

Advances in Obesity Treatment: Clinical Highlights from the NAASO 2003 Annual Meeting

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Overweight and obesity are becoming epidemic worldwide, and the United States ranks high among developed nations for prevalence of these conditions. Approximately 300,000 adult deaths in the United States each year are attributable to unhealthy diet habits and physical inactivity.¹ Nearly two-thirds of U.S. adults are overweight (BMI > 25 mg/kg²) or obese (BMI > 30 mg/kg²).² From 1960 to 2000, the prevalence of obesity more than doubled, with most of the increase occurring in the past 20 years.²

Less than one-third of U.S. adults report regular leisure-time physical activity (defined as light or moderate activity of at least 30 minutes in duration five times or more per week and/or vigorous activity of at least 20 minutes in duration three times or more per week). Forty percent of adults report no leisure-time physical activity at all.³

Obesity is the major environmental risk factor for developing type 2 diabetes; an estimated 70% of diabetes risk in the United States can be attributed to excess weight.⁴ Individuals who are overweight or obese also have higher rates of hypertension and dyslipidemia. Obesity is associated with a 50–100% increased risk of death from all causes. Most of the increased risk is from cardiovascular disease (CVD).⁵ The life expectancy of a moderately obese person may be shortened by 2–5 years.⁶

As the prevalence of overweight and obesity has increased in the United States, so have related health care costs, both direct and indirect. The estimated total health care cost of diabetes in 2001

was \$122.9 billion,⁷ and that attributable to excess weight was \$98 billion.⁴

Because of sobering facts such as these, the American Diabetes Association and the North American Association for the Study of Obesity (NAASO) announced in 2002 their intent to work together to combat the growing problem of obesity. One of their earliest efforts was a jointly sponsored meeting on obesity held October 11–15, 2003, in Fort Lauderdale, Fla. This meeting brought together clinicians and researchers to create a forum to present and discuss the current and future states of obesity management.

This article offers an overview of some of the clinical highlights of this meeting that may provide useful information to those who care for people affected by two of the biggest health challenges facing us today: obesity and diabetes. Topics include: 1) which diet is better for weight loss—low-carbohydrate, low-fat, or low-calorie; 2) the relationship between obesity and polycystic ovarian syndrome (PCOS); and 3) promising future obesity treatments now in the clinical research pipeline.

IN BRIEF

This article offers highlights from the 2003 annual meeting of the North American Association for the Study of Obesity, which was co-sponsored by the American Diabetes Association. Topics include recent research into various diets for weight loss, the relationship between obesity and polycystic ovarian syndrome, and future treatments of obesity.

Does Type of Diet Matter?

The debate on low-carbohydrate versus low-fat diet for weight loss had more fuel thrown on its fire from discussions of this topic in symposia and oral presentations of clinical studies. In a symposium titled “Dietary Approach to Weight Reduction and Maintenance,” three clinical investigators, Gary D. Foster, PhD, of the University of Pennsylvania School of Medicine, in Philadelphia; David Ludwig, MD, PhD, of Childrens’ Hospital in Boston; and Arne V. Astrup, MD, DrMedSci/PhD, of the Royal Veterinary and Agricultural University in Denmark, discussed findings from research studies into varying the macronutrient composition, glycemic index, and total calorie content of diets. In a separate presentation titled “12-Week Feeding Weight Loss Comparison: Low-Fat Vs. Low-Carbohydrate (Ketogenic) Diets,” Penelope Greene, MD, of the Harvard School of Public Health in Cambridge, Mass., discussed the findings of her study.

Dr. Foster discussed three recently published studies comparing low-fat and low-carbohydrate diets. In a study by Brehm et al.,⁸ 53 healthy, obese (BMI = 33.6 kg/m²) female volunteers were randomized for 6 months to either an *ad libitum* very-low-carbohydrate diet (20–60 g/day) or a calorie-restricted diet with 30% of the total calories as fat (55% carbohydrate, 15% protein). The women were examined at baseline, 3 months, and 6 months. Results showed that despite ingesting approximately the same number of calories, women on the very-low-carbohydrate diet lost signifi-

cantly more weight than did those on the calorie-restricted diet (8.5 vs. 3.9 kg). All subjects improved their lipid profiles over the course of the study. Researchers concluded from these findings that the low-carbohydrate diet may be more effective than calorie restriction alone for short-term weight loss.

In another study by Samaha et al.,⁹ 132 severely obese (BMI = 43 kg/m²) men and women with either diabetes (39%) or metabolic syndrome (43%) were assigned to either a low-carbohydrate or a calorie-restricted low-fat diet for 6 months. Seventy-nine subjects completed the study, which showed that those on the low-carbohydrate diet lost significantly more weight (5.8 vs. 1.9 kg) and had greater decreases in triglycerides and improvements in insulin sensitivity than those on the low-fat diet.

In a study performed by Foster et al.,¹⁰ 63 obese (BMI ~ 34 kg/m²) men and women were randomized to either a low-carbohydrate, high-protein, high-fat (Atkin's) diet or a low-calorie, high-carbohydrate, low-fat (conventional) diet for 12 months. At 3 months and 6 months, those on the low-carbohydrate diet had lost more weight than those on the conventional diet (6.8 vs. 2.7 %, and 7 vs. 3.2% of body weight, respectively), but the difference in weight at 12 months was no longer significant. There were no differences in total or LDL cholesterol concentrations, but those on the low-carbohydrate diet had increases in HDL and decreases in triglyceride levels compared with the conventional group. Both diets resulted in significantly decreased insulin levels after an oral glucose load.

Dr. Greene et al.¹¹ found that people eating an extra 300 calories a day on a very-low-carbohydrate diet lost a similar amount of weight during a 12-week study as those on a low-fat diet. The study design included carefully controlled caloric intake using prepared foods in 21 obese (BMI = 33 kg/m²) subjects. One-third were assigned to a low-fat (LF diet) of 1,500–1,800 kcal/day, with 55% carbohydrate, 15%

protein, and 30% fat, and two-thirds were assigned to a low-carbohydrate diet consisting of 5% carbohydrate, 30% protein, and 65% fat, and including either 1,500–1,800 kcal/day (LC1) or 1,800–2,100 kcal/day (LC2). All groups lost weight: 8% in the LF group, 11% in LC1 group, and 10% in LC2 group. This was a trend toward greater weight loss in LC2 group compared with the LF group, despite the higher caloric content, with the LC1 group losing the most. Waist circumference also declined in all three groups by 7, 11, and 10%, respectively.

Dr. Ludwig's presentation focused on the effects of the glycemic index (GI) of foods. The GI classification is based on the principle that all forms of carbohydrate can be digested or converted to glucose. Digestion rate affects blood glycemic and insulinemic responses. Classifying foods according to the magnitude of the glycemic response, or the GI, has been proposed as a system of classifying dietary carbohydrate. Highly refined or processed carbohydrate at one end of the spectrum will have a higher GI than unprocessed or nonstarchy carbohydrate. The clinical significance of the GI remains controversial, however. Studies are mixed and have shown both lower and higher GI diets to be associated with greater satiety, reduced hunger, and more weight loss.

According to Dr. Ludwig, a compensatory increase in high-GI carbohydrate consumption is one potential adverse effect of consuming a standard low-fat diet. Since these foods cause a large transient increase in postprandial blood glucose and insulin (and decreased glucagon) levels, these hormonal changes could predispose to nutrient storage and weight gain, as well as rapid return of hunger sensations and excessive caloric intake. To extend this further, chronic consumption of such foods could lead to increased risk for the development of diabetes and CVD.

He cited a study published in *Diabetes Care*,¹² in which 11 healthy overweight (BMI = 28 kg/m²) men were assigned to either a low-GI (LGI) or

high-GI (HGI) diet for 5 weeks and then crossed over after a washout period to the other diet for 5 weeks. The LGI diet resulted in lower postprandial plasma glucose and insulin profiles, as expected, but also lower triacylglycerol levels and a decrease in body fat mass, with a tendency to increased lean body mass.

There was also a trend toward decreased total cholesterol. Such changes over time might be beneficial to the risks for diabetes and CVD. The 5-week LGI diet was not associated with improvement in insulin sensitivity.

Dr. Astrup, the third speaker in the dietary symposium, stated his belief that the wealth of evidence in the literature still supports caloric restriction as being more important to weight loss than the macronutrient content of the diet, but said he favors low-fat diets as more beneficial to lipid profiles and risk of diabetes. He cited the results from National Institutes of Health (NIH)-sponsored Diabetes Prevention Program,¹³ a multicenter trial in individuals with impaired glucose tolerance and, therefore, great risk for diabetes. In this study, a low-fat, calorie-restricted diet, together with regular physical activity, accomplished a sustained 5% weight loss and significantly lowered the incidence of diabetes development. Other components of dietary intake that are beginning to be scientifically examined for their potential role in weight loss are protein and fiber content and calcium intake, all of which have been associated with improved weight loss in some small studies.

So is content or calorie count more important for weight loss? Does the low-carbohydrate, high-protein, high-fat (Atkin's) diet promote greater weight loss and improved lipid levels compared with more standard diets? Can people on low-carbohydrate diets really eat more and still lose weight? Will long-term (that is, lifetime) ingestion of high-fat foods in fact result in more obesity and worsened lipid profiles? One conclusion from these studies is that, while low-carbohydrate diets may be effective in the short term in creating initial

weight loss, concerns still exist about the potential effects of these diets over the longer term, even if adherence is possible.

Is the GI of foods important or, again, is it more important to watch the calories? The presenters agreed that many answers to diet questions remain unknown.

To paraphrase a comment from Dr. Astrup in his discussion, “Whatever dietary approach is used only works as long as it continues.” For now, then, the best diet choice may be whichever diet is likely to gain patient acceptance, willingness, and adherence. Longer and larger studies are needed before specific recommendations regarding dietary content can be made.

Metabolic Syndrome, Obesity, and PCOS

As part of a symposium titled “Obesity as a Women’s Health Issue,” Andrea Dunaif, MD, of Northwestern University in Evanston, Ill., presented “Obesity and Reproduction: Insights From the Polycystic Ovary Syndrome.” PCOS affects an estimated 7–10% of premenopausal women, causing menstrual disturbances and infertility.

PCOS classically is defined as hyperandrogenism with chronic ovulatory disturbances. The underlying etiology of PCOS is unknown, but it is strongly associated with insulin resistance and is frequently included in lists of conditions associated with the metabolic syndrome (Table 1). Its recognition is important not only for reproductive health, but also because its associated insulin resistance means that women with PCOS have an increased risk for developing CVD.

Table 1. Clinical Features of the Metabolic Syndrome in Women¹⁶

- Abdominal obesity: waist circumference >35 inches
- Triglycerides ≥ 150 mg/dl
- HDL cholesterol <50 mg/dl
- Blood pressure ≥ 130/≥ 85 mmHg
- Fasting blood glucose ≥ 110 mg/dl

Some 50–80% of affected women are obese, and obesity has an independent effect to worsen the underlying insulin resistance. Women with PCOS have a sevenfold increased risk for developing type 2 diabetes compared with women without PCOS.

Weight loss should be a target in obese women with PCOS because of its many beneficial effects. Weight loss improves insulin sensitivity, menstrual regularities, and fertility rates. Studies involving high- and low-protein diets have not shown particular advantages in obese women with PCOS.

Pharmacological treatment of obesity in PCOS should specifically target the metabolic risks for diabetes and CVD. The use of insulin-sensitizing agents has been widely studied in PCOS. Both thiazolidinediones and metformin have been shown to decrease insulin and androgen levels, resulting in restoration of ovulation, improved fertility, and improved insulin sensitivity. This is the advantage of insulin-sensitizing agents over other more traditional therapies for PCOS; these agents directly address the metabolic derangements that characterize this disorder. Whereas the thiazolidinediones are often associated with mild weight gain, metformin has been shown to be associated with decreases in BMI and specifically visceral fat in women with PCOS.¹⁴

Promising Future Obesity Treatments

Great excitement exists over the potential of agents derived from gastrointestinal or gastrointestinal-related hormones to affect hunger and satiety. The development of drugs based on the exploitation of the actions of agonists or antagonists of hormones that act specifically on the appetite and do not have more generalized effects (e.g., on immune or other metabolic functions) would create agents with high efficacy and good safety profiles. Examples of hormones that are associated with inhibition of food intake include glucagon-like-peptide-1 (GLP-1), oxyntomodulin, peptide YY (PYY), and human pancreatic polypeptide.

GLP-1 is made in the gut, pancreas, and hypothalamus and has effects in the gut and the brain to delay gastric emptying, decrease hunger, and promote weight loss. When injected before a meal, it increases insulin and decreases glucagon levels postprandially, beneficial effects in overweight diabetic patients to both improve glucose control and promote weight loss. Exenatide, a synthetically developed exendin, is a GLP agonist with prolonged GLP-like effects.

Oxyntomodulin and PYY also appear to be particularly promising hormones that have GLP-like actions. Oxyntomodulin is an extended glucagon-like hormone made in the brain that not only potently reduces food intake, but also increases energy expenditure. PYY is made in the gut by endocrine cells and reduces food intake, an effect that is particularly prolonged. PYY levels have been found to be low in obese individuals.

Another plausible strategy in drug development is the creation of antagonists to hormones that increase food intake. Hormones that could be targets for antagonist intervention include ghrelin and neuropeptide Y (NPY). Ghrelin is made in the gut but is active in the hunger center of the brain. NPY is made in the brain and acts through six receptors in the central nervous system.¹⁵

Studying appetite-modulating hormones provides increased knowledge about the control of appetite, food intake, energy regulation, and weight control. This undoubtedly will result in safe and effective drug interventions in the future to prevent weight gain and assist with weight loss and maintenance for patients with weight problems.

For More Information

For those who wish to keep abreast of the latest developments and recommendations in weight management, as well as earn continuing medical education credits, NAASO will soon be launching a program offering a free evening symposium in 18 major metropolitan areas.

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Structured for primary care providers, the program, titled “Understanding and Treating Obesity,” will highlight various topics including the pathophysiology of obesity, the metabolic syndrome, current pharmacological and nonpharmacological treatment strategies, and the roles of diet, exercise, and behavior modification for weight loss. For more information, check the NAASO Web site, www.naaso.org, or contact Phase Five Communications at 866-215-2122 or obesity@ghgroup.com. More information about obesity can also be found on the American Diabetes Association Web site, www.diabetes.org, and on the NIH Web site, www.health.nih.gov.

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