

Pre-Treatment Fasting Plasma Glucose and Insulin As Determinants of Weight Loss Success: The New Nordic Diet Study



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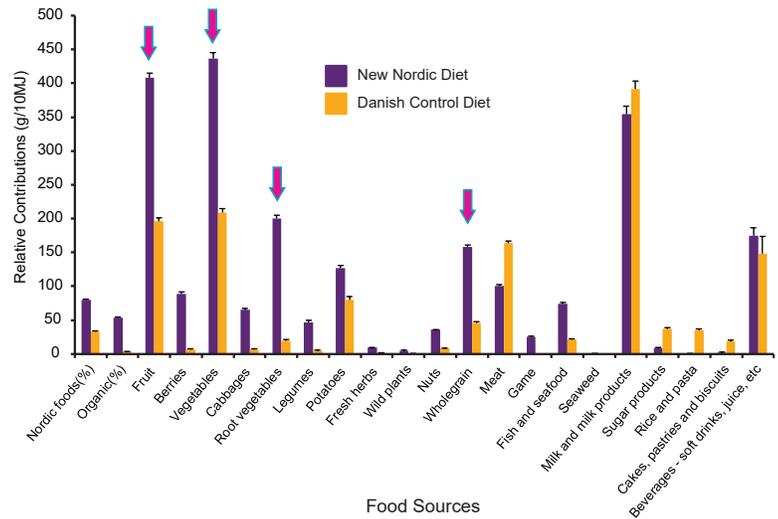
INTRODUCTION

- The struggle to identify an optimal diet to curb the global obesity and diabetes epidemics has largely failed, giving rise to numerous fad diets.¹ This underscores the fact that no single dietary weight loss/maintenance strategy is appropriate for all individuals, and justifies development personalized strategies based on predictive biomarkers, especially for those afflicted with disorders of insulin action and glucose metabolism.
- 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 Increasing natural dietary fiber intake has been shown to influence subjective appetite and prevent weight gain, which may occur via multiple mechanisms.³ Further, increasing relative dietary contributions of fat and protein may confer weight loss benefits in some individuals by altering appetite-regulating hormones such as ghrelin, GLP-1, and PYY.⁴⁻⁶ Abundance of healthy dietary fats and fibers from plant-sources is a defining characteristic of Mediterranean and Mediterranean-like diets.
- A Mediterranean diet high in fat and dietary fiber was shown to elicit greater weight loss among individuals with type 2 diabetes.^{7,8} Similarly, a recent analysis of the 5-year PREDIMED study demonstrates that compared to subjects with normal fasting plasma glucose, subjects with elevated fasting plasma glucose exhibit enhanced weight loss on two *ad libitum*, high-fat Mediterranean diets (see Estruch ADA#78-LB). These results and others presented at this congress (see Hjorth ADA#73-LB, Urban ADA#75-LB, Astrup ADA#201-OR, and Hjorth ADA#202-OR) suggest that glycemic status (and insulin) predict response to diet regimens that are higher in fat and/or abundant in dietary fibers.
- The purpose of this analysis was to explore fasting plasma glucose and insulin as predictors of weight loss during either a 26-week *ad libitum*, Mediterranean-like New Nordic Diet or a habitual, Western-like Danish control diet.

METHODS

- This was a re-analysis of the OPUS Supermarket Intervention (SHOPUS) study conducted in Denmark⁹ in which subjects with increased waist circumference were randomly assigned to receive either an *ad libitum* New Nordic Diet (NND) or a habitual, Western-like Danish control diet for 26 weeks.
 - The NND as previously described¹⁰ is a whole food approach characterized by being very high in dietary fiber, wholegrain, fruit, berries, and vegetables, whereas the control diet was designed to match the macronutrient composition of the average consumed diet in Denmark, which contains a slightly higher fat content. For both diets, food and beverages were provided from a study shop free of charge. Relative food intakes and nutrient compositions of the NND and Danish control diet are shown in **Figure 1**.
- For this re-analysis, baseline fasting plasma glucose (FPG) levels were used to categorize subjects as being normoglycemic (FPG < 100 mg/dL) or having prediabetes (FPG ≥ 100 to 125 mg/dL) and median fasting plasma insulin (FPI, 72.9 pmol/L), derived from the prediabetes group, was used to dichotomize subjects into low and high FPI groups.
- Differences in weight change between glycemic and insulinemic categories were analyzed by linear mixed models comprised of fixed effects including gender, age, and body mass index as well as random effects for subjects. Differences in weight change between diets were compared within and between each FPG, FPI, and FPG+FPI group through pairwise comparisons using post hoc t-tests. An *a priori* α -level of 0.05 was established for statistical significance.

Figure 1: Comparison of food source intakes for the New Nordic and Danish Control Diets in the 26-week SHOPUS⁹ study. Arrows denote sources of interest, all differences between diets were significantly different ($P < 0.001$) except for milk and milk products, and beverages. Subjects in the New Nordic Diet group also consumed significantly greater amounts of dietary fiber ($P < 0.001$).



RESULTS

- Baseline characteristics of the SHOPUS re-analysis population are provided in **Table 1**. Given that subjects with prediabetes were older, had a higher body weight, and by definition, had higher fasting plasma glucose concentrations ($P < 0.05$), all subsequent analyses were adjusted for these variables.
- Overall, subjects who completed both Danish Control diet and NND lost weight. However, mean weight loss in the NND group was 3.22 kg greater at the end of the 26-week intervention ($P < 0.001$, **Figure 2**).

Fasting Plasma Insulin as a Predictor of Weight Loss (Figure 3)

- Subjects with low FPI lost 4.09 kg (95%CI 2.91 to 5.2) more weight on the NND than the Control diet ($P < 0.001$), whereas subjects with high FPI lost only 1.61 kg (95%CI 0.28 to 2.94) more ($P = 0.02$). Consequently, a 2.48 kg (95% CI, 0.70 to 4.26) greater responsiveness to the NND was observed in subjects with low FPI ($P = 0.006$).

Fasting Plasma Glucose as a Predictor of Weight Loss (Figure 4)

- Subjects with prediabetes lost 6.04 kg (95%CI 4.05 to 8.02) more on the 26-week *ad libitum* NND compared with the Danish Control diet ($P < 0.001$), whereas subjects who were normoglycemic lost only 2.20 kg (95%CI 1.21 to 3.18) more ($P = 0.001$). Consequently, a 3.84 kg (95% CI, 1.62 to 6.06) greater responsiveness to the NND was observed in subjects with prediabetes ($P = 0.001$).

Fasting Plasma Insulin and Glucose as Predictors of Weight Loss (Figure 5)

- Subjects with prediabetes and low FPI lost 6.27 kg (95%CI 3.51 to 9.02) more on the 26-week *ad libitum* NND compared with the Danish Control diet ($P < 0.001$), whereas no difference between diets was observed for subjects who were normoglycemic with high FPI ($P = 0.89$).

	Glycemic Category	
	Normoglycemic (FPG < 100 mg/dL)	Prediabetes (FPG ≥ 100-125 mg/dL)
N	37	139
Age	51.5 (44.9;57.8)*	37.2 (29.2;49.8)
Gender		
Female (%)	54.1	74.1
Male (%)	46.0	25.9
Body weight (kg)	94.9 (86.8;101.6)*	85.0 (75.3;100.6)
BMI (kg/m ²)	30.7 (28.9;33.9)	28.9 (26.4;31.9)
BMI category		
Normal (%)	5.4	13.0
Overweight (%)	32.4	45.3
Obese (%)	62.2	41.7
Fasting glucose (mg/dL)	104.4 (100.8;108.0)*	91.8 (86.4;95.4)
Fasting insulin (pmol/L)	73 (46;116)	64 (41;90)

Table 1: Baseline characteristics of SHOPUS re-analysis population, stratified by glycemic categories. Data presented as mean ± SD, median (IQR), or proportions. BMI = Body mass index; WC = Waist circumference; FPG = Fasting Plasma Glucose. * $P < 0.05$ between glycemic categories.

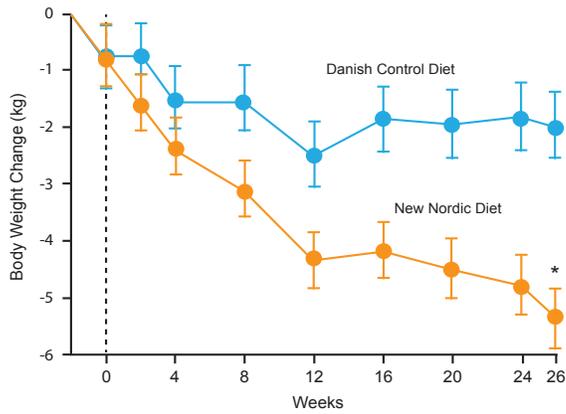
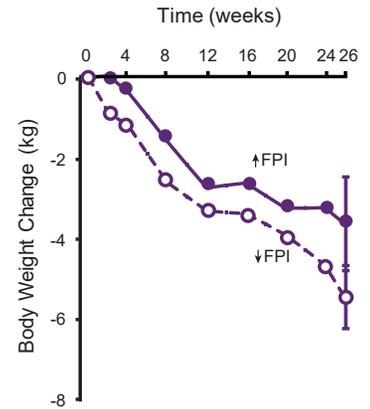
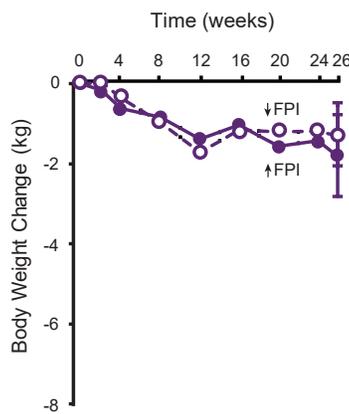


Figure 2: Body weight changes (\pm SEM) of all subjects who completed a 26-week Danish Control (n=56) and New Nordic (n=91) diet intervention ($*P < 0.001$). Dashed line represents time of randomization. Redrawn from reference 9.

Figure 3: Body weight changes (\pm SEM) in subjects with high or low fasting plasma insulin (FPI) at baseline who consumed either a Danish Control (panel A) or New Nordic Diet (panel B). Danish Control Diet: \uparrow FPI (n=23), \downarrow FPI (n=31), New Nordic Diet: \uparrow FPI (n=40), \downarrow FPI (n=51).

A. Danish Control Diet

B. New Nordic Diet



A. Danish Control Diet

B. New Nordic Diet

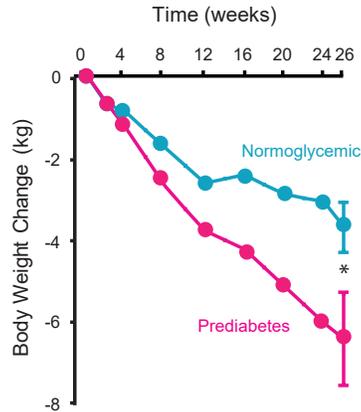
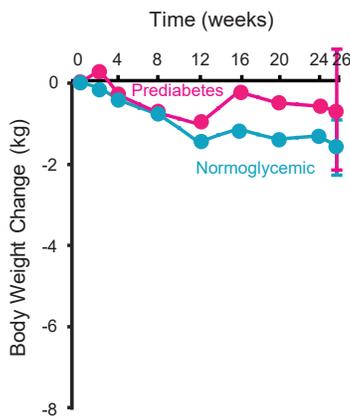


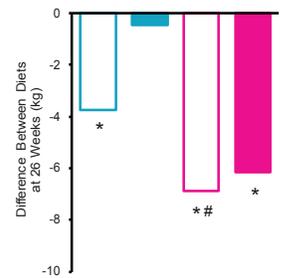
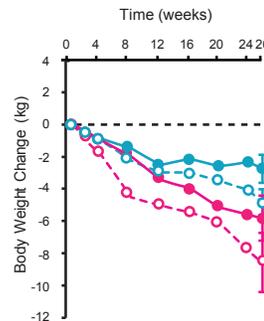
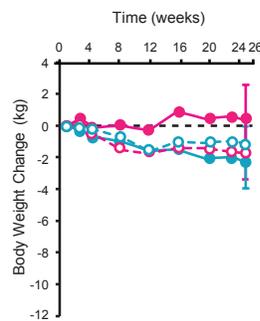
Figure 4: Body weight changes (\pm SEM) in subjects who were normoglycemic or had prediabetes at baseline, and consumed either a Danish Control (panel A) or New Nordic (panel B) diet. Danish Control Diet: normoglycemic (n=44), prediabetes (n=10), New Nordic Diet: normoglycemic (n=70), prediabetes (n=21). $*P < 0.001$ between glycemic categories.

Figure 5: Body weight changes (\pm SEM) during a Danish Control (panel A) or New Nordic (panel B) diet, in subjects stratified by baseline glycemic status and fasting plasma insulin levels. Diet responsiveness (panel C) was assessed as the difference in body weight between diets at week 26. Danish Control Diet: normoglycemic/ \uparrow FPI (n=18), normoglycemic/ \downarrow FPI (n=26), prediabetes/ \uparrow FPI (n=5), prediabetes/ \downarrow FPI (n=5), New Nordic Diet: normoglycemic/ \uparrow FPI (n=28), normoglycemic/ \downarrow FPI (n=42), prediabetes/ \uparrow FPI (n=12), prediabetes/ \downarrow FPI (n=9). $*P < 0.05$ vs. zero, $\#P < 0.05$ vs. other glycemic/insulin groups.

A. Danish Control Diet

B. New Nordic Diet

C. Responsiveness to New Nordic Diet



DISCUSSION

- In this re-analysis of the SHOPUS⁹ study, we confirmed that not only are pre-treatment fasting plasma insulin and glucose independent biomarkers of weight loss on a Mediterranean-like, *ad libitum* New Nordic Diet that is very high in dietary fiber, wholegrain, fruit, berries, and vegetables, but that combining fasting plasma insulin and glucose yielded increased predictive power to identify diet-specific responders. While all subjects lost more weight on the NND compared with a control that was Western-like and approximates the average Danish diet, subjects specifically with prediabetes and low fasting plasma insulin responded better on the NND than any other group analyzed. This is consistent with other analyses presented at this congress demonstrating that this prediabetes with low FPI phenotype also responds preferentially to diets that are lower in glycemic load (**Hjorth ADA#202-OR**) or *ad libitum* diets that are higher in relative amounts of fat to carbohydrate (**Astrup ADA#201-OR**).
- While the dietary interventions were uniquely controlled in this study – food was provided throughout to all subjects free of charge using a “shop” model – glycemic index was not registered. Therefore, we cannot rule out that a lower glycemic index of the NND could partly be responsible for the differences observed in this analysis.
- While there are several central (CNS) and peripheral mechanisms by which PFG and FPI could influence satiety and ultimately weight loss,¹¹⁻¹² we cannot conclude if these particular biomarkers were responsible for the weight-loss effects observed here or, whether there are other markers or mechanisms involved. For example, the NND employed in this study was rich in whole grains and dietary fibers and strong evidence suggests a role for particular gut microbiota in their fermentation and production of metabolites, such as short-chain fatty acids, that can improve insulin sensitivity and facilitate weight loss.¹³
- 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 and fasting insulin levels has the potential to underestimate effects among subjects, particularly those with prediabetes.

CONCLUSIONS

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

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