

# Pretreatment Fasting Plasma Glucose Determines Weight Loss on High-Fat Diets: The PREDIMED Study

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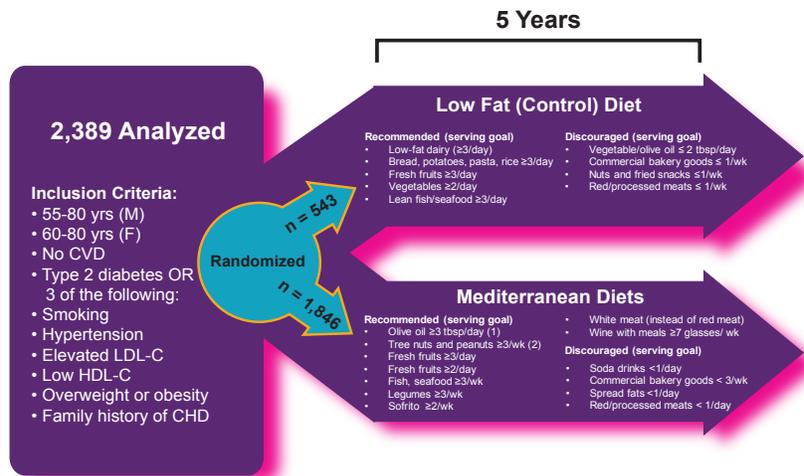
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## INTRODUCTION

- The struggle to identify an optimal diet to curb the global obesity and diabetes epidemics has largely failed. This underscores the fact that no single dietary weight loss/maintenance strategy is appropriate for all individuals, and development of personalized strategies based on predictive biomarkers is necessary, especially for those afflicted with disorders of insulin action and glucose metabolism.
- Two systematic reviews and meta-analyses found no differences in weight loss in subjects with type 2 diabetes between a low-carbohydrate diet, a low-glycemic-index diet, or a high-protein diet, when compared to a control diet.<sup>1,2</sup> Conversely, a Mediterranean diet high in fat and dietary fiber elicited greater weight loss among individuals with type 2 diabetes.<sup>3,4</sup> These results suggest that measures of glycemic status may determine, in part, response to specific diet regimens. However, attempts to establish whether glycemic status predicts or determines weight loss response have also been inconsistent and require further elucidation.<sup>6-7</sup>
- **The purpose of this analysis was to explore glycemic status as a predictor (or determinant) of weight loss and long-term (5-year) maintenance in response to two *ad libitum*, high-fat Mediterranean diets or a moderate-fat control diet.**

## METHODS

- This was a re-analysis of 1,846 subjects who completed the multicenter PREDIMED (Prevención con Dieta Mediterránea)<sup>11</sup> trial, and for whom fasting plasma glucose at baseline and complete data for yearly body weight measurements were available. In PREDIMED, subjects were randomized to consume one of two *ad libitum* Mediterranean diets supplemented with either 1L extra-virgin olive oil per week or 30 g of mixed nuts per day, or a moderate-fat control diet that reduced total energy intake by approximately 227 kcal/day for ~5 years (**Figure 1**).
- For this re-analysis, subjects in the two Mediterranean diet groups were combined, and baseline fasting plasma glucose (FPG) levels were used to stratify subjects into one of four glycemic categories: <100 mg/dL, 100-114.9 mg/dL, 115-125.9 mg/dL, and ≥126 mg/dL. The rationale for subdividing subjects into these groups was inspired by an independent analysis suggesting an FPG cut-off of 115 mg/dL to be an important predictor of weight loss on diets varying in fat and carbohydrates.<sup>9</sup>
- Differences in weight change between glycemic categories were analyzed by repeated measures linear mixed models comprised of fixed (gender, age, baseline weight, type 2 diabetes, hypertension, and hypercholesterolemia), and random (subjects and field center) effects. Differences in weight change between diets were compared within and between each FPG group through pairwise comparisons using post hoc t-tests. An *a priori*  $\alpha$ -level of 0.05 was established for statistical significance.



**Figure 1:** Analysis of subjects from the PREDIMED (Prevención con Dieta Mediterránea)<sup>11</sup> study. Subjects in Mediterranean diet groups were supplemented with either 1L extra-virgin olive oil per week (1) or 30 g of mixed nuts per day (2). CVD = cardiovascular disease, CHD = coronary heart disease

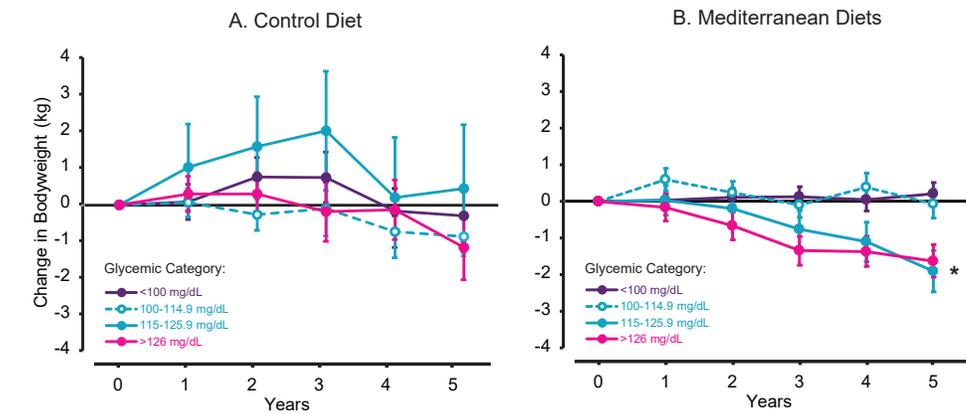
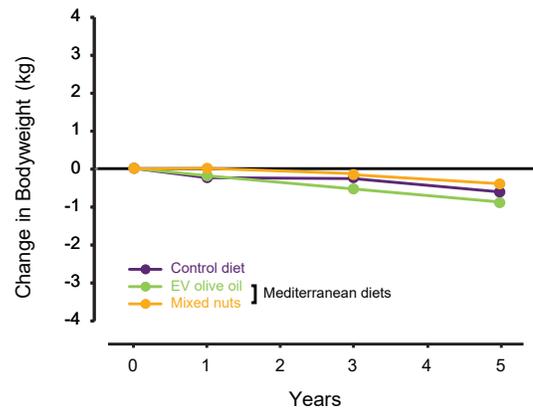
## RESULTS

- Subjects in both Mediterranean diet groups increased consumption of vegetables, legumes, fruits, and fish and decreased consumption of meat, sweets, and dairy products. However, only differences in legumes and fish/seafood were significant between the Mediterranean and control diet groups ( $P < 0.0001$  for all). Self-reported reduction in energy intake was more pronounced in the control group compared to subjects consuming either Mediterranean diets ( $P < 0.0001$ ).<sup>10</sup>
- Subjects in the Mediterranean diet groups with elevated FPG were generally older, and had a higher baseline body weight and BMI compared to subjects with FPG < 100 mg/dL (**Table 1**).
- In the overall population, slight weight losses ranging from -0.40 to -0.88 kg were similar between subjects consuming either the control diet or either Mediterranean diet for 5 years (**Figure 2**).
- Five-year weight change in subjects randomized to the control diet was -0.29 kg (CI: -1.59 to 1.01) in normoglycemic subjects, -0.84 kg (CI: -1.88 to 0.20) and -0.45 kg (CI: -3.04 to 3.93) in the low- and high-, respectively, and -1.14 kg (CI: -2.83 to 0.56) in subjects with prediabetes with type 2 diabetes ( $P = 0.004$  for overall difference, however, no difference was found between any of the four glycemic groups) (**Figure 3A**).
- Weight change among subjects randomized to both Mediterranean diets was -0.20 kg (CI: -0.84 to 0.43) in the FPG < 100 mg/dL group, -0.06 kg (CI: -0.84 to 0.72) and -1.92 kg (CI: -3.04 to 0.79) in the FPG = 100-114.9 mg/dL and 115-125.9 mg/dL groups, respectively, and -1.63 kg (CI: -2.51 to -0.75) in the FPG > 126 mg/dL group ( $P=0.004$  for overall difference between groups) (**Figure 3B**). Consequently, subjects with a baseline FPG  $\geq 115$  mg/dL ( $n=771$ ) lost significantly more weight (-1.64 kg (CI: -2.29 to -0.99)) than participants with FPG < 115 mg/dL ( $n=1075$ ) (-0.19 kg (CI: -0.66 to 0.30)) ( $P < 0.001$ ).
- When diet responsiveness was assessed by calculating the difference in body weights between control and Mediterranean diets for each glycemic category, a significant difference of 2.36 kg ( $P = 0.049$ ) favoring the Mediterranean diet was only observed in the FPG = 115 to 125.9 mg/dL group (**Figure 4**).

	Fasting Plasma Glucose (mg/dL)				P-value
	<100 (n=746)	100-114.9 (n=329)	115-125.9 (n=174)	≥126 (n=597)	
Age	42.3 ± 5.9 <sup>ab</sup>	40.5 ± 6.7 <sup>a</sup>	45.2 ± 5.6 <sup>b</sup>	43.1 ± 9.4 <sup>ab</sup>	<0.001
Gender (% F/M)	71.2/28.8	42.5/57.5	53.8/46.2	80/20	0.005
Height (cm)	169 ± 9 <sup>a</sup>	174 ± 10 <sup>*</sup>	166 ± 9 <sup>a</sup>	166 ± 6 <sup>a</sup>	<0.001
Body weight (kg)	95.0 (86.7;105.0) <sup>a</sup>	107.6 (94.6;121.6) <sup>b</sup>	90.1 (86.6;98.8) <sup>ac</sup>	107.5 (93.4;112.5) <sup>bc</sup>	<0.001
BMI (kg/m <sup>2</sup> )	32.9(30.7;35.9) <sup>a</sup>	35.3(32.4;39.0) <sup>bc</sup>	32.0(31.2;36.2) <sup>ab</sup>	38.5(33.2;43.1) <sup>c</sup>	<0.001
WC (cm)	100.2 ± 10.4	100.2 ± 10.4	100.2 ± 10.4	100.2 ± 10.4	0.005
Type 2 diabetes (%)	12.5	33.0	74.5	94.0	

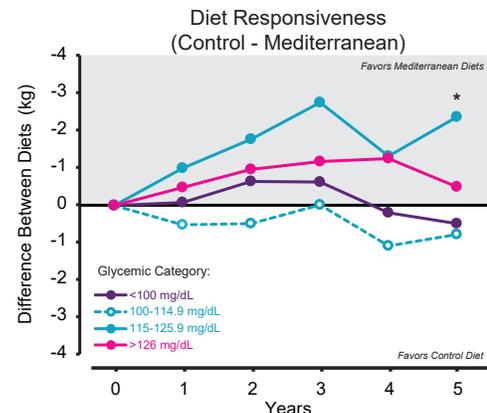
**Table 1:** Baseline characteristics of PREDIMED subjects randomized to receive two different Mediterranean diets, stratified by glycemic categories. Data presented as mean ± SD, median (IQR), or proportions. BMI = Body mass index; WC, Waist circumference. Letters within a row (a,b,c) indicate significant differences ( $P < 0.05$ ).

**Figure 2:** Similar changes in body weight over 5 years in all subjects consuming two *ad libitum* Mediterranean diets supplemented with either 1L extra-virgin (EV) olive oil per week (-0.88 kg, n=2,524) or 30 g of mixed nuts per day (-0.40 kg, n=2,433), or a moderate-fat control diet (-0.60 kg, n=2,420). No significant differences were observed between any group, at any time. Redrawn from reference 10.



**Figure 3:** Five-year body weight changes in subjects who consumed a moderate-fat control diet (panel A, n=543) or two *ad libitum* Mediterranean diets (panel B, n=1,846). A significant effect ( $*P = 0.004$ ) was observed between glycemic categories who consumed a Mediterranean diet, and subjects with FPG > 115 mg/dL lost significantly more weight than subjects with FPG < 115 mg/dL. Data shown as mean ± SE.

**Figure 4:** Diet responsiveness (body weight difference between Control – Mediterranean diets) between subjects in four glycemic categories. \*A significant difference ( $P = 0.049$ ) in responsiveness favoring the Mediterranean diet was observed in the FPG = 115-125.9 mg/dL group.



## DISCUSSION

- In recent decades, a perception that dietary fat is unhealthy and leads to increased body weight has resulted in decreased fat consumption in the U.S. population. However the multicenter, longitudinal PREDIMED (Prevención con Dieta Mediterránea) trial in ~7,500 subjects provided first-level evidence that *ad libitum* Mediterranean diets – which are characterized by a high relative consumption of vegetable fats – elicit cardiovascular protection<sup>8</sup> and not only do *not* increase body weight, but result in slight (-0.40 to -0.88 kg) reductions over 5 years.<sup>10</sup>
- In this re-analysis of the PREDIMED population, we confirmed that fasting plasma glucose is an important biomarker of weight loss on high-fat, *ad libitum* diets. Specifically, subjects with FPG greater than 115 mg/dL lost significantly more weight when consuming high-fat, *ad libitum* Mediterranean diets, compared to a moderate-fat, moderately-hypocaloric control diet. Therefore, it is possible that the overall weight changes originally reported in PREDIMED<sup>10</sup> were predominantly driven by subjects with impaired glycemia.
- Interestingly, the observations reported here are consistent with analyses of other independent studies presented at this conference, in which: subjects with type 2 diabetes lost significantly more weight on a 10-week high-fat, hypocaloric diet, whereas normoglycemic individuals were more responsive to a low-fat diet (**Astrup ADA#201-OR**), and subjects with prediabetes were more responsive to a Mediterranean-like, *ad libitum* New Nordic Diet (**Astrup ADA#792-P**). Further, given that subjects with prediabetes and low fasting insulin levels in these studies were shown to be more responsive to higher-fat diets, it is possible that further stratification of subjects with FPG = 100-114.9 mg/dL in PREDIMED by fasting insulin levels would have enabled detection of diet-specific responders in this group.
- 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 status has the potential to underestimate effects among subjects with prediabetes and type 2 diabetes.

## CONCLUSIONS

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

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