Pretreatment Fasting Plasma Glucose and Insulin Determine Long-Term Dietary Weight Loss Success on Low-Carbohydrate vs. Low-Fat Diet

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INTRODUCTION

- The struggle to curb the current obesity epidemic by an optimal diet for weight management has largely failed, giving rise to numerous fad diets.[1]
- Caloric restriction, although effective in the short-term, is frequently derailed by biologic feedback mechanisms that stimulate appetite, reduce dietary compliance, and ultimately lead to a rebound of energy intake and weight gain.[2] Chronic studies of low-fat versus low-carbohydrate diets have yielded inconsistent and conflicting results, which are likely explained by metabolic heterogeneity within, and between, the different subject populations.
- Collectively, these observations underscore that no single dietary weight loss/maintenance strategy is appropriate for all individuals, and predictors or determinants of dietary weight loss are essential.
- While a few relatively small (21-81 subjects) studies have attempted to establish whether fasting insulin levels or indices of insulin secretion predict weight loss response to low carbohydrate (glycemic load) and low fat (high glycemic load) diets, results have been equivocal.[3-7]
- Attempts to establish whether pretreatment glycemic status predicts or determines weight loss response have been inconsistent.[8-9]
- **The purpose of this analysis was to explore fasting plasma glucose and insulin as predictors of weight loss and maintenance during 24 months of either a low-carbohydrate, high-protein, high-fat (Atkins) diet, or a high-carbohydrate, low-fat, low-calorie diet.**

METHODS

- This was a re-analysis of a previously reported study[10], in which subjects were randomized to receive either a low-carbohydrate, high-protein, high-fat (Atkins) *ad libitum* diet, or a conventional high-carbohydrate, low-fat, hypocaloric diet for 24 months (**Figure 1**).
- For this re-analysis, baseline fasting plasma glucose (FPG) levels were used to stratify subjects as being normoglycemic (FPG < 100 mg/dL) or having prediabetes (FPG ≥ 100 to 125 mg/dL) and median fasting plasma insulin (FPI, 11 mIU/L), derived from the prediabetes group, was used to dichotomize subjects into low and high FPI groups.
- Differences in weight change between FPG and FPI groups (and the combination of the two) were analyzed by generalized linear mixed model comprising fixed (gender, baseline weight), and random (subjects) effects. An *a priori* α-level of 0.05 was established for statistical significance.

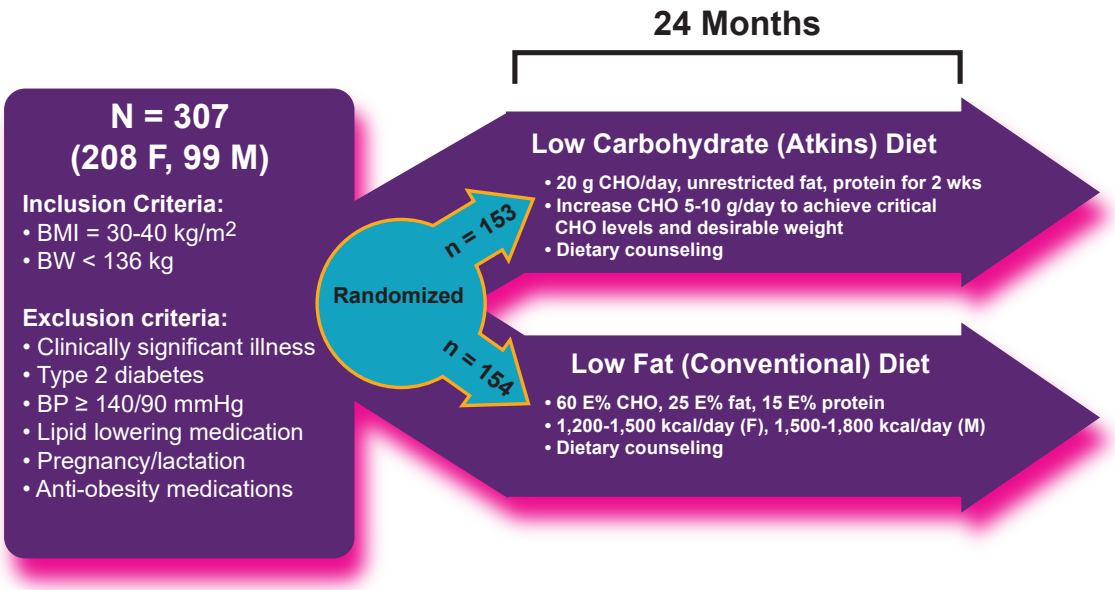

Figure 1: Twenty-four month, low-carbohydrate vs. low-fat diet study design[11]. CHO = carbohydrate, E% = percent energy in kcals, BMI = Body Mass Index, BW = Body Weight

RESULTS

- In the original 24-month study[10], the overall subject population was 45.5 ± 9.7 (SD) years of age with a mean BMI of 36.1 ± 3.5 kg/m^2. Both diet intervention groups were balanced with respect to age, gender, race/ethnicity, and anthropometric measures.
- Overall, both diet groups lost between 11.3-12.2 kg within 6 months (**Figure 2**). Subsequently, subjects regained 4.0-5.9 kg (35-48%) of their lost weight, but still maintained a net loss of 6.4-7.3 kg at 24 months. No significant differences in body weight were observed between the two diets at any time point.

Fasting Plasma Insulin as a Predictor of Weight Loss

- **Low-carbohydrate diet:** Significant differences in body weight response were observed between subjects with low and high FPI (**Figure 3**). While both FPI groups lost 12.6 ± 0.9 and 11.6 ± 1.0 kg within 6 months, subjects with low FPI exhibited a significantly lower body weight (3.7 kg) at 24 months compared with subjects with a high FPI (P = 0.013).
- **Low-fat diet:** Subjects achieved a body weight nadir between -11.4 ± 1.0 and -12.0 ± 0.8 kg within 12 months, and had regained 2.8-4.3 kg (25-36%) of their lost weight by 24 months. No differences in body weight were observed, at any time, between subjects with low and high FPI.
- While subjects in the low FPI group responded similarly to the low-fat and low-carbohydrate diets, subjects in the high FPI group maintained a 3.28 ± 1.31 kg lower body weight at 24 months when consuming a low-fat diet.

Fasting Plasma Glucose as a Predictor of Weight Loss

- Subjects who were normoglycemic or had prediabetes demonstrated similar body weight responses to either a low-fat or a low-carbohydrate diet (**Figure 4**). Similarly, no differences in body weight responsiveness between the two diets was observed (normoglycemic Δ_{diets} = -1.55 ± 1.06 kg, P = 0.141, prediabetes Δ_{diets} = -0.57 ± 2.06 kg, P = 0.783).

Fasting Plasma Insulin and Glucose (Combined) as Predictors of Weight Loss

- When subjects with prediabetes were further stratified according to a FPI above or below 11 mIU/L, a marked difference (13.28 kg) in extreme dietary responses was observed (**Figure 5**). Subjects with prediabetes and low FPI tended to lose more weight when consuming a low-carbohydrate diet (Δ_{diets} = -6.09 ± 3.52 kg, P = 0.084), whereas subjects with prediabetes and high FPI lost significantly more weight on a low-fat diet (Δ_{diets} = -7.19 ± 2.52 kg, P = 0.004).

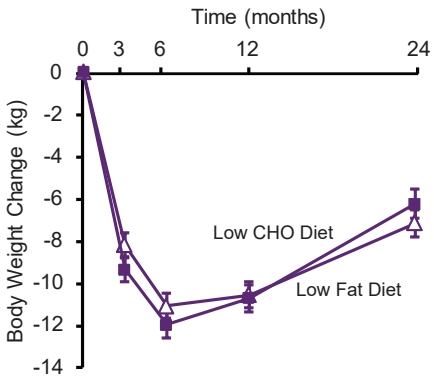

Figure 2: Body weight changes in all subjects who consumed either a low-carbohydrate, high-protein, high-fat (Atkins) diet (solid squares, n = 139), or a high-carbohydrate, low-fat, low-calorie diet (open triangles, n = 145). Data presented as mean ± SEM.

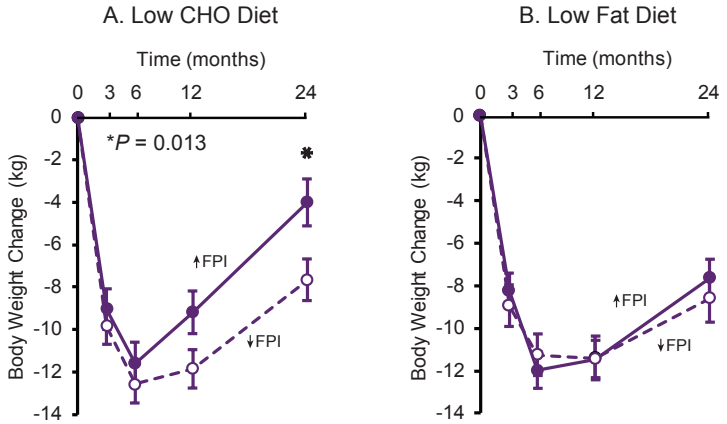

Figure 3: Body weight changes in subjects with high or low FPI at baseline who consumed either a low-carbohydrate (panel A) or a low-fat (panel B) diet. Low CHO: ⬆ FPI (n=56), ⬇ FPI (n=66), Low Fat: ⬆ FPI (n=55), ⬇ FPI (n=76).

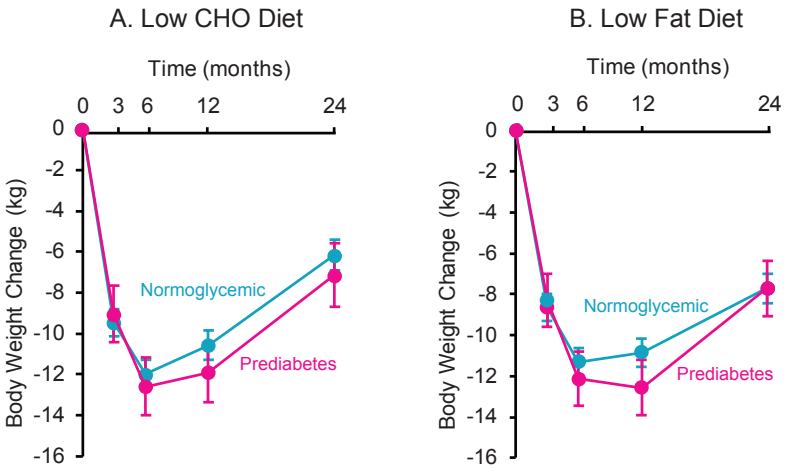

Figure 4: Body weight changes in subjects who were normoglycemic or had prediabetes at baseline, and consumed either a low-carbohydrate (panel A) or a low-fat (panel B) diet. Low CHO: normoglycemic (n=99), prediabetes (n=24), Low Fat: normoglycemic (n=103), prediabetes (n=26).

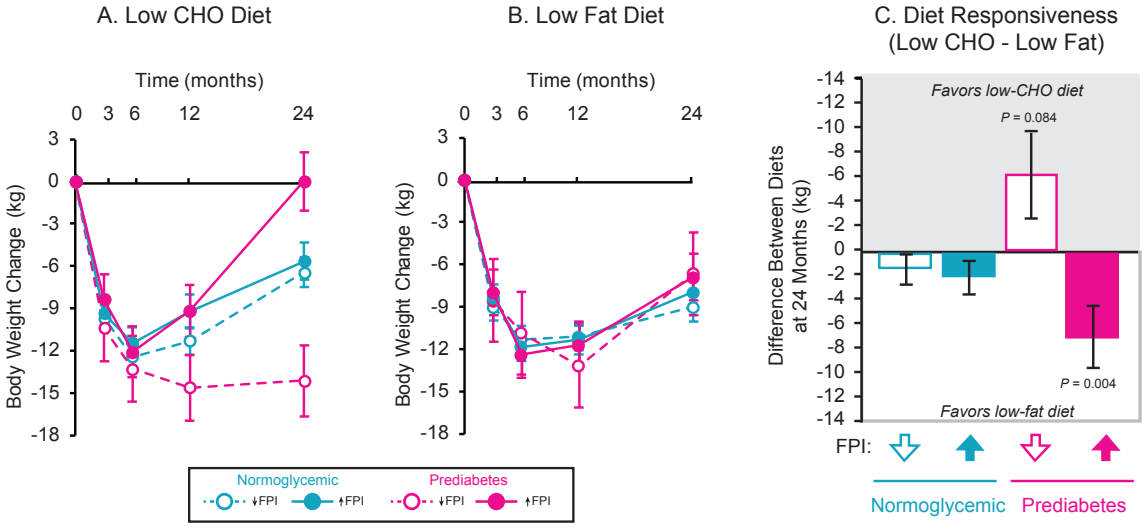

Figure 5: Body weight changes in subjects stratified by baseline glycemic status and fasting plasma insulin status during 24 months of a low-carbohydrate (panel A) or low-fat (panel B) diet. Diet responsiveness (panel C) in each group was assessed as the difference in 24-month body weight between low-carbohydrate and low-fat diets. Low CHO: normoglycemic/⬆ FPI (n=41), normoglycemic/⬇ FPI (n=57), prediabetes/⬆ FPI (n=15), prediabetes/⬇ FPI (n=9), Low Fat: normoglycemic/⬆ FPI (n=56), normoglycemic/⬇ FPI (n=47), prediabetes/⬆ FPI (n=20), prediabetes/⬇ FPI (n=6).

DISCUSSION

- Despite two profoundly different diets eliciting nearly identical changes in body weight, substantial long-term, diet-specific body weight responses were observed when subjects were stratified according to their pre-treatment FPG and FPI levels. Overall, subjects achieved a similar degree of weight loss within 3-6 months irrespective of diet, FPG, or FPI levels, but differences between groups emerged with respect to weight regain in the subsequent 18-21 months.
- Pre-treatment glycemic status did not affect response to the dietary interventions. Subjects who were normoglycemic were equally responsive to both low-fat and low-carbohydrate diets.
- Conversely, pre-treatment FPI was determinant of response to a low-fat/hypocaloric diet: subjects with high FPI maintained a lower weight at 24 months compared to a low-carbohydrate diet. While a greater response to a low-fat diet in this analysis appears to conflict with previous reports in subjects with high fasting insulin[3] or insulin response to an oral glucose tolerance test[7], differences in the methodology of insulin assessment, cross-study diet characteristics (such as glycemic load), and subject phenotypes may partially explain differences. For example, mean FPG of subjects in the studies cited above[3,7] ranged between 85-90 mg/dL, whereas the low-fat response in this analysis occurred in subjects with prediabetes and high FPI (**Figure 5** and discussed below).
- Combination of pre-treatment FPG with FPI yielded additive biomarkers of dietary response in subjects with prediabetes: a marked 13.28 kg difference in 24-month diet responses was observed between those with a FPI either above or below median values (11 mIU/mL). Specifically, subjects with prediabetes and lower FPI were more responsive to a low-carbohydrate (Atkins) *ad libitum* diet, whereas subjects with prediabetes and higher FPI were more responsive to a low-fat, hypocaloric diet. Another interesting suggestion of these findings is that caloric restriction, per se, may not be of primary importance in all patients.
- Over the past several decades, numerous trials have compared various diets for the management of obesity, based on the assumption that a single dietary strategy is appropriate for all individuals. Our results clearly demonstrate that failure to consider the glycemic and insulin status of subjects has the potential to confound effects among those with prediabetes, and potentially overestimate effects among subjects who are normoglycemic.

CONCLUSIONS

- These novel results, along with other analyses of large, international diet studies presented at this congress (**73-LB**, **75-LB**, **78-LB**, **792-P**, **201-OR**, **202-OR**), demonstrate that easily accessible biomarkers such as fasting plasma glucose and plasma insulin are and strong predictors of dietary weight loss success and represent a significant step forward in personalized weight management.

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