, participants then received 3 weight-loss maintenance test diets in random order, each for a 4-week period. The composition of the diets were high-carbohydrate (60% of energy from carbohydrate, 20% from fat and 20% from protein), moderate-carbohydrate (40% from carbohydrate, 40% from fat and 20% from protein), and low-carbohydrate (10% from carbohydrate, 60% from fat, 30% from protein). The diets were isocaloric, and designed to maintain weight loss. Meals were prepared in the metabolic kitchen at the Brigham and Women's Hospital, Boston, MA, and were consumed on site or packaged for consumption at home. Participants were admitted to a research unit for a 4- day hospitalization at baseline and at the end of each weight-loss maintenance diet period. The study protocol was approved by the Boston Children's Hospital and Brigham and Women's Hospital institutional review boards. Additional details of the protocol were previously presented ([22]).

Outcome measures

The independent variables of interest were measures of insulin dynamics, specifically insulin-30, insulin secretion by C-peptide deconvolution analysis, hepatic insulin sensitivity and HOMA insulin resistance index. Following an overnight fast, an oral glucose tolerance test (OGTT) was performed with 75 grams dextrose (Trutol, Thermo Fisher Scientific Inc., Waltham, MA) at baseline and the end of each weight-loss maintenance diet period, with blood sampling at −10, −5, 0, +10, +20, +30, +60, +90, and +120 minutes. Glucose concentrations were measured by enzymatic reference method (LabCorp, 001818), insulin concentrations were measured by chemiluminescent assay (Beckman Coulter, Chaska MN) and C-peptide concentrations were measured by competitive radioimmunoassay (Siemens Medical Solutions Diagnostics, Los Angeles, CA). The insulin concentration at 30 minutes after glucose consumption was used as a measure of insulin response (insulin-30) ([4–6]). Basal, maximal and total insulin secretion were analyzed by deconvolution analysis of C-peptide concentrations in response to OGTT using ISEC "I(nsulin-)SEC(retion)" software, provided courtesy of Dr. Roman Hovorka ([23]). Hepatic insulin sensitivity was calculated as the inverse of the product of the glucose area under the curve (AUC) with insulin AUC during the first 30 minutes of OGTT, based on Abdul-Ghani et al ([24]). HOMA was calculated as the product of the fasting glucose and fasting insulin levels ([25]).

Body composition assessment was measured at baseline and the end of the 12-week weight loss run-in period by dual-energy x-ray absorptiometry (DXA, Discovery A, Hologic, Inc., Waltham, MA). REE and total energy expenditure (TEE) were measured prior to weight loss and end of each weight-loss maintenance diet period. REE was measured by indirect calorimetry (VMAX, Encore 29n, Viasys Healthcare, Inc., Yorba Linda, CA). TEE was measured under free-living conditions using doubly-labeled water methodology with stable isotope analysis performed at Baylor College of Medicine, Houston, TX.

Statistics

Relationships between baseline measures of insulin dynamics and study completion were evaluated by logistic regression. Baseline relationships between insulin dynamics and metabolic parameters were evaluated by Pearson correlation for continuous variables or t-test for dichotomous variables.

Relationships between baseline insulin dynamics and change in body composition parameters during the Run In diet were evaluated in two methods. The primary analysis was performed using multivariate linear regression, where the dependent variable was change in body composition and independent variable of interest was the specific measure of insulin dynamics with covariates of age, gender and baseline body mass index (BMI). The secondary analysis was based on a previous observation that fat loss can be predicted by initial fat mass and energy deficit ([26]). We constructed a model of post-weight loss fat mass with independent variables of pre-weight loss fat mass, change in total mass, age and gender and obtained the model residuals. We then evaluated the relationship between the model residuals and measures of insulin dynamics using linear regression.

Relationships between baseline insulin dynamics and REE were evaluated by linear repeated measures model with covariates of age, gender, baseline BMI, dietary composition, treatment order and order of measurement period. Within this model of REE, insulin-30 and treatment order were also tested for effect modification. Subsequent analyses included respective measures of change in body composition achieved during weight loss (e.g. change in lean mass) as covariates.

Regression coefficients were standardized for presentation. For a subset of outcomes, regression coefficients from this model were converted to differences in outcome measure (e.g. body composition or REE) between the 10^{th} and 90^{th} centiles of baseline insulin dynamics measures to provide a clinically relevant estimate of effect size within the observed range in our cohort The 10^{th} centile of insulin-30 roughly coincided with reasonable approximation of normal insulin response ([10]). The effects of weight loss on measures of insulin dynamics were assessed using a pooled comparison of data from all three weight-loss maintenance diets to pre-weight loss levels.

Statistical significance was considered to be a 2-sided alpha value of $P \leq 0.05$. Results presented are mean ± standard error of the mean unless otherwise specified. Hepatic insulin sensitivity was log-transformed for analysis, and outliers for hepatic insulin sensitivity were excluded using an outlier-deletion algorithm as previously reported ([22]).

Results

Thirty-two participants entered the weight loss phase, 24 were randomized and 21 completed the protocol. Participant demographics, as previously reported ([22]), and baseline characteristics including biochemical parameters are presented in **Tables 1 and 4.** Mean change in BMI during each diet period is reported in the Supplemental Figure and did not materially differ between groups.

Participants who did and did not complete the study did not differ by baseline measures of insulin dynamics, including insulin-30 (mean±standard deviation 761±556 vs. 555±225 pmol/L, respectively, P=0.28), hepatic insulin sensitivity (0.82±0.57 vs. 0.90±0.47 unit, P=0.51) or HOMA (2.57±1.55 vs. 2.22±1.06, P=0.51).

Relationship of insulin dynamics with baseline body composition and REE

Baseline insulin-30 was positively associated with baseline BMI (r=0.47, P=0.03) and HOMA (r=0.46, P=0.03, adjusted for BMI P=0.43) and negatively associated with hepatic insulin sensitivity (r=−0.86, P<0.0001, adjusted for BMI P= 0.0002). Insulin-30 was not associated with baseline body composition parameters or REE (Table 2). Insulin-30 correlated strongly with parameters obtained from deconvolution analysis of C-peptide, including insulin secretion at 30 minutes (r=0.76, P=0.0003), maximal insulin secretion (r=0.66, P=0.003), basal insulin secretion (r=0.72, P=0.0008) and total insulin secretion (r=0.71, P=0.001).

Baseline basal insulin secretion by C-peptide deconvolution analysis (r=0.40, P=0.03), baseline HOMA (r=0.75, P<0.0001) and hepatic insulin sensitivity (r=−0.50, P=0.04), but not maximal (r=0.13, P=0.60) or total (r=0.25, P=0.33) insulin secretion by deconvolution analysis, were significantly associated with baseline BMI. Baseline HOMA was positively associated with body composition parameters including total mass (r=0.52, P=0.02), fat mass (r=0.50, P=0.02) and trunk fat (r=0.56, P=0.008, Table 2). Baseline insulin measures did not predict time to achieve goal weight loss (data not shown).

Insulin dynamics and changes in body composition during weight loss maintenance

In the primary model, baseline insulin-30 was prospectively associated with changes in fat mass (standardized β=0.385, corresponding to 1.7 kg difference between 10^{th} and 90^{th} centile of insulin-30, P=0.04, Figure 1), trunk fat mass (standardized β=0.449, 10^{th}-90^{th} difference 1.6 kg, P=0.006), and % lean mass (standardized β=−0.434, 10^{th}-90^{th} difference −1.7%, P=0.05), after weight loss (Table 3). In contrast, insulin secretion as assessed by deconvolution analysis (basal, maximal and total), hepatic insulin sensitivity and HOMA were not associated with changes in body composition. In the secondary model of post-weight loss fat mass, adjusting for baseline fat mass, change in total mass, age and gender, results were qualitatively similar (insulin-30 standardized β=0.048, P=0.05; basal insulin secretion standardized β=0.013, P=0.66; maximal insulin secretion standardized β=−0.001, P=0.97; total insulin secretion standardized β=0.011, P=0.71).

Insulin dynamics and changes in REE during weight loss maintenance

Higher baseline insulin-30 predicted lower REE during weight loss maintenance (standardized β=−0.341, −312 kcal/d difference between 10^{th} and 90^{th} centile of insulin-30, P=0.008, Table 3). This relationship remained significant after adjustment for changes in body composition during the Run In diet (Supplemental Table). Notably, diet sequence order was a strong effect modifier of the relationship between insulin-30 and REE (standardized β=−1.104, 10^{th}-90^{th} difference −991 kcal/d when starting with high-carbohydrate diet, standardized β=−0.883, 10^{th}-90^{th} difference −793 kcal/d when starting with moderate-carbohydrate diet, and standardized β=−0.269, 10^{th}-90^{th} difference −241 kcal/d when

starting with low-carbohydrate diet, P=0.005 for effect modification, Figure 2). That is, consuming the low-carbohydrate diet first strongly attenuated the relationship between insulin-30 and REE.

Higher basal (standardized β=−0.274, 10^{th}-90^{th} difference −133 kcal/d, P<0.0001), maximal (standardized β=−0.216, 10^{th}-90^{th} difference −95 kcal/d, P=0.0002) and total (standardized β=−0.212, 10^{th}-90^{th} difference −116 kcal/d, P=0.002) insulin secretion from deconvolution analysis predicted lower REE during weight loss maintenance (Table 3). These relationships remained significant after adjustment for changes in body composition during Run In diet (Supplemental Table).

Higher HOMA predicted lower REE during weight-loss maintenance (standardized β= −0.394, −350 kcal/d difference between 10^{th} and 90^{th} centile of HOMA, P=0.002) (Table 3). Race modified the relationship between HOMA and REE such that the relationship was strongest in whites (standardized β=−0.532), intermediate in blacks (standardized β=−0.334) and weakest in Asians (standardized β=0.131).

Lower hepatic insulin sensitivity also predicted lower REE during weight-loss maintenance (standardized β=0.217, 225 kcal/d difference between 10^{th} and 90^{th} centile of hepatic insulin sensitivity, P=0.0003) (Table 3). Results were similar with all subjects included in this analysis.

Effects of weight loss on insulin dynamics

Insulin-30 decreased significantly in response to weight loss (P=0.006 for pooled response), without specific effect of dietary composition (baseline 761±122 pmol/L, high-carbohydrate 553±73 pmol/L, moderate-carbohydrate 483±60 pmol/L and low-carbohydrate 470±61 pmol/L, P=0.16 for diet effect, Table 4). In addition, baseline insulin-30 (β =−0.550, P=0.0003) and change in lean mass (β =0.059 pmol/L per g, P=0.05) were independent predictors of change in insulin-30 as an outcome measure, adjusting for age, gender, baseline BMI, diet and treatment order.

Basal insulin secretion, as assessed from C-peptide deconvolution analysis, decreased in response to weight loss (P<0.0001 for pooled response), with differential effect of diet (baseline 2.69±0.19 pmol/kg/min, high-carbohydrate 2.15±0.24 pmol/kg/min, moderate-carbohydrate 1.95±0.12 pmol/kg/min, low-carbohydrate 1.85±0.19 pmol/kg/min, P=0.02, Table 4). Time to maximal insulin secretion after oral glucose varied significantly by diet (baseline 47±6 minutes, high-carbohydrate 46±7 min, moderate-carbohydrate 55±7 min and low-carbohydrate 66±8 min, P=0.04, Table 4).

HOMA improved significantly with weight loss (P<0.0001), without effect of dietary composition (baseline 2.57±0.34, high-carbohydrate 1.30±0.10, moderate-carbohydrate 1.16±0.09, low-carbohydrate 1.13±0.12, P=0.24, Table 4). Hepatic insulin sensitivity improved with weight loss (P=0.004), with differential effect by diet (baseline 0.72±0.09 units, high-carbohydrate 1.15±0.16 units, moderate-carbohydrate 1.31±0.19, low-carbohydrate 1.54±0.24, P=0.03, Table 4).

Conclusion

In this study, we observed that high insulin response at baseline – as assessed by the novel measure insulin-30 – predicts adverse changes in body composition after weight loss in the setting of a rigorously controlled feeding study. At the same amount of weight loss, individuals with high insulin response lose relatively more lean mass and less fat mass than those with low insulin response. This novel result extends prior research in which insulin secretion was shown to modify the effect of dietary composition on total weight loss in *ad libitum* settings ([7,10]). While previous data suggest that post-weight-loss insulin sensitivity is associated with greater increases in fat mass ([27]), our data indicate that pre-weight-loss measures of insulin action (hepatic insulin sensitivity and HOMA) did not predict changes in body composition – underscoring the potential significance of baseline insulin response in body weight regulation. In the pre-weight loss state, insulin response is positively associated with BMI, but not with other body composition parameters. This observation implies that the effects of insulin response on body composition are unmasked or exacerbated by the physiological stress of weight loss. Of note, conventional proxy measures of insulin secretion (C-peptide deconvolution analysis) did not predict changes in body composition

Baseline insulin dynamics, using both novel and conventional measures, were strong, negative predictors of weight-loss induced declines in REE, such that participants with higher insulin response, insulin secretion by deconvolution analysis, and insulin resistance had the largest declines. This relationship persisted despite adjustment for body composition changes and dietary macronutrient content. The mean difference in REE between the lowest and highest centiles of insulin response was approximately 310 kcal/day – a potentially major metabolic effect. By comparison, the difference in TEE when participants consumed the low-carbohydrate diet vs. high-carbohydrate diet (as previously reported) was approximately 325 kcal/day ([22]).

These adverse effects of insulin response on body composition and resting energy expenditure have potential implications to weight loss maintenance and risk of weight regain. Insulin directs glucose and lipids to storage forms, thereby decreasing the availability of these metabolic fuels in the blood. Especially during negative energy balance, high insulin secretion would tend to restrain release of lipids from adipose tissue, thereby sequestering the primary metabolic fuel in the fasting state. Consequently, the body would necessarily rely to a greater degree on alternative fuels, including amino acids from muscle, to fuel gluconeogenesis. Over time, a shift in substrate utilization in this direction could explain the relatively smaller loss of fat tissue and greater loss in lean tissue observed after weight loss among individuals with high insulin secretion. Reduced availability of circulating metabolic fuels could also explain the lower energy expenditure associated with this phenotype, as previously hypothesized ([12]).

In addition, we found that the relationship between insulin response and REE was modified by dietary composition during weight loss maintenance. The inverse association between baseline insulin response and change in REE was almost fully attenuated when the low-carbohydrate diet was consumed first. The 20 minute delay in time to peak insulin secretion during OGTT on the low vs. high carbohydrate diet suggests a relevant mechanism.

Following a period of diminished stimulation from a low carbohydrate diet, the pancreatic *beta*-cell becomes less reactive to high glycemic index carbohydrate, and this change persists for at least 1 month after carbohydrate intake is increased. In effect, the relationship between dietary intake and early phase insulin response may be "reset" – at least for a time – after consumption of a low carbohydrate diet. Thus, while major contributors to insulin secretion status are non-modifiable genetics, early life influences), a specific change in dietary composition may confer protection for individuals with high insulin response from the adverse metabolic effects of this phenotype, although the duration of this effect is unknown.

A limitation of this study is small sample size, especially for subgroup analyses, which is likely reflected in the borderline P-values for a subset of our analyses. Insulin dynamics were not associated with study completion, but the 13% post-randomization attrition rate may impact the generalizability of the study. In addition, we employed indirect measures of insulin dynamics, most notably insulin-30. We do not know why insulin-30 better predicted change in body composition then deconvolution analysis. Insulin-30 may be a good proxy for early-phase events related to *beta*-cell function. However, unlike C-peptide deconvolution analysis, insulin-30 does not address the dynamic balance of insulin release and clearance, and does not capture the late post-prandial response. This discrepancy comprises an important interpretive limitation of the study that warrants exploration in future research. At the same time, insulin-30 is simpler to calculate (without need for a computer program) – an advantage for translation to the clinical setting. In addition, these associations, though prospective in nature, can only suggest causal mechanisms and do not provide proof of causal direction. While we do not have a direct measure of dietary compliance, we did observe a clear differentiation between the diets in other metabolic parameters (e.g. HDL, triglycerides and respiratory quotient) to suggest excellent adherence. Strengths of these analyses, based on the parent study, include a cross-over design to minimize confounding by inter-individual differences, the use of accurate and precise outcome measures, and the ability to conduct diet-phenotype assessment based on important physiological measures.

In conclusion, this study suggests that novel and conventional measures of insulin dynamics influence the metabolic and body composition responses to weight loss, highlighting a phenotype at risk for weight regain. Additional research is needed to confirm these preliminary findings, explore dietary interventions, such as carbohydrate restriction or staged dietary approaches, that may attenuate the adverse effects of high insulin response and improve long-term weight loss maintenance among individuals with this phenotype.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank the study participants and nursing staff at the BCH and BWH Clinical and Translational Studies Units.

Funding: R01DK072428 and K24DK082730 from the National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland; M01RR02172 from the National Center for Research Resources, National Institutes

of Health, to the Boston Children's Hospital General Clinical Research Center; M01RR02635 from the National Center for Research Resources, National Institutes of Health, to the Brigham and Women's Hospital General Clinical Research Center; UL1RR02575801 from the National Center for Research Resources, National Institutes of Health, to the Harvard Catalyst Clinical and Translational Science Center; New Balance Foundation; T32 DK007477-31 from the National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, Maryland; and F32HL122080-01 from National Heart, Lung and Blood Institute

Abbreviations

TEE	Total energy expenditure
REE	resting energy expenditure
IS	insulin sensitivity
insulin-30	insulin concentration at 30 minutes
BMI	body mass index
DXA	dual-energy x-ray absorptiometry

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What is already known about this subject?

- Individual responses to weight loss may vary by phenotype, conceptually providing an opportunity for individualized obesity treatment.
- High insulin secretion is associated with excessive weight gain, especially among individuals consuming a high-carbohydrate/low-fat diet.

What does this study add?

- We demonstrate that individuals with high insulin response experience changes in body composition and resting energy expenditure during weight loss maintenance that would predispose to weight regain.
- The inverse relationship between insulin response and energy expenditure during weight loss maintenance was strongly attenuated by consumption of a low-carbohydrate diet.
- This study highlights a novel obesity-related phenotype that may respond especially well to carbohydrate restriction.

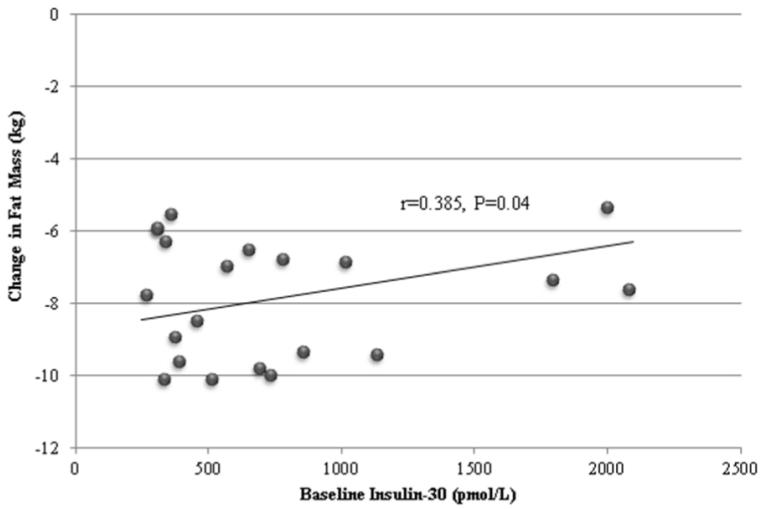

Figure 1.
Relationship of baseline insulin-30 with change in fat mass during weight loss.

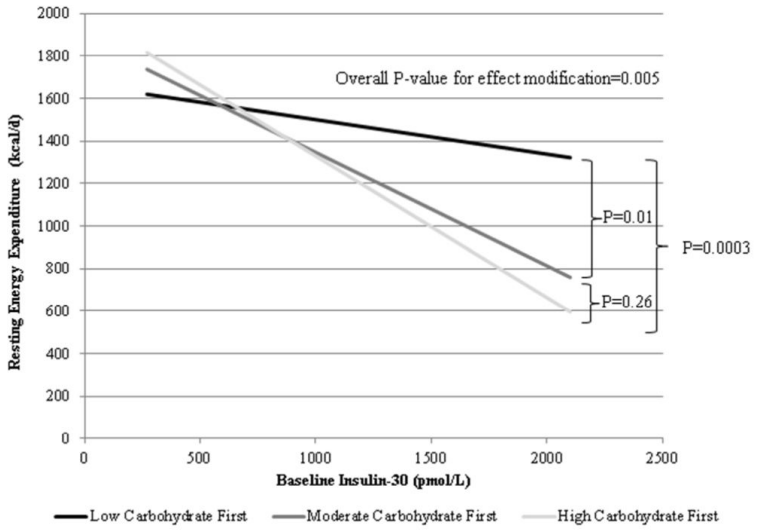

Figure 2.

Effect modification by diet of the relationship between baseline insulin-30 and REE during weight loss maintenance. This schematic representation is stratified by first diet in sequence order to demonstrate effect modification.

Table 1

Patient demographics and baseline characteristics (N=21)

Demographics	
Age (y)	30.3 ± 5.7
Gender	
Male	13 (62%)
Female	8 (38%)
Race	
White	4 (19%)
Black	8 (38%)
Asian	4 (19%)
Other	5 (24%)
Hispanic Ethnicity	4 (19%)
Body composition	
BMI (kg/m^2)	34.4 ± 4.9
Total mass (kg)	104.0 ± 18.5
Lean mass (kg)	66.4 ± 15.4
Lean mass % of total	63.6 ± 7.7
Fat mass (kg)	34.7 ± 9.0
Fat mass % of total	33.6 ± 7.9
Trunk fat (kg)	17.5 ± 4.8
Energy expenditure	
Total energy expenditure (kcal/d)	3248 ± 762
Resting energy expenditure (kcal/d)	1784 ± 376

Results reported as N (%) or mean±standard deviation

Subset of data previously reported in Ebbeling et al. ([22])

Baseline insulin measures reported in Table 4

Table 2

Baseline relationships of insulin dynamics with demographics, body composition and energy expenditure

	Insulin-30		Basal Insulin Secretion		Maximal Insulin Secretion		Total Insulin Secretion		Hepatic insulin sensitivity		HOMA-IR	
	r	**P-value**	**r**	**P-value**	**r**	**P-value**	**r**	**P-value**	**r**	**P-value**	**r**	**P-value**
Demographics												
Age	−0.26	0.25	−0.30	0.23	−0.14	0.58	−0.18	0.49	0.05	0.86	−0.10	0.67
Gender	-	0.56	-	0.05	-	0.18	-	0.12	-	0.66	-	0.72
Body composition												
BMI	0.47	0.03	0.50	0.03	0.13	0.60	0.25	0.33	−0.50	0.04	0.75	<0.0001
Total mass	0.23	0.31	0.23	0.35	−0.23	0.36	−0.08	0.76	−0.32	0.22	0.52	0.02
Lean mass	0.10	0.67	0.07	0.77	−0.32	0.19	−0.25	0.32	−0.22	0.42	0.33	0.14
% Lean mass	−0.14	0.54	−0.23	0.35	−0.31	0.21	−0.35	0.17	0.08	0.76	−0.14	0.54
Fat mass	0.31	0.17	0.36	0.14	0.10	0.70	0.25	0.33	−0.29	0.28	0.50	0.02
% Fat mass	0.17	0.47	0.27	0.29	0.33	0.19	0.37	0.15	−0.11	0.69	0.18	0.44
Trunk fat	0.26	0.25	0.41	0.09	0.02	0.93	0.20	0.43	−0.30	0.26	0.56	0.008
Energy expenditure												
Resting energy expenditure	0.20	0.40	0.20	0.42	−0.21	0.41	−0.11	0.67	−0.29	0.27	0.40	0.07

P-value for gender calculated by Student's t-test; remainder calculated by Pearson correlation

Table 3

Relationship between baseline insulin-related measures and changes in body composition and resting energy expenditure (REE)

	Baseline insulin-30		Baseline basal insulin secretion		Baseline maximal insulin secretion		Baseline total insulin secretion		Baseline hepatic insulin sensitivity		Baseline HOMA-IR	
	Standardized β	P-value	Standardized β	P-value	Standardized β	P-value	Standardized β	P-value	Standardized β	P-value	Standardized β	P-value
During weight loss												
Δ Lean Mass[a]	−0.375	0.17	−0.305	0.27	−0.265	0.29	−0.358	0.17	0.477	0.13	0.152	0.68
Δ % Lean[a]	−0.434	0.05	−0.299	0.23	−0.067	0.77	−0.206	0.41	0.351	0.53	−0.084	0.78
Δ Fat Mass[a]	0.385	0.04	0.137	0.53	0.023	0.91	0.051	0.81	−0.100	0.71	0.197	0.45
Δ % Fat[a]	0.430	0.05	0.303	0.22	0.067	0.77	0.207	0.40	−0.172	0.57	0.118	0.70
Δ T runk Fat Mass[a]	0.449	0.006	0.218	0.18	0.138	0.36	0.149	0.35	−0.214	0.28	0.218	0.36
During weight loss maintenance												
Δ REE[b]	−0.341	0.008[c]	−0.274	<0.0001 [c]	−0.216	0.0002[c]	−0.212	0.002 [c]	0.217	0.0003[c]	−0.394	0.002[c]

[a] Adjusted for age, gender and baseline BMI

[b] Adjusted for age, gender, baseline BMI, diet composition, time and diet sequence

[c] P≤0.05 after adjustment for body composition parameters achieved during weight loss (see Supplemental Table for details)

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Table 4

Effects of weight loss and dietary composition on insulin secretion variables

	Baseline	High carbohydrate	Moderate carbohydrate	Low carbohydrate	P-value for pooled weight loss effect	P-value for diet effect
Insulin-30 (pmol/L)	761 ± 122	553 ± 73	483 ± 60	470 ± 61	0.006	0.16
Basal insulin secretion (pmol/kg/min)	2.69 ± 0.19	2.15 ± 0.24	1.95 ± 0.12	1.85 ± 0.19	<0.0001	0.02
Maximal insulin secretion (pmol/kg/min)	14.4 ± 1.54	14.1 ± 1.47	13.8 ± 0.88	13.0 ± 0.97	0.16	0.24
Total insulin secretion (pmol/kg*2h)	1271 ± 129	1049 ± 76	1140 ± 85	1106 ± 92	0.06	0.45
Time of maximal insulin secretion (min)	47 ± 6	46 ± 7	55 ± 7	66 ± 8	0.04	0.05
Hepatic insulin sensitivity[a]	0.72 ± 0.09	1.15 ± 0.16	1.31 ± 0.19	1.54 ± 0.24	0.004	0.03
HOMA-IR	2.57 ± 0.34	1.30 ± 0.10	1.16 ± 0.09	1.13 ± 0.12	<0.0001	0.24

Mean ± SEM, adjusted for age, gender, baseline BMI, diet composition, time and diet sequence

[a]Two values excluded from analysis. Units calculated per Abdul-Ghani et al. ([24])

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