Insulin Sensitivity Determines the Effectiveness of Dietary Macronutrient Composition on Weight Loss in Obese Women

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Abstract

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Objective: To determine whether macronutrient composition of a hypocaloric diet can enhance its effectiveness and whether insulin sensitivity (Si) affects the response to hypocaloric diets.

Research Methods and Procedures: Obese nondiabetic insulin-sensitive (fasting insulin < 10 μU/mL; n = 12) and obese nondiabetic insulin-resistant (fasting insulin > 15 μU/mL; n = 9) women (23 to 53 years old) were randomized to either a high carbohydrate (CHO) (HC)/low fat (LF) (60% CHO, 20% fat) or low CHO (LC)/high fat (HF) (40% CHO, 40% fat) hypocaloric diet. Primary outcome measures after a 16-week dietary intervention were: changes in body weight (BW), Si, resting metabolic rate, and fasting lipids.

Results: Insulin-sensitive women on the HC/LF diet lost 13.5 $\pm$ 1.2% ($p < 0.001$) of their initial BW, whereas those on the LC/HF diet lost 6.8 $\pm$ 1.2% ($p < 0.001$; $p < 0.002$ between the groups). In contrast, among the insulin-resistant women, those on the LC/HF diet lost 13.4 $\pm$ 1.3% ($p < 0.001$) of their initial BW as compared with 8.5 $\pm$ 1.4% ($p < 0.001$) lost by those on the HC/LF diet ($p < 0.04$ between two groups). These differences could not be explained by changes in resting metabolic rate, activity, or intake. Overall, changes in Si were associated with the degree of weight loss ($r = -0.57$, $p < 0.05$).

Discussion: The state of Si determines the effectiveness of macronutrient composition of hypocaloric diets in obese women. For maximal benefit, the macronutrient composition of a hypocaloric diet may need to be adjusted to correspond to the state of Si.

Key words: CHO, fat, insulin resistance

Introduction

Successful dietary interventions are based on a significant reduction in caloric intake, relative to energy expenditure (1). The question of whether the macronutrient composition of hypocaloric diets has an impact on the effectiveness of these diets, however, has gained substantial interest with the popularization of low-carbohydrate (CHO)[1] (LC), hypocaloric dietary regimens (2–11).

Total body insulin sensitivity (Si) is an overall measure of the ability of insulin to regulate glucose uptake and metabolism (12,13). Insulin-resistant (IR) individuals require higher than normal levels of insulinemia to maintain normal glycemia. Thus, either fasting or postprandial hyperinsulinemia prevents the development of impaired glucose toler-

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[1] Nonstandard abbreviations: CHO, carbohydrate; LC, low CHO; Si, insulin sensitivity; IR, insulin resistant; IS, insulin sensitive; HC, high CHO; LF, low fat; HF, high fat; BW, body weight; GCRC, General Clinical Research Center; RMR, resting metabolic rate; RQ, respiratory quotient; FFA, free fatty acid; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

ance or diabetes until an insulin secretory defect becomes apparent (14). The magnitude of insulin resistance, however, varies widely among obese and nonobese individuals (15–17). In addition, very few studies have prospectively examined the impact of the state of Si (or insulin resistance) on weight loss in general (18–20), and none has explored the possibility that the state of Si might affect individual responses to macronutrient composition of the hypocaloric diet.

To examine this possibility, we put forth a working hypothesis that macronutrient composition of a hypocaloric diet (daily deficit of 400 kcal) might be an important variable in the effectiveness of this diet in individuals with differing levels of Si. Furthermore, we hypothesized that if in the insulin-sensitive (IS) individuals, insulin promotes better use of dietary CHOs, perhaps through increased dietary induced and/or cellular thermogenesis compared with the IR individuals, we might observe a greater weight loss in the IS group on a high-CHO (HC) hypocaloric diet. In contrast, IR individuals might display a lesser response to an HC diet and respond better to an LC hypocaloric diet.

The present study was designed to examine this hypothesis. Obese nondiabetic women were recruited to participate in this study and were segregated into IS or IR groups based on their fasting insulinemia. Subjects in each group were randomized to receive either an HC/low-fat (LF) or an LC/high-fat (HF) energy-matched hypocaloric diet for 16 weeks. Primary outcome variables included changes body weight (BW) as well as changes in Si and lipids. Energy intake and resting energy expenditure were measured before and after the dietary intervention to assess the mechanism of weight loss under these experimental conditions.

Research Methods and Procedures

Forty-four obese, healthy normoglycemic women 23 to 53 years old with BMI of 30 to 35 kg/m^2 were screened, and 21 of them were enrolled and completed the 16-week intervention. Subjects were included in the study if they were IS as determined by a fasting insulin level of <10 μU/mL ($N = 12$) or IR as determined by a fasting insulin level of >15 μU/mL ($N = 9$). Individuals with intermediate levels of fasting insulin were excluded. The study was approved by the Colorado Multiple Institutional Review Board, and all subjects gave informed consent.

Subjects were first placed on a standard control diet (55% CHO, 30% fat, and 15% protein) for 3 days and were admitted to the General Clinical Research Center (GCRC) at the University of Colorado Hospital the evening before the baseline assessment. After an overnight fast, they underwent resting metabolic rate (RMR) and respiratory quotient (RQ) measurements by indirect calorimetry using the 2900 metabolic cart (SensorMedics, VIASYS Healthcare, Conshohocken, PA). Blood was sampled for baseline assessments, and subjects underwent an insulin modified intravenous glucose tolerance test to measure Si (13,21). Within a week of these studies, subjects underwent body composition measurement by DXA using the model DPX whole-body scanner (Lunar Radiation Corp., Madison, WI).

Subjects from both groups were then randomized to receive a hypocaloric diet (400 kcal deficit/d) comprised of either 60% CHO, 20% fat, and 20% protein (HC/LF) or 40% CHO, 40% fat, and 20% protein (LC/HF) for the following 16 weeks. Estimates of daily energy intake were made using 3-day food diary, 3-day control diet, and baseline RMR plus an activity factor. The polyunsaturated to monounsaturated to saturated fatty acid ratio (1:1:1) and fiber and cholesterol content of the diets were identical in both diets. All food was prepared and provided by the GCRC kitchen. (Sample menus can be provided on request.) Participants picked up their diet every 3 days but ate the majority of the food at home. The subjects were otherwise free-living and were expected not to consume food outside of the diet but could have eaten food in addition to or other than the diet. Subjects were asked to maintain their usual activity pattern and were regularly questioned regarding activity. Once a week, subjects were weighed and met with a dietitian to determine compliance. After 16 weeks of dietary intervention, subjects were readmitted to the GCRC for final assessments. These assessments were identical to the baseline assessments described above. Baseline and final assessments included blood for insulin, glucose, free fatty acids (FFAs), leptin, total cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglycerides.

Sample size determination was performed using data from McLaughlin et al. (18) examining the effects of baseline Si on weight loss in obese women. A sample size of four to six subjects per group would be able to detect a 3- to 4-kg difference at a power of 0.80 and α of 0.05. The descriptive data are presented as mean $\pm$ SD as per convention, and all other data are presented in graphical form as the mean $\pm$ SE. The data for change in BW were calculated as the BW at the baseline visit minus the BW after 16 weeks of hypocaloric diet and are expressed as absolute BW change in kilograms or as a percentage change from baseline. Statistical analysis was performed with SigmaStat statistical software (Jandel Scientific, San Rafael, CA). Significance tests were two-sided with significance set at level 0.05. Change in BW was the primary outcome analyzed. Two-way ANOVA was performed to compare baseline characteristics between groups (IS vs. IR, LF diet vs. HF diet). The relationships among the different baseline measures of Si [fasting insulin, homeostasis model assessment (22), quantitative insulin-sensitivity check index (23), and Si] were examined using the Pearson Product Correlation. A three-way repeated measures ANOVA with change in BW as the outcome variable was used. Repeated measures ANOVA were also used to examine changes in Si, insulin,

Table 1. Baseline subject characteristics (mean ± SD)

	Insulin sensitive		Insulin resistant	
	HC/LF ($N = 6$)	LC/HF ($N = 6$)	HC/LF ($N = 4$)	LC/HF ($N = 5$)
Age (years)	43.5 ± 8.9	41.3 ± 8.9	36.8 ± 8.9	43.6 ± 8.9
Body weight (kg)	83.4 ± 4.6	92.2 ± 11.5	86.7 ± 7.4	82.5 ± 9.4
BMI (kg/m^2)	30.8 ± 1.3	33.1 ± 1.7	33.0 ± 3.0	32.2 ± 1.8
Body fat (%)	46.5 ± 3.3	45.9 ± 1.9	50.0 ± 1.0	47.8 ± 5.0
Insulin (μU/mL)	7.17 ± 1.72	7.00 ± 1.41	20.8 ± 3.86*	18.40 ± 3.51*
Glucose (mg/dL)	86.8 ± 6.91	90.2 ± 1.33	90.0 ± 5.48	85.4 ± 8.02
HOMA	1.52 ± 0.38	1.54 ± 0.30	4.53 ± 0.61*	3.83 ± 0.74*
QUICKI	0.36 ± 0.02	0.36 ± 0.01	0.31 ± 0.01*	0.31 ± 0.01*
Si	5.83 ± 4.52	4.41 ± 2.22	3.04 ± 1.64†	1.83 ± 1.21†
Total cholesterol (mg/dL)	210 ± 54	184 ± 38	152 ± 36	198 ± 40
HDL-cholesterol (mg/dL)	59 ± 8.8	47 ± 9.3	32 ± 6.13	42 ± 12.6
LDL-cholesterol (mg/dL)	124 ± 30	110 ± 34	98 ± 29	121 ± 27
Triglycerides (mg/dL)	136 ± 104	132 ± 48	124 ± 23	173 ± 86
Free fatty acids (μEq/L)	858 ± 270	659 ± 85	691 ± 83	836 ± 164
Leptin (ng/mL)	26.1 ± 11.9	30.8 ± 10.8	28.4 ± 12.7	37.4 ± 21.7

HOMA, homeostasis model assessment; QUICKI, quantitative insulin-sensitivity check index; Si, insulin sensitivity; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
* $p < 0.001$ between insulin-sensitive and -resistant groups; † $p < 0.05$ between insulin-sensitive and -resistant groups.

lipids, fatty acids, leptin, and RMR. Finally, the relationship between the changes in BW and changes in Si were examined using the Pearson Product Correlation.

Results

Subject Characteristics

Subject characteristics are summarized in Table 1. BW, BMI, percentage body fat, RMR, and RQ were similar in all groups. The IR group displayed significantly greater fasting insulin concentrations than the IS group ($p < 0.05$), in agreement with the selection criteria. In addition, the IR group had a significantly lower quantitative insulin-sensitivity check index (23) score and Si index and a significantly greater homeostasis model assessment (21) score than the IS group (Table 1). The baseline levels of lipids, FFAs, and leptin were not significantly different among the groups.

Impact of Hypocaloric Diets on Weight Loss

As seen in Figure 1, 16 weeks of hypocaloric diet resulted in weight loss in all individuals, supporting a well-established concept that low caloric intake produces weight loss. The participants were subjected to 400 kcal deficit/d, which translates to a total energy deficit of 44,800 kcal over the study. Using previously published data, 1 kg of weight loss translates into an energy deficit of ~7300 kcal in women (24). Thus, we anticipated a weight loss of ~6.1 kg (44,800 kcal deficit × 1 kg weight loss/7300 kcal deficit). There was no significant difference between this theoretical weight loss and the actual weight loss in the groups that lost lesser weight (i.e., the IR on the LF/HC and the IS on the LC/HF, p for comparisons of 0.151 and 0.429 respectively). Those groups that lost more weight (i.e., IR individuals on the LC/HF diet and the IS individuals on the HC/LF diet) lost significantly more than this theoretical weight ($p = 0.002$ and 0.004, respectively) (Figure 1, A and B). Among the IR individuals, those randomized to the LC/HF hypocaloric diet lost 13.4 ± 1.3% (11.1 ± 1.1 kg) of their initial BW as compared with 8.5 ± 1.4% (7.4 ± 1.0 kg) lost in those randomized to the HC/LF hypocaloric diet ($p = 0.02$ for diet effect within the IR group). In contrast, IS individuals randomized to the HC/LF hypocaloric diet lost 13.5 ± 1.2% (11.3 ± 1.0 kg) of their initial BW, whereas those randomized to the LC/HF hypocaloric diet lost 6.8 ± 1.2% (6.2 ± 1.0 kg) of their initial weight ($p < 0.001$ for diet effect within the IS group). In addition, among individuals randomized to the LC/HF diet, those identified as being IR lost significantly more weight than those identified as IS ($p = 0.001$). In contrast, individuals randomized to the HC/LF

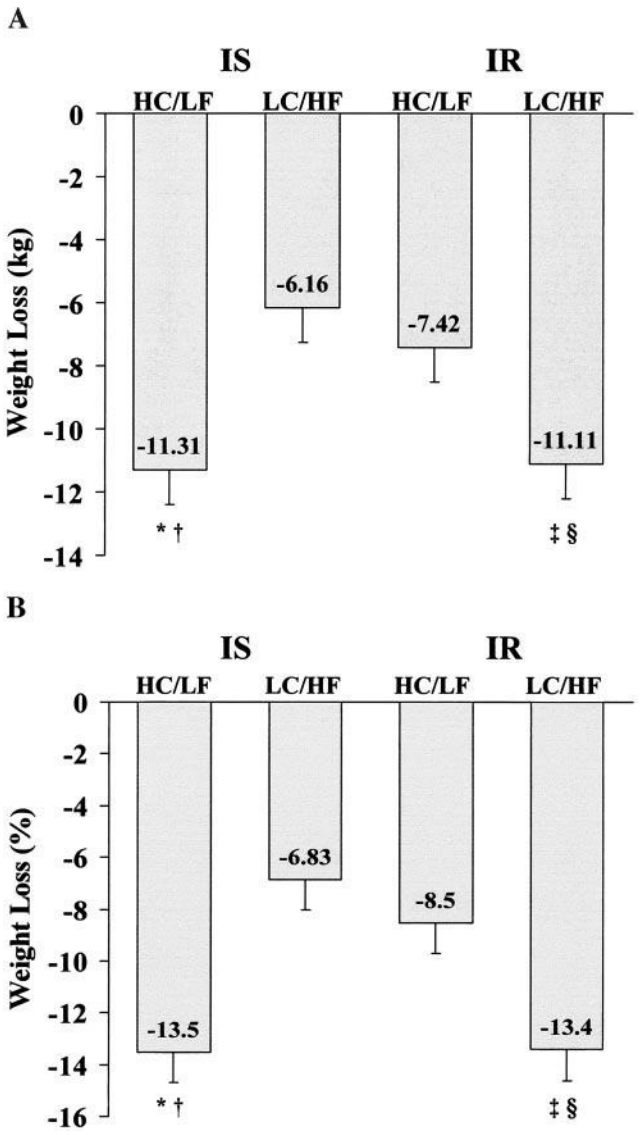

Figure 1: Absolute (A) and percentage (B) change in BW in IS and IR women randomized to 16 weeks of hypocaloric HC/LF or LC/HF diet. (*) $p < 0.01$ for diet effect within IS group. (†) $p < 0.05$ for Si effect within HC/LF diet. (‡) $p < 0.05$ for diet effect within IR group. (§) $p < 0.01$ for Si effect within LC/HF diet.

diet lost significantly more weight if they were identified at baseline to be IS as opposed to IR ($p = 0.01$).

Impact of Weight Loss on Metabolic Profile

Fasting insulinemia improved in both IS and IR groups (IS, 7.08 ± 1.26 to 5.42 ± 0.82 μU/mL, $p = 0.008$; IR, 19.57 ± 0.89 to 8.84 ± 0.95 μU/mL, $p < 0.001$) with a significantly greater improvement in the IR group ($p < 0.001$). Similarly, although the mean Si did not change in the IS patients (5.12 ± 0.83 to 4.16 ± 0.95, $p = 0.35$), this parameter improved substantially in the IR groups (3.04 ± 1.44 to 3.87 ± 1.20, $p = 0.028$; $p = 0.005$ for difference between Si groups), suggesting that weight loss in the IR patients improves their Si. Overall, the change in Si correlated with the degree of weight loss ($r = -0.57$, $p < 0.05$). Weight loss at the end of the 16-week intervention period had a favorable but not significant effect on total cholesterol, low-density lipoprotein (LDL) cholesterol, and HDL cholesterol in all groups (Table 2). Triglycerides also improved with weight reduction in all groups except for the IR group randomized to the HC/LF diet ($p = 0.003$). This group, in fact, demonstrated an increase in their triglyceride concentrations (from 124 ± 15 to 157 ± 10 mg/dl, $p < 0.05$). As predicted, leptin concentrations decreased in all groups with weight loss regardless of the macronutrient composition of the hypocaloric diet.

Measures of Energy Balance

IS subjects in the LC/HF group and IR subjects in the HC/LF group lost the expected amount of weight for the caloric deficit imposed (24). In contrast, IS individuals on HC/LF and IR patients on LC/HF hypocaloric diets lost almost twice the expected amount of weight (Figure 1). All subjects received all of their food from the GCRC. Careful and frequent dietary recalls revealed no detectable differences between the groups that lost the expected amount of weight and those that lost more weight. Thus, although we cannot definitively rule out differences in energy intake as the etiology for the differences in weight loss, differences in energy expenditure seem to be a more plausible explanation. We addressed the energy expenditure side of the equation only through self-report and RMR. Overall, when all subjects were pooled, RMR was found to be decreased (1304 ± 36 to 1221 ± 43 kcal/d, $p = 0.03$); however, there were no significant changes in RMR in any of the four groups when analyzed separately, and no group or diet interactions were found. Therefore, changes in RMR could not account for the weight loss differences observed.

Discussion

The salient feature of this investigation is that the state of Si profoundly influenced the response to a distinct macronutrient composition of hypocaloric diet. Moderately obese women who were IS at baseline responded better to an HC/LF hypocaloric diet than to an LC/HF hypocaloric diet. On the other hand, equally moderately obese women who were more IR at baseline responded better to an LC/HF hypocaloric diet than to an HC/LF one.

The most important point of this discussion is why the IS group on an HC/LF diet and the IR group on an LC/HF diet lost almost twice the amount of weight as their counterparts on the opposite diets. All subjects lost at least the expected amount of weight on a hypocaloric diet (daily deficit of 400

Table 2. Changes in metabolic parameters from baseline to the end of the hypocaloric diet period (Week 16) in the different groups (mean ± SE)

	Insulin sensitive				Insulin resistant			
	HC/LF ($N = 6$)		LC/HF ($N = 6$)		HC/LF ($N = 4$)		LC/HF ($N = 5$)	
	Baseline	Week 16	Baseline	Week 16	Baseline	Week 16	Baseline	Week 16
Si	5.8 ± 1.2	4.0 ± 0.9	4.4 ± 1.2	4.0 ± 1.0	3.0 ± 1.4	3.9 ± 1.2	1.8 ± 1.3	4.0 ± 1.0*
Insulin (μU/mL)	7.2 ± 1.1	4.2 ± 1.2†	7.0 ± 1.1	6.6 ± 1.2	20.8 ± 1.3	10.4 ± 1.4†§	18.4 ± 1.2	7.2 ± 1.3†§
Total cholesterol (mg/dL)	210 ± 22	196 ± 23	184 ± 16	163 ± 14†	152 ± 18	170 ± 16¶	198 ± 18	176 ± 22
HDL-C (mg/dL)	59 ± 4	54 ± 5	47 ± 4	46 ± 4	32 ± 3	40 ± 4	42 ± 6	39 ± 4
LDL-C (mg/dL)	124 ± 12	118 ± 16	110 ± 14	97 ± 10	98 ± 14	103 ± 17	121 ± 12	116 ± 18
Triglycerides (mg/dL)	136 ± 42	118 ± 26	132 ± 20	103 ± 16‡	124 ± 15	157 ± 10‡¶	173 ± 38	106 ± 21‡
Free fatty acids (μEq/L)	858 ± 110	813 ± 113	659 ± 34	532 ± 113	691 ± 48	718 ± 80	836 ± 74	801 ± 64
Leptin (ng/mL)	26 ± 5	10 ± 2†	31 ± 4	25 ± 4‡	28 ± 7	25 ± 5	37 ± 10	18 ± 4‡

* $p < 0.001$ for an insulin sensitivity effect within the LC/HF diet; † $p < 0.01$; ‡ $p < 0.05$ for an effect within the subgroup; § $p < 0.001$ for an insulin sensitivity effect; ¶ $p < 0.05$ for a diet effect within the insulin-resistant group.

kcal). Using the conversion that 1 kg of BW loss is due to a deficit of ~7300 kcal in women (24), the expected weight loss in this study was 6.1 kg in 16 weeks. Therefore, individuals who lost ~6 kg in 16 weeks displayed an adequate and predictable weight loss. So, what is the mechanism that allowed others to lose twice as much weight? All subjects received their food from the GCRC, and their dietary recalls revealed no differences in caloric intake. They consumed their portions entirely and did not supplement their diet, per reports and frequent dietary recalls. There was no indication to believe that the subjects who lost more weight would have consumed 400 kcal/d less than was provided to them, although this cannot be definitively ruled out without a study on a locked metabolic ward.

Therefore, we believe that the energy expenditure side of the equation deserves specific attention. Activity questionnaires and recall showed no difference, and changes in RMR and RQ were not significantly different among the groups. Although the thermic effect of feeding was not measured, this is a small component of total energy expenditure and likely could not explain the big differences in weight loss. Other components of energy expenditure including sleeping metabolic rate or NEAT could also have played a role. Levine et al. (25) have shown that after overfeeding 1000 kcal for 8 weeks, there was a 10-fold variation in fat gain, and this was related to energy expenditure not accounted for by changes in activity, thermic effect of feeding, or RMR. The authors have attributed this energy expenditure to a nonexercise activity thermogenesis (25). Alternatively, because approximately one-third of any 24-hour period is spent sleeping, alterations in sleeping metabolic rate could have accounted for these differences (26). Closer attention to both sides of the energy balance equation is needed in future studies.

The human forkhead family transcription factor FOXC2 has been shown to be present in both white and brown adipose tissues and to play an important role in regulating the expression of uncoupling protein 1, thus potentially influencing energy expenditure. Overexpression of FOXC2 has also been shown to prevent dietary induced obesity and insulin resistance in mice (21). Although the precise mechanisms of up-regulation of FOXC2 is unknown, its expression has been shown to be enhanced by insulin and an HF diet (27,28). With this in mind, we measured expression of adipose tissue FOXC2 in a subset of participants (IS, $N = 8$; IR, $N = 7$) before and after the dietary intervention (27). Preliminary data suggest differential expression of FOXC2 in the IS and IR individuals in response to diets differing in macronutrient composition. In those two groups who lost the most weight, the dietary intervention resulted in substantial increases in FOXC2 expression, whereas in the two groups with lesser weight loss, FOXC2 expression remained unchanged. Although these preliminary findings

suggest an important role for FOXC2 as a regulator of adipocyte metabolism, they must be confirmed in a larger study.

It should be noted that after weight loss, Si improved significantly in the IR cohort, posing a question of whether the LC/HF diet would remain the optimal diet for weight maintenance. Data from the National Weight Control Registry of people who were successful in losing and maintaining reduced weight show that despite wide variation in the methods used to lose weight, there was a remarkable similarity in how they maintained the weight loss, including a diet that was, on average, 24% fat (29). Therefore, a transition to an HC/LF diet might be the optimal method for weight maintenance.

A few limitations to this study must be discussed. First, overall, the number of subjects per group studied was small. The power to detect an Si-diet interaction was 0.97, and the differences found between the diets were significant. Second, because the study was not performed on a locked metabolic ward, it is certainly possible that there was noncompliance with the offered diets. The groups that lost the lesser amounts of weight had the expected amount of weight loss; therefore, we conclude that they were compliant with the designed caloric deficit. It is difficult to imagine that the groups who lost twice as much weight as expected reduced their intake to that degree. Finally, we did not measure total energy expenditure or the thermic effect of feeding. We, therefore, cannot be certain that the differences in weight loss among the groups were not due to greater activity or feeding thermogenesis. By questionnaires and interviews, we could not detect a change in physical activity in this already sedentary population.

Although the debate about the most accurate and practical way of assessing Si continues (primarily because of poorly standardized measurements of insulinemia) (30–33), our study demonstrated a strong correlation between fasting insulinemia and the Si index, as determined by Bergman's minimal model, in individuals with insulin levels below 10 and above 15 μU/mL ($r = 0.50$, $p < 0.05$). For the purpose of this study, to achieve the best separation between IS and IR groups, we deliberately excluded individuals with insulin levels between 10 and 15 μU/mL. In our patients, fasting insulinemia and an unamended fasting glucose-to-insulin ratio seemed to segregate individuals into distinct groups of Si. Because we excluded individuals with insulinemia between 10 and 15 μU/mL, we cannot comment on usefulness of those intermediate values in practical assessment of their Si.

In conclusion, the state of Si determines the effectiveness of macronutrient composition of hypocaloric diets in obese women. Clearly, to lose weight, patients must be on a hypocaloric diet. To obtain maximal benefit, the macronutrient composition of a hypocaloric diet may need to be adjusted to fit the state of Si. IS individuals (those with fasting insulin levels below 10 μU/mL) should be recommended to consume an HC/LF hypocaloric diet (60% CHO and 20% fat). IR individuals (those with fasting insulinemia of above 15 μU/mL) should be recommended a diet containing 40% CHO and 40% fat (LC/HF). The short-term changes seen in this study have not been demonstrated to be durable over longer periods of time as seen in longer term studies lasting up to a year (5).

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