apies become available. Research on transplantation with the use of umbilical-cord blood[7] or cellular therapy without long-term engraftment[8] is under way in attempts to improve overall outcomes.

In 2010, the answer to the question of who should receive an allogeneic stem-cell transplant requires a careful analysis of risk factors. This analysis should include an evaluation of the biology of the leukemia, cytogenetic and molecular genetic findings, and evidence of disease resistance to chemotherapy. Numbers of patients will increase as more matched, unrelated donors of cord blood, peripheral blood, or bone marrow are identified.[3,7,9] Patients older than 65 years of age are increasingly considered for transplantation.[3,10] Progress in the next decade will be possible with a commitment to support and simplify both established standards of care and clinical research studies. Such progress will require collaborative activities among governmental agencies, the pharmaceutical industry, and transplantation centers. Continued research into reduction of both mortality that is preceded by relapse and mortality that is not preceded by relapse as well as late effects must be an ongoing priority in the treatment of high-risk hematologic cancers.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

From the Masonic Cancer Center, the Department of Laboratory Medicine and Pathology, and the Department of Pediatrics, University of Minnesota, Minneapolis.

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Weight-Loss Maintenance — Mind over Matter?

David S. Ludwig, M.D., Ph.D., and Cara B. Ebbeling, Ph.D.

Many people can lose weight in the short term by reducing their intake of calories with the use of a variety of diets, ranging from low-fat to very-low-carbohydrate. However, few people successfully maintain their weight loss.[1] One explanation for the poor efficacy of conventional diets relates to psychological factors, since the motivation to adhere to restrictive regimens diminishes with time, especially in an environment with virtually instantaneous availability of food. A second, perhaps more fundamental, explanation is that weight loss elicits physiological adaptations — principally an increase in hunger and a decrease in resting energy expenditure[2] — that oppose ongoing weight loss.

In the search for more effective strategies, diets that are low in glycemic index and moderately high in protein merit special consideration. The glycemic index describes the way in which foods affect blood glucose levels in the postprandial period, controlled for the amount of carbohydrate.[3] The glycemic load, the arithmetic product of the glycemic index and the amount of carbohydrate, predicts postprandial glycemic response among foods with widely varying carbohydrate contents.[4] Most highly processed grain products have a high glycemic index, whereas minimally processed grains, whole fruits, legumes, and nonstarchy vegetables tend to have a moderate or low glycemic index.

The mechanisms relating glycemic response to the regulation of body weight have been examined in controlled feeding studies.[5] Meals with a low glycemic index or glycemic load elicit acute hormonal and metabolic changes that may decrease hunger and energy intake. During weight loss, a reduction in glycemic load may attenuate the decline in resting energy expenditure that is thought to promote weight regain.[6] Recently, a meta-analysis indicated that diets in which there was a reduction in the glycemic index produced moderately more weight loss than control diets,[7] although the quality of the clinical trials has been limited by their small size, a failure to show adherence to treatment, and confounding.

The glycemic response to carbohydrates is lowered when protein is ingested simultaneously, since protein delays gastric emptying and stimulates insulin secretion. Protein also displaces carbohydrates, as opposed to fat, from the diet because foods high in protein are also typically high in fat. Therefore, higher-protein diets tend to have a reduced glycemic load and might promote weight loss, at least in part, through the mechanisms discussed above.

In addition, diets that are based on these principles may be less psychologically burdensome, because they do not severely restrict any macronutrient or major food group. However, the 2010 U.S. Department of Agriculture Dietary Guidelines Advisory Committee considers the effectiveness of reducing the glycemic index to be unproven. Similarly, there is a lack of consensus regarding the optimal protein level for achieving and maintaining weight loss. A study in this issue of the *Journal* from the Diet, Obesity, and Genes (Diogenes) project[8] addresses these knowledge gaps.

Investigators from eight European countries randomly assigned 773 participants who had lost at least 8% of their initial body weight to one of four test diets, using a two-by-two factorial design (low-glycemic-index vs. high-glycemic-index diets and low-protein vs. high-protein diets), or to a fifth, control, diet. Assessment of dietary intake showed that there was a modest difference of about 5 glycemic-index units between the low-glycemic-index and high-glycemic-index groups and a difference of about 5 percentage points in protein content between the high-protein and low-protein groups. After 6 months, body weight differed by about 2 kg among the groups, with a direct relationship to glycemic load — lowest in the group assigned to the low-glycemic-index–high-protein diet, intermediate in the groups assigned to the low-glycemic-index–low-protein and the high-glycemic-index–high-protein diets, and highest in the group assigned to the high-glycemic-index–low-protein diet. Of note, study completion rates were significantly better among participants in the low-glycemic-index and high-protein diet groups.

The study has several notable strengths, including the large number of participants and a multicenter, multinational design, providing evidence of effectiveness and generalizability. The apparent control for treatment intensity and behavioral methods across groups (although not across countries) allows for a fair testing of dietary hypotheses. Furthermore, the investigative team appears to have had scientific balance; one senior member had espoused a skeptical view of the glycemic index,[9] providing confidence that the study was conducted and interpreted without unconscious bias. The primary limitation of the study is the short duration of follow-up. A 2-kg difference in body weight, by itself, has limited practical implications. But a diet that could effectively prevent weight regain over the long term would have major public health significance. In this regard, the 12-month and longer follow-up data will be informative.

The observed effects on body weight were obtained from small mean differences in glycemic index and protein among the groups. In principle, more powerful methods for effecting behavioral change and improved availability of low-glycemic-index foods may facilitate the long-term adoption of diets with a substantially lower glycemic load and result in larger effects on body weight. Moreover, a low-glycemic-index diet may reduce the risk of diabetes and heart disease independently of body weight,[5] and data addressing this possibility will be forthcoming from the Diogenes trial.

The present study contrasts, but does not necessarily conflict, with data reported by Sacks et al.,[10] who assigned 811 people to one of four diets that differed in the percentage of total energy derived from carbohydrate, protein, and fat. In contrast to the protocol in the Diogenes trial, participants in all four groups were counseled to consume carbohydrates with a low glycemic index. Similar to the results in the Diogenes trial,

the protein content of the diets at 6 months differed by only about 5 percentage points. After 2 years, no significant difference in body weight was found among the groups, although among subjects who completed the study, those who consumed higher-protein diets weighed about 1 kg less than those who consumed lower-protein diets (P=0.11).[10] Together, these two studies suggest that the ratio of carbohydrate to fat has relatively little importance for weight control among persons consuming a low-glycemic-index diet, and higher protein intake may have additional benefits.

The Diogenes study provides reassurance regarding three long-standing concerns about glycemic index: that measured values apply to individual foods only and have no relevance to mixed meals, that effects observed in clinical trials arise from confounding by macronutrients or fiber, and that the concepts are confusing and impractical for the general public. Indeed, the higher study-completion rate in the low-glycemic-index groups provides compelling evidence of the practicality of low-glycemic-index diets.

Several recent clinical trials have shown no significant difference in weight loss among various popular diets, leading to the notion that dietary composition is less important than adherence to a diet, whatever it might be. However, this conclusion does not consider the fundamental relationship between psychology and physiology. A person's ability to maintain adherence over time may be influenced by the way in which a diet affects hunger and metabolism. Additional research is needed to clarify the mechanisms by which dietary composition regulates body weight and to devise novel strategies to effect behavioral changes.

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From the Optimal Weight for Life Program, Department of Medicine, Children's Hospital; and the Department of Pediatrics, Harvard Medical School — both in Boston.

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Proton-Pump Inhibitors and Birth Defects — Some Reassurance, but More Needed

Allen A. Mitchell, M.D.

Limited data on safety are usually available when new medications are first marketed, but for appropriate ethical reasons, safety studies of the use of medications during pregnancy are rarely conducted before marketing. Because we must await postmarketing studies to resolve questions of fetal safety,[1] it becomes critical to identify medications that are commonly used during pregnancy and to study them quickly. The report on proton-pump inhibitors (PPIs) in this issue of the *Journal*[2] is therefore both timely and important.

Taking advantage of a series of linked databases covering every live-born infant in Denmark, Pasternak and Hviid identified increasingly high rates of prescriptions for PPIs filled in the weeks before conception and throughout pregnancy. They estimated that antenatal exposure to a PPI among infants born between 2005 and 2008 peaked at about 2%; exposure during the first trimester, when teratogenic risk is greatest, was about 0.7%. This pattern is not unique to Denmark; in our Slone Birth Defects Study, the fre-