

Dietary Composition and Weight Loss: Can We Individualize Dietary Prescriptions According to Insulin Sensitivity or Secretion Status?

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There is considerable uncertainty over whether any one dietary pattern broadly facilitates weight loss or maintenance of weight loss, and current dietary guidelines recommend a spectrum of dietary composition for the general population. However, emerging evidence suggests that specific dietary compositions may work better for identifiable groups of overweight/obese individuals based on their individual metabolic status. In particular, characteristics of insulin dynamics, such as insulin sensitivity or insulin secretion status, may interact with diets that vary in macronutrient composition to influence the weight loss achieved with a hypocaloric diet.

Key words: dietary composition, insulin secretion, insulin sensitivity, weight loss

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doi: 10.1301/nr.2006.oct.435–448

INTRODUCTION

The prevalence of overweight and obesity has increased dramatically in the United States and worldwide. In 2002, 69% of men and 62% of women in the United States were overweight or obese.¹ The cause of obesity is multifactorial, but lifestyle changes, in particular reduc-

ing energy intake, are the cornerstone of current approaches to weight loss and prevention of weight regain.^{2,3} However, weight loss (by any means) is recognized to be difficult to achieve and maintain, and there is considerable uncertainty over whether any one dietary pattern is broadly more effective than another.^{4–6} One promising area for improvement in the field of weight loss concerns whether individual-specific dietary recommendations may result in greater effectiveness of weight loss than group recommendations—in other words, whether different individuals respond better to different types of diets. In particular, there is animal and human evidence to suggest that insulin dynamics, such as insulin sensitivity and insulin secretion, play a role in body weight regulation and therefore these parameters may affect individual responses to hypocaloric diets. Furthermore, specific dietary factors that influence these parameters may theoretically interact with subject-specific characteristics of insulin dynamics to influence the effect of hypocaloric diets with varied macronutrient composition on weight loss and maintenance.

We performed a systematic review of observational and intervention human studies to address the following questions: 1) Are baseline insulin sensitivity and insulin secretion associated with future weight change, and might these parameters affect individual responses to hypocaloric diets? and 2) is there an interaction between either insulin sensitivity or insulin secretion and the macronutrient composition of hypocaloric diets that influences adherence to a weight loss program?

We conducted a review in MEDLINE of the English-language literature for observational and interventional (aiming at weight loss) human studies on the effect of baseline insulin sensitivity and insulin secretion on energy balance and future weight. Search terms included insulin sensitivity, insulin secretion, weight, dietary composition, and related terms. Additional publications were identified from citations from the recovered articles, review articles, and personal reference lists. We excluded letters, abstracts, and conference proceedings that were not published in full in peer-reviewed journals.⁷ We

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This research was supported by National Institutes of Health grant K23-DK61506 (to A.G.P.) and US Department of Agriculture cooperative agreement No. 58-1950-4-401 (to S.B.R.).

also excluded studies in children because insulin dynamics are evolving during childhood, especially during puberty,^{8,9} and studies involving diabetic patients because they exhibit impaired and shifting insulin dynamics, insulin secretion in response to weight loss differs between diabetics and non-diabetics,¹⁰ and these individuals often try intentional weight loss (which may confound the relationship between insulin dynamics and weight in observational studies). Studies of less than 4 weeks follow-up or with fewer than eight participants were excluded. Qualitative synthesis of data was performed. We did not perform meta-analysis due to lack of uniformity in measuring predictor variables among the studies. Indices of insulin sensitivity and insulin secretion used in the reviewed studies are described in Table 1.

DIETARY MACRONUTRIENT COMPOSITION AND WEIGHT IN THE GENERAL POPULATION

Over the last decades, nutrition recommendations from national organizations have focused on prevention of chronic diseases such as cardiovascular disease and cancer, and there are no clear recommendations on macronutrient composition for weight control. As a result, a variety of dietary compositions have been proposed for

weight loss, and multiple popular diets with widely varied compositions are promoted.¹¹⁻¹³ Most concentrate on altering the relative contributions of fat and carbohydrate in the diet.

The role of dietary fat in the obesity epidemic has been a hotly debated topic for decades and remains unresolved. On theoretical grounds, dietary fat content can influence energy intake and body weight based on its higher energy density, higher palatability, and perhaps specific metabolic effects.¹⁴ The question of whether the consumption of a high-fat diet leads to weight gain and whether lower-fat diets can promote weight loss has been reviewed by our group previously.¹⁴⁻¹⁶

Studies that provided recommendations to lower fat intake have typically showed modest weight loss, while studies that provided the lower-fat diet showed greater weight loss, suggesting that adherence to a dietary regimen is of utmost importance. Based on these and other data, previous dietary guidelines have focused on lowering dietary fat,¹⁷ even though several groups have pointed out that the rising prevalence of obesity in the United States has occurred during a time when the percentage of dietary energy from fat has decreased, an association that clearly undermines the validity of the recommendations.¹⁸⁻²⁰

Table 1. Indices of Insulin Secretion and Insulin Sensitivity

Insulin Secretion		
Index	Procedure	Derivation of Index
INS ₃₀	75 g OGTT	Insulin value at 30 min after glucose load is given
OGTT-INS _{AUC-3hr}	75 g OGTT	Insulin AUC for the first 3 hours after glucose load is given
OGTT-INS _{D30}	75 g OGTT	(Insulin value at 30 min – insulin value at 0 min)/glucose value at 30 min
OGTT-CIR _{gp}	75 g OGTT	Corrected insulin release at the glucose peak
MTT-INS _{AUC-4hr}	Mixed Meal	Insulin AUC for the first 4 hours after a mixed meal is given
MTT-INS _{AUC-8hr}	Mixed Meal	Insulin AUC for the first 8 hours after two mixed meals are given
AIR _g	FSIVGTT ⁹⁴	Insulin AUC in the first 10 min after intravenous glucose administration
Disposition index	FSIVGTT	A measure of pancreatic function = Si × AIR _g
Insulin Sensitivity		
Index	Procedure	Derivation of Index
Fasting insulin	Serum	Fasting insulin
QUICKI	Fasting serum and plasma	= 1/[log(insulin, mU/L) + log(glucose, mg/dL)]
HOMA-IR	Fasting serum and plasma	=[(glucose, mmol/L) × (insulin, mU/L)]/22.5
OGTT-INS ₁₂₀	75 g OGTT	Insulin value at 120 min after glucose load is given
Insulin sensitivity	FSIVGTT	Insulin-mediated glucose disposal estimated by minimal model
M	Euglycemic hyperinsulinemic clamp	Amount of glucose necessary to maintain euglycemia during hyperinsulinemic conditions

AIR_g, acute insulin response to glucose; AUC, area-under-the-curve; CIR_{gp}, corrected insulin response at glucose peak; FSIVGTT, frequently sampled intravenous glucose tolerance test; HOMA-IR, homeostasis model assessment-insulin resistance; INS, insulin; MTT, meal tolerance test; OGTT, oral glucose tolerance test; QUICKI, quantitative insulin sensitivity check index.

In a recently published large trial that was initiated in 1993, postmenopausal women were randomized to a group receiving dietary advice to reduce ad libitum fat intake and replace it with vegetables, fruits, and grains or to a group receiving diet-related educational material.²¹ Women in the intervention group reported decreased fat and energy intake, had modest weight loss at 1 year, and maintained slightly lower weight (0.4 kg) than control women after an average of 7.5 years of follow-up. The results of this study are confounded by the intensive behavioral therapy that participants in the active low-fat group received, which may have led to additional behavioral changes favorable to weight loss. Therefore, from this and similar studies, it is difficult to differentiate the direct effects of the low-fat dietary composition on energy balance from the behavioral aspects of the intervention.

Diets high in fat and low in carbohydrate are frequently promoted for weight loss in popular books, and the scientific evidence has been reviewed.^{5,22} In the 94 highly heterogeneous and short-duration dietary interventions that have been conducted, participant weight loss was associated with decreased caloric intake and increased diet duration but not with reduced carbohydrate content. Since publication of the systematic reviews, there have been a number of larger and longer-duration trials of very-low-carbohydrate diets. All of these studies reported significantly more weight loss in the low-carbohydrate diet compared with the reduced-fat diet at 6 months,²³⁻²⁶ but the weight loss difference was attenuated in studies extended to 1 year.^{24,27}

In addition to changing the amount of carbohydrate, an alternative way of modifying the carbohydrate component (or glycemic load, GL = glycemic index [GI] × carbohydrate amount) of the diet is to lower the glycemic index (GI) of ingested carbohydrates. However, there remains considerable controversy over the efficacy of low-GI diets for weight loss.²⁸ The GI is defined as the area under the glycemic response curve during a 2-hour period after consumption of 50 g of carbohydrate, and values are expressed relative to the effect of white bread or glucose.^{29,30} There have been several intervention trials (with a duration of 1 month or more) that have attempted to change the dietary GL moderately either by changing the amount or the GI of the ingested carbohydrate. These studies had conflicting results. Most found no change in weight between low- and high-GL diets,³¹⁻³⁶ but a few found more weight loss with the low-GL diet.^{37,38} Definitive conclusions are difficult to draw because these trials varied widely in methodology, but it appears that ad libitum, low-GL diets, including very-low-carbohydrate diets, cause significant weight loss initially, which is not, however, maintainable in the long term.^{24,27,37,38}

The studies summarized above have helped to pro-

long scientific uncertainty over whether low-carbohydrate or low-fat diets are the most effective for long-term weight control: overall, there appears to be little evidence for substantial quantitative differences in long-term group mean weight loss between low-fat and low-carbohydrate diets. However, targeting identifiable populations with specific macronutrient compositions based on physiological principles has barely been addressed to date, and may provide a new route to greater effectiveness in weight loss programs and prevention of weight gain.

INSULIN SENSITIVITY AND WEIGHT

It is well established that obesity is associated with low insulin sensitivity or insulin resistance,³⁹ however, the temporal relationship between insulin resistance and obesity is not clear. In other words, it is not known whether insulin resistance precedes the development of obesity and plays a role in modulating future weight and response to hypocaloric diets.

Observational Studies of Insulin Sensitivity and Weight

In most observational studies, baseline insulin resistance measured in a variety of ways (Table 2) has been associated with less future weight gain in a variety of populations.^{10,40-47} However, the reverse association, that insulin resistance is associated with future weight gain, was seen in some studies,^{47,48} and no association was reported in other studies.^{45,49-52} From the available studies, it is difficult to draw definitive conclusions because most did not adjust for important contributors to energy balance and weight (e.g., physical activity, smoking, etc.) and were performed in widely varying populations with different genetic backgrounds, age, baseline weight, and degree of insulin resistance. For example, three studies were done in Pima Indians,^{10,40,43} who are considered to be genetically predisposed to obesity and insulin resistance, and tend to gain weight over time compared with age- and sex-matched non-Pima controls.⁵³ In summary, although our current understanding of the relationship between insulin sensitivity and weight is far from complete, it appears that insulin sensitivity, especially among young people and the less obese, is associated with future weight gain, while insulin resistance may provide a shield against future weight gain.

Insulin Sensitivity and Response to Hypocaloric Diets

A few intervention studies have examined whether insulin sensitivity modifies the effect of diets on weight

Table 2. Observational Studies Examining the Association Between Insulin Sensitivity Status and Future Weight Gain in Adults Without Diabetes

Study	Subject Characteristics			Index of Insulin Sensitivity at Baseline (predictor variable)*		Follow-up (years)	Association Between Index of Insulin Sensitivity and Outcome (weight)		Comments
	N	BMI (kg/m ²) mean or range	Age (yr), mean or range	Other			Sensitivity	Outcome	
Swinburn 1991 ⁴⁰	193	34	25	M/F Pima Indians	Si	3.5	Si	Si associated with weight gain; effect more pronounced in the less obese at baseline	Adjusted for age, sex, baseline weight, resting energy expenditure
Valdez 1994 ⁴¹	1493	24–28	25–64	M/F Caucasian or Hispanic	FI	8	FI	FI negatively associated with weight gain among obese	Adjusted for age, sex, baseline weight, ethnicity
Hoag 1995 ⁴²	789	26	53	M/F Caucasian or Hispanic	FI	4.3	FI	FI negatively associated with weight gain; effect stronger in obese	Adjusted for age, sex, baseline weight, ethnicity, smoking
Schwartz 1995 ⁴³	97	34	25	M/F Pima Indians	M	3	M	M associated with weight gain	Adjusted for age, sex, baseline weight, Si
Sigal 1997 ⁴⁴	107	25	33	M/F Offspring of type 2 diabetes patients	Si, FI	16.7	Si, FI	Si associated with weight gain; FI not associated with weight gain; high AIR _g and Si had the most weight gain	Adjusted for age, baseline weight, Si
Folsom 1998 (CARDIA) ⁴⁵	3636	25	25	M/F Caucasian or black	FI	7	FI	Not associated with weight gain	Adjusted for age, sex, race, baseline weight, smoking
Folsom 1998 (ARIC) ⁴⁵	11,179	27	54	M/F Caucasian or black	FI	6	FI	FI negatively associated with weight gain	Adjusted for age, sex, race, baseline weight, smoking
Lazarus 1998 ⁴⁸	376	27	62	M	FI	9	FI	FI associated with weight during first 3-year period; negatively associated with weight during second 3-year period	No adjustments
Zavarani 1998 ⁵⁰	647	25	40	M/F	OGTT-INS ₁₂₀	14	OGTT-INS ₁₂₀	Not associated with weight gain	No adjustments; menopause confounding results
Gould 1999 ⁵⁹	767	25	53	M/F Caucasian	FI, OGTT-INS ₁₂₀	4.4	FI, OGTT-INS ₁₂₀	FI, OGTT-INS ₁₂₀ not associated with weight gain	
Weyer 2000 ¹⁰	151	NR (mean weight 94 kg)	26	M/F Pima Indians	M	2.6	M	M associated with weight gain	
Wedick 2001 ⁴⁶	725	25	65	M/F Caucasian	FI, HOMA-IR	8	FI, HOMA-IR	FI/HOMA-IR associated with weight loss	Adjusted for age, baseline weight
Mayer-Davis 2003 ⁴⁹	554	27	30–69	M/F Caucasian, black, or Hispanic	FI, Si	5	FI, Si	FI, Si not associated with weight gain	Adjusted for age, sex, race, energy intake, alcohol, physical activity, smoking, baseline weight, demographics, behavior change
Mosca 2004 ⁵⁶	782	25	51	M/F Caucasian or Hispanic	QUICKI	11	QUICKI	QUICKI with high fat consumption associated with weight gain	Adjusted for age, sex, race, alcohol, physical activity, baseline weight, energy intake
Howard 2004 ⁴⁷	3389	27	62	F Postmenopausal, multiple ethnicities	FI, HOMA-IR	3	FI, HOMA-IR	FI, HOMA-IR associated with weight in lean women; negatively associated with weight in obese women	Adjusted for age, baseline BMI, physical activity, energy intake; latter two not associated with weight change
Silver 2006 ⁵²	N = 105	23	28	M/F	Si	26	Si	Si not associated with weight gain	Adjusted for age, sex; weight self-reported

*See Table 1 for a description of indices of insulin sensitivity.

AIR_g, acute insulin response to glucose; BMI, body mass index; FI, fasting insulin; HOMA-IR, homeostasis model assessment-insulin resistance; INS₁₂₀, insulin level 2 hours after glucose loading; NR, not reported; OGTT, oral glucose tolerance test; QUICKI, quantitative insulin sensitivity check index; Si, insulin sensitivity.

loss. In a post hoc analysis of non-controlled, non-randomized weight loss trials in women, McLaughlin et al.⁵⁴ found no difference in weight loss in response to a hypocaloric diet when subjects were stratified by baseline insulin sensitivity. All subjects received a diet typical of the American diet (43% carbohydrate, 15% protein, 42% fat). In another weight loss study in women given a hypocaloric diet, those with central adiposity who had higher insulin resistance (and also higher insulin secretion) lost more weight compared with a group of woman with peripheral adiposity who had lower insulin resistance (and lower insulin secretion).⁵⁵

Insulin Sensitivity and Response to Hypocaloric Diets of Varying Macronutrient Composition

One observational study examined future weight in relation to the interaction between baseline insulin resistance and specific dietary composition.⁵⁶ In that study, after adjustment for a variety of factors including energy intake, those with high baseline insulin resistance showed more weight gain if they consumed a diet high in fat (>45% daily energy intake), an observation seen primarily in women.

In contrast, two intervention trials with a small number of subjects have reported that hypocaloric diets with lower GL may be more effective at promoting weight loss in individuals with higher insulin resistance at baseline.^{57,58} In a study by Baba et al.,⁵⁷ insulin-resistant (fasting insulin, 39 mU/L) obese men lost more weight when provided with a low-carbohydrate/high-protein diet vs. a high-carbohydrate/low-protein diet for 4 weeks. In the study by Cornier et al.,⁵⁸ a provided low-GL diet was more effective in women with more insulin resistance at baseline (based on higher fasting insulin), while a provided high-GL diet was more effective in those who were more insulin sensitive (based on lower fasting insulin). Self-reported energy intake and resting metabolic rate were the same in all four groups. Although the authors speculated that changes in other non-measured components of energy expenditure (feeding thermogenesis, greater physical activity, non-exercise activity thermogenesis, sleeping metabolic rate) may account for the differences, it is more likely that unreported differences in compliance were a contributing factor. Neither of these two studies adjusted for age, baseline weight, or other variables that may contribute to energy balance. Insulin resistance is usually associated with high insulin secretion; however, the interaction between insulin secretion status and diet was not examined in either of these studies.

In a recent trial by our laboratory, described in more detail below, baseline insulin resistance (by HOMA-IR) after adjustment for age, sex, and baseline weight, did

not predict weight loss in response to diets of varied GL.³⁵ However, although overweight, our participants were not particularly insulin resistant (mean fasting insulin 11.5 mU/L) and the study was small, so the absence of high insulin resistance at baseline may have not allowed us to detect an interaction between insulin resistance and dietary composition on weight loss. Further studies in this area are clearly needed.

INSULIN SECRETION AND WEIGHT

Only a few studies have examined the relationship between insulin secretion and weight (Table 3). In an observational study by Sigal et al.⁴⁴ of young adult offspring of two parents with type 2 diabetes, acute (first-phase) post-challenge hyperinsulinemia (as measured by acute insulin response to glucose, AIRg) was a predictor of future weight gain independent of age or baseline weight. The authors attempted to distinguish the effect of insulin sensitivity from that of insulin secretion (given their close correlation) by stratifying the cohort into four groups with respect to median values for insulin sensitivity and insulin secretion. The group with both high baseline AIRg and insulin sensitivity exhibited the most weight gain over time. The authors speculated that insulin sensitivity may play a permissive role for the effect of insulin hypersecretion on weight gain.⁴⁴ In other words, in this model, insulin hypersecretion would lead to weight gain only if a certain threshold of insulin sensitivity is reached. The combination of high insulin sensitivity and secretion is not common but may be important in relation to certain macronutrient compositions, as discussed later.

Two other studies found no association between AIRg and future weight.⁴⁹⁻⁵² One study of young individuals followed participants for 26 years, with weight being self-reported and no adjustment made for important confounders (physical activity, dietary composition, etc.).⁵² The other study in older individuals adjusted for a variety of potentially confounding variables including energy intake.⁴⁹ Since increased energy intake is one mechanism by which insulin hypersecretion may influence future weight, as discussed below, adjusting for energy intake may explain the null association in this study.

Two studies in Pima Indians provide conflicting results. The earlier study⁴³ found that elevated baseline insulin secretion (after either an oral or intravenous glucose challenge) was inversely correlated with weight gain 3 years later, after adjusting for insulin sensitivity (which was positively associated with future weight gain). However, in a more recent, larger study in Pima Indians,¹⁰ no association was seen between stimulated insulin release (as measured by AIRg) and future weight.

Table 3. Observational Studies Examining the Association Between Insulin Secretion Status and Future Weight Gain in Adults Without Diabetes

Study	Subject Characteristics			Follow-up (years)	Index of Insulin Secretion at Baseline (predictor variable)*		Association Between Index of Insulin Sensitivity and Outcome (weight)	Comments
	N	BMI (kg/m ²) mean or range	Age (y), mean or range		Other			
Schwartz 1995 ⁴³	97	34	25	3	M/F Pima Indians	MTT-INS _{AUC-4hr} OGTT-INS _{AUC-3hr} AIR _g	All measures negatively associated with weight gain	Adjusted for age, sex, baseline weight, Si
Sigal 1997 ⁴⁴	107	25	33	16.7	M/F Offspring of type 2 diabetes patients	AIR _g	AIR _g associated with weight gain	Adjusted for age, baseline weight, Si
Gould 1999 ⁵⁹	767	25	53	4.4	M/F Caucasian	OGTT-INS _{D30}	OGTT-INS _{D30} not associated with weight gain in males; OGTT-INS _{D30} negatively associated with weight gain in females > 50y AIR _g not associated with weight gain	No adjustments; menopause confounding results
Weyer 2000 ¹⁰	151	NR (mean weight 94 kg)	26	2.6	M/F Pima Indian	AIR _g		
Mayer-Davis 2003 ⁴⁹	554	27	30–69	5	M/F	AIR _g , DI	AIR _g , DI not associated with weight gain	Adjusted for age, sex, race, energy intake, alcohol, physical activity, smoking, base weight, demographics, behavior change
Silver 2006 ⁵²	105	23	28	26	M/F	AIR _g	AIR _g not associated with weight gain	Adjusted for age, sex; weight was self-reported

*See Table 1 for a description of the indices of insulin secretion.

AIR_g, acute insulin response to glucose; AUC, area under the curve; BMI, body mass index; DI, disposition index; INS, insulin; MTT, meal tolerance test; NR, not reported; OGTT, oral glucose tolerance test.

Gould et al.⁵⁹ also found a negative association between baseline insulin secretion (based on an oral glucose tolerance test) and future weight gain in Caucasians women over age 50 but not in younger women or men. The changes in body composition that occur during menopause and the lack of adjustment for hormone therapy and other variables may have confounded the results of this study.

Insulin Secretion and Response to Hypocaloric Diets

There has been very limited exploration of the effects of insulin secretion on weight loss response to hypocaloric diets in intervention trials (Table 4). Initial evidence for an important role of insulin secretion in energy balance and weight loss comes from pharmacologic studies in which insulin secretion was suppressed with pharmacologic agents and weight loss response assessed. In one such study, obese participants were all given a hypocaloric diet and then randomized to either placebo or diazoxide, a K^+ [ATP] channel agonist that decreases insulin secretion and is used in the medical management of insulinomas.⁶⁰ Compared with the placebo group, the diazoxide group lost more weight (4.6 vs. 9.5 kg, respectively) while on the hypocaloric diet, supporting an important role for insulin secretion in modifying weight loss in response to caloric restriction.

In another pharmacologic study in obese individuals, insulin secretion was suppressed by octreotide-LAR, a somatostatin analog used in various endocrine hypersecretory conditions, without a concomitant lifestyle intervention.⁶¹ For the entire cohort, significant insulin suppression was achieved with accompanied weight loss and decreased self-reported carbohydrate craving. In a post hoc analysis, participants who lost the most weight exhibited the highest suppression in pancreatic beta-cell activity and the highest reduction in carbohydrate cravings and intake. During the baseline oral glucose tolerance test, this group exhibited a rapid increase and a high peak in insulin level, followed by a rapid decline, suggesting that first-phase insulin hypersecretion (first 30 min) may be particularly important. Although insulin-independent effects of octreotide cannot be ruled out (such as effects on incretins, gastric motility, etc.), the results of this pharmacologic study, which was done without an accompanied caloric restriction prescription, provide further support for an important role of insulin hypersecretion in the genesis of obesity.

There are other types of data that are broadly consistent with the hypothesis that insulin secretion status influences weight loss. In a study of women given a hypocaloric diet for weight loss, those with central adiposity who also had higher insulin secretion and higher

insulin resistance lost more weight compared with a group of woman with peripheral adiposity who had lower insulin secretion and lower insulin resistance.⁵⁵ In contrast, in a post hoc analysis of a non-randomized, non-controlled, short-term intervention study in women given a hypocaloric diet (43% carbohydrate, 15% protein, and 42% fat), the baseline integrated insulin response (as measured by the meal tolerance test, $MTT-INS_{AUC-8hr}$) to two consecutive meal challenges did not predict weight loss in response to the diet.⁵⁴ However, this study was small ($N = 20$) and no adjustments were made for other important factors such as menopausal status.

In summary, the contribution of insulin secretion to future weight and response to hypocaloric diets, including those that vary in macronutrient composition, is controversial and its effects are difficult to isolate from insulin resistance. However, baseline insulin secretion status may be important with regard to dietary macronutrient composition, as discussed below.

INSULIN SECRETION AND RESPONSE TO HYPOCALORIC DIETS OF VARYING MACRONUTRIENT COMPOSITION

Although the topic of whether insulin secretion affects the ability of overweight individuals to lose weight in response to a non-specific hypocaloric diet is a new and important area for study, the influence of insulin hypersecretion in modulating weight loss may be particularly important for specific dietary compositions, in particular diets that differ in GL.^{29,62} This hypothesis is suggested by animal studies^{63,64} and results from a recent human study in our laboratory.³⁵

As described above, weight loss studies with varied macronutrient composition, including those using the concept of the dietary GL, have shown conflicting results for heterogeneous groups of individuals.^{31,32,34,37,65-67} As a result, currently there is no general consensus about the relative benefits or disadvantages of these types of diets for weight loss in the general population. However, our new findings³⁵ may provide an explanation for the conflicting results seen in human studies of weight loss utilizing a variety of macronutrient compositions, since none of these studies examined the effects of the different diets stratified by baseline insulin secretion or other measures of metabolic status.

We recently completed a small, randomized, double-blind, controlled feeding trial in healthy overweight adults to examine the weight loss effects of two hypocaloric diets differing in GL. Participants were randomized for 24 weeks to a provided diet with either a high GL (60% carbohydrate, 20% protein, 20% fat, fiber 15 g/1000 kcal, mean estimated daily GI of 86 and GL of 116 g/1000 kcals) or a low GL (40% carbohydrate, 30%

Table 4. Weight Loss Intervention Studies That Have Examined the Interaction between Glucose-Insulin Dynamics Status and Weight in Adults Without Diabetes

Study	Subject Characteristics			Type of Study	Duration (weeks)	Predictor of Metabolic Profile*	Study Arms and Intervention		Outcome: Weight (kg)	Comments
	BMI (kg/m ²) mean or range	Age (y) mean or range	Other							
Casimirri 1998 ⁵⁵	34	41	F	No control	16	OGTT, FI	1. Higher FI and OGTT-INS, <i>n</i> = 10 2. Lower FI and OGTT-INS, <i>n</i> = 10 All subjects received hypocaloric diet (20% protein, 30% fat, 50% carbohydrate)		-13 -8.6	No changes in energy intake!
Alemzadeh 1998 ⁶⁰	41	30	M/F	RCT	8	AIR _g	1. Diazoxide (lower AIR _g), <i>n</i> = 12 2. Placebo (higher AIR _g), <i>n</i> = 12 All subjects received hypocaloric diet (Optifast)		-9.5 -4.6	No changes in REE; no changes in carbohydrate/fat oxidation; no adjustments
Baba 1999 ⁵⁷	35	NR	M FI > 25 mU/L	RCT	4	FI	1. LC/HP, <i>n</i> = 7 2. HC/LP, <i>n</i> = 6 Hypocaloric diet (80% REE) provided to all subjects		-8.3 -6.0	No comparison group with lower FI (higher insulin sensitivity); no adjustments
McLaughlin 1999 ⁵⁴	31	42	F	No control post hoc	8	MTT-INS _{AUC-8hr} M	1. IR and high INS _{AUC-8hr} , <i>n</i> = 10 2. IS and low INS _{AUC-8hr} , <i>n</i> = 10 Hypocaloric diet (liquid formula) provided to all subjects		-9.3 -9.1	Only diet successes were followed; no adjustments
Velasquez-Mieyer 2003 ⁶¹	44	39	M/F	No control post hoc	24	OGTT-CIRgp	All subjects received Octreotide-LAR monthly, <i>n</i> = 44 all subjects		-3.6	Post-hoc: Those with more weight loss had higher insulin suppression and less carbohydrate craving and intake; no lifestyle intervention prescribed; high responders had higher BMI at baseline; no adjustments
Cornier 2005 ⁵⁸	30-35	23-53	F	RCT	16	FI	1. IS (FI < 10) HC/LF diet, <i>n</i> = 6 2. IS (FI < 10) LC/HF diet, <i>n</i> = 6 3. IR (FI > 15) HC/LF diet, <i>n</i> = 4 4. IR (FI > 15) LC/HF diet, <i>n</i> = 5 All subjects provided with hypocaloric diet (400 kcal deficit)		-13.5 -6.8 -8.5 -13.4	Self-reported energy intake; RMR did not change among 4 groups; no adjustments
Pittas 2005 ⁵⁵			M/F	RCT	24	INS ₃₀ , HOMA-IR	1. Low INS ₃₀ HG diet, <i>n</i> = 8 2. Low INS ₃₀ LG diet, <i>n</i> = 8 3. High INS ₃₀ HG diet, <i>n</i> = 8 4. High INS ₃₀ LG diet, <i>n</i> = 8 All subjects provided with hypocaloric HG or LG diet (70% of TEE)		-8 -5.3 -6.2 -10	No adjustments for physical activity

*See Table 1 for a description of indices of insulin sensitivity or insulin secretion.

AIR_g, BMI, body mass index; CIR_{gp}, corrected insulin response at glucose peak; FI, fasting insulin; LC, low carbohydrate; HC, high carbohydrate; HF, high fat; HG, high glycemic load; HOMA-IR, homeostasis model assessment-insulin resistance; INS₃₀, insulin level 30 minutes after glucose loading; IR, insulin-resistant; IS, insulin-sensitive; LF, low fat; LG, low glycemic load; OGTT, oral glucose tolerance test; RCT, randomized placebo controlled trial; RMR, resting metabolic rate.

protein, 30% fat, fiber 15 g/1000 kcal, mean estimated daily GI of 53 and GL of 45 g/1000 kcal) at 30% calorie restriction compared with baseline individual energy needs. In a post hoc multivariate prediction analysis, we examined whether the weight loss effects of the two diets varied according to baseline insulin secretion and insulin resistance. Simple indices of insulin secretion, insulin level 30 minutes after glucose loading (INS₃₀) and homeostasis model assessment-insulin resistance (HOMA-IR) were examined for their ability to predict change in weight from baseline to 6 months. A total of 32 (25 women and 7 men) out of 34 enrolled participants completed the 6-month intervention. At baseline, mean fasting glucose was 84 mg/dL and insulin was 11.5 mU/L. Both groups achieved statistically significant ($P < 0.001$) weight loss compared with their baseline weight. Adjusted for baseline weight and other baseline variables, weight loss was equivalent in the two groups both at 3 and 6 months.

In multivariate prediction models, there was no diet \times HOMA-IR interaction, but there was a diet \times INS₃₀ interaction ($P = 0.02$). Therefore, we examined the weight data stratified into two groups separated by the median INS₃₀ value (Figure 1). Participants with relatively high baseline INS₃₀ lost more weight if randomized to the low-GL diet compared with the high-GL diet ($P < 0.05$). In participants with relatively low baseline INS₃₀, those in the high-GL diet group lost more weight than those in the low-GL diet group, but the difference was not statistically significant. We concluded that in healthy overweight individuals examined without

respect to their baseline metabolic profile, calorie-restricted diets of varying GL result in equivalent weight loss. However, based on the multivariate analysis, a calorie-restricted diet low in GL led to more weight loss in those who had relatively higher stimulated insulin secretion at baseline.³⁵

Our participants were not particularly insulin resistant, and therefore the lack of relative insulin resistance in those with high insulin release may have predisposed this group of individuals to weight gain. This was suggested by the data from Sigal et al.,⁴⁴ and was reversed by a low-GL diet. However, because of our small number of participants, we were unable to test the hypothesis that insulin sensitivity plays a permissive role, so further research in this area is needed.

MECHANISMS LINKING INSULIN DYNAMICS, WEIGHT, AND DIETARY COMPOSITION

Insulin is a primary hormonal mediator of energy balance and storage, with multiple effects on the periphery (muscle, liver, and adipose tissue) and central nervous system (CNS). Therefore, changes in the insulin axes have been proposed as having an important role in the dysregulation of energy balance leading to obesity, although the exact mechanisms are far from clear.

In the periphery, insulin secreted after a meal acts as an anabolic hormone, promoting fuel storage and favoring weight gain. From an evolutionary point of view, insulin hypersecretion in response to a meal may have conferred a survival advantage by increasing the efficiency of energy storage in adipose tissue (the “thrifty genotype hypothesis”).⁶⁸ In our society, where food is readily available, this characteristic may lead to excessive weight gain and fat accumulation. This hypothesis is in accord with studies that found an association between insulin secretion and weight gain,^{44,69,70} although not all studies have found this association.^{10,49,52}

Evidence of an association between insulin hypersecretion and weight gain comes from medical conditions such as insulinomas, which are pancreatic beta cell tumors that secrete excessive insulin independent of blood glucose concentration. Patients with insulinomas report hyperphagia and significant weight gain.⁷¹ Additional evidence comes from iatrogenic insulin hypersecretion in patients with type 2 diabetes treated with insulin secretagogues, which leads to weight gain and fat accumulation.^{72,73}

A mechanism that can explain the association between insulin hypersecretion, especially post-challenge hyperinsulinemia, and future weight gain is the development of hypoglycemia (absolute or relative) in the post-absorptive period, which produces a pattern of increased hunger, frequent snacking, and increased energy in-

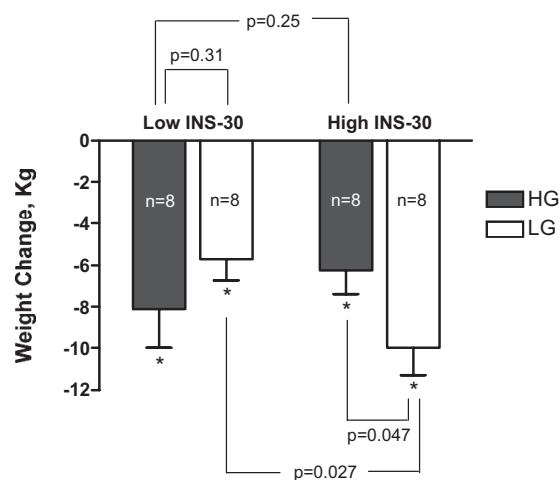


Figure 1. Mean (SEM) weight change during a 6-month feeding study of a high- (HG) vs. a low- (LG) glycemic load diet in overweight adults stratified by baseline insulin secretion based on serum insulin at 30 minutes after a 75 g oral glucose tolerance test. Low INS-30, <473 pmol/L (66 mU/L); High INS-30, >473 pmol/L. P values are adjusted for baseline weight. * $P < 0.005$ for within-group change in weight from baseline. From Pittas et al., 2005³⁵; used with permission.

take.⁷⁴⁻⁷⁸ This is thought to be the primary cause of weight gain in medical or iatrogenic conditions associated with insulin hypersecretion,⁷¹⁻⁷³ although variations in glycemia within the normal physiologic range are probably only one of several factors in overall energy regulation.^{76,79} However, there is also evidence to suggest that relative hypoglycemia contributes to increased energy intake in healthy, non-obese individuals.⁷⁶

There are also animal⁸⁰ and human⁸¹ data suggesting that acute hypersecretion of insulin may increase hunger without the intermediate step of hypoglycemia. In a rat model of obesity, lesions in the ventromedial hypothalamus cause excessive insulin secretion, hyperphagia, and weight gain, all of which are blocked by pancreatic vagotomy.⁸²⁻⁸⁴ In healthy human subjects, short-term infusion of insulin induces hunger, carbohydrate cravings, and hyperphagia, which are unrelated to changes in blood glucose concentration.^{85 81}

Insulin is also known to have a centrally mediated effect on food intake and body weight regulation, with higher insulin levels in the CNS associated with reduced appetite and caloric intake, causing weight loss.⁸⁶⁻⁸⁹ In this case, the central (catabolic) effects of insulin apparently attempt to counteract its peripheral (anabolic) effects that would favor weight gain. Which specific effects of insulin predominate, the central or peripheral, is not clear. In observational studies, younger age and lower weight (both associated with increased insulin sensitivity) are associated with weight gain, while older age and higher weight (both associated with insulin resistance) are associated with attenuation of weight gain or weight loss.^{10,41,44,46,47,51,69} It is possible that the peripheral effects of insulin may be more pronounced when the individual is leaner and younger, when energy storage is needed, while the central effects of insulin may be more pronounced when insulin resistance and the accompanied hyperinsulinemia develop in association with aging and obesity.

The association of insulin resistance with less future weight gain seen in certain studies^{10,40-47} may therefore be explained by a negative feedback loop in which as weight increases, insulin resistance rises, which leads to persistently elevated circulating insulin levels, which in turn slows down the rate of weight gain via insulin's central effects. Increased circulating insulin levels during insulin resistance signal satiety to the CNS, thereby limiting food intake and decreasing insulin levels during weight loss, thus reducing satiety and promoting weight gain. The development of insulin resistance may also have peripheral effects that lead to decreased carbohydrate oxidation, which would, in turn, increase fat oxidation limiting fat storage and leading to weight loss or attenuation of weight gain.^{40,88} Therefore, the development of insulin resistance and consequent hyperinsulin-

emia can be seen as physiologic adaptations to obesity that attenuate further weight gain via the effects of insulin in the CNS and periphery to maintain stable weight.^{88,90,91}

Insulin Sensitivity vs. Insulin Secretion

The inconsistency seen among studies of insulin dynamics and future weight may, at least in part, be due to the difficulty in isolating insulin sensitivity from insulin secretion, as these two measures are closely and inversely correlated.^{40,43} Namely, it is difficult to determine whether the hyperinsulinemia (fasting or postprandial) seen in obese individuals is due to excessive and inappropriate insulin secretion or if it constitutes an appropriate (compensatory) response to increased insulin resistance necessary for maintaining euglycemia. Indeed, a positive association between insulin sensitivity and future weight gain was seen in Pima Indians, but the association was attenuated after adjusting for baseline insulin secretion (which is low in insulin-sensitive individuals).⁴³

Fasting vs. Post-Prandial Insulin Secretion

A distinction should also be made between prevailing hyperinsulinemia (measured during fasting) and post-challenge insulin secretion. Insulin hypersecretion in response to a meal, which is short-lived, may have a predominant peripheral anabolic effect that would favor weight gain. On the other hand, chronic hyperinsulinemia, which reflects insulin resistance, may have a predominant effect on the brain to decrease appetite and lower food intake,^{87,88} which may counteract the peripheral anabolic effects of the acute burst of insulin secretion that would favor weight gain. In other words, the acute effect of insulin hypersecretion may be different from the chronic persistent hyperinsulinemia that develops in obese individuals and in genetically predisposed individuals such as Pima Indians.^{40,43} There is also evidence that first-phase insulin secretion may be more important than second-phase or persistent hyperinsulinemia.^{44,61}

Interaction Between Insulin Secretion and Insulin Sensitivity

Insulin sensitivity and secretion may also interact with each other to influence weight, as shown in the study by Sigal et al.,⁴⁴ in which those with high insulin secretion and insulin sensitivity gained the most weight. The net effect on weight depends on whether insulin secretion is an appropriate response to insulin resistance. In that case, the hyperinsulinemia may serve as an

adaptation to weight maintenance. But if insulin hypersecretion is excessive in relation to insulin resistance, then insulin hypersecretion may promote weight gain via its actions as an anabolic hormone, promoting lipid and carbohydrate storage in peripheral tissues. Therefore, acute hyperinsulinemic response may be an early determinant of obesity but only in the context of normal or increased insulin sensitivity (i.e., inappropriate for the degree of insulin sensitivity). This observation may also explain the result seen in Pima Indians, a population with high insulin resistance that may not be characteristic of the population at large, where insulin release was negatively associated with weight gain.⁴³

While the combination of increased insulin secretion and sensitivity is probably uncommon, this combination may be more prevalent in individuals who consume a high-GL diet. If an individual is genetically insulin sensitive and predisposed to insulin hypersecretion, then high-GL diets are likely to promote insulin secretion, leading to fuel storage via insulin's anabolic action.

INSULIN DYNAMICS AND HIGH-GL DIETS

Although baseline insulin dynamics may play a subtle role in energy regulation and the pathogenesis of obesity, the insulin axis may become quantitatively more important in the setting of varied macronutrient dietary composition, especially by diets that vary in GL.

Hypersecretion of insulin in response to a high-GL diet has been proposed as one mechanism for the weight gain seen in rats fed a high-GI diet.⁶³ A high-GL diet appears to elicit short-term metabolic responses, including an increase in post-prandial insulin concentration. Post-challenge insulin secretion, which is a significant contributor to high circulating insulin levels in obese persons, favors fatty acid uptake, inhibits lipolysis, and favors energy storage, all mechanisms leading to weight gain. Therefore, it is possible that recurrent insulin hypersecretion induced by chronic exposure to high-GL diets may play a role in the pathogenesis of obesity in susceptible individuals (those with high insulin secretion).

In addition to post-prandial relative hyperinsulinemia and post-absorptive relative hypoglycemia, high-GL diets may also lead to other post-prandial metabolic changes, including an increase in counterregulatory hormones (cortisol, glucagon, growth hormone), which may further contribute to hunger and increased energy intake in the post-absorptive period.⁹² All of these mechanisms may be exacerbated in individuals with high insulin secretory capacity at baseline, which could make them more susceptible to weight gain upon exposure to a high-GL diet. If this hypothesis holds true, then a low-GL diet in predisposed individuals may prove

beneficial by decreasing insulin excursion and breaking the vicious cycle. This is in accord with both animal data⁶⁴ and the results of our study,³⁵ as we found that healthy overweight adults with relatively high rates of insulin secretion during a standard oral glucose tolerance test lost significantly more weight when assigned to a low-GL diet than a high-GL diet.

Observational vs. Intervention Studies

It is important to note that, in relation to how metabolic profile influences weight, there are differences between short vs. long-term follow-up periods and between active weight loss vs. maintenance of weight loss. The baseline insulin dynamics may influence short-term future weight and weight loss during the active phase of lifestyle changes. However, long-term energy balance and weight maintenance may be further influenced by the change in insulin dynamics, other metabolic variables, and of course lifestyle factors. Weight loss leads to improvements in insulin sensitivity, which in turn affects insulin release, and these changes may be permissive or resist further weight loss. Yost et al.⁹³ reported that improvement in insulin sensitivity with weight loss predicts future weight gain during the maintenance period. This also needs to be taken into consideration in future studies. For example, re-characterization of the metabolic profile at the beginning of the weight maintenance phase may be needed to examine how the changed metabolic profile influences weight maintenance. One may speculate that, after attaining weight loss with a specific macronutrient composition, to achieve weight maintenance, dietary composition may need to change over time to accommodate the changing metabolic profile.

CONCLUSION

Current dietary guidelines recommend a spectrum of dietary composition for the general population, but emerging evidence suggests that specific dietary compositions may work better for identifiable groups of overweight/obese individuals based on their insulin dynamics. In particular, subject-specific insulin secretion status and perhaps insulin sensitivity may interact with diets that vary in glycemic load to influence the weight loss response to a hypocaloric diet. Appropriately powered clinical studies and, ultimately, randomized controlled trials of dietary composition and weight loss in participants with varied insulin sensitivity and insulin secretion are needed to further clarify the role of individualizing dietary prescriptions in long-term weight control.

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