The prevalence of obesity has increased dramatically over the last few decades, not only in North America, but also in Europe, Latin America, North Africa, and many parts of Asia. Using the World Health Organization definitions for obesity (body mass index [BMI] ≥30 kg/m²) and overweight (BMI, 25.0–29.9 kg/m²) shows that about 1 in 3 middle-aged adults in the United States is obese and 2 in 3 are overweight or obese. Thus, excess body weight is a global public health problem that is most serious in the United States.

Plasma levels of C-reactive protein (CRP) and interleukin-6 rise with increasing levels of BMI and fall with weight loss. Elevated levels of these biomarkers reflect an enhanced inflammatory state, possibly caused by insulin resistance and dyslipidemia associated with overweight and obesity. Consequently, measurement of CRP and related biomarkers is likely to be informative for comparisons of dietary strategies for weight loss.

Overweight and obesity result from a long-term imbalance between energy intake and energy expenditure. Although diet and exercise are the most important modifiable determinants of body weight, regulation of appetite and satiety involves more complex factors, including genetic, hormonal, behavioral, psychological, social, and environmental factors. Many individuals who are overweight or obese have great difficulty in reducing their body weight by 5% to 10% through modification of diet and exercise habits. Low-calorie diets are successfully associated with an initial weight loss, but weight regain after weight loss is a major limitation of most diets regardless of differences in their macronutrient content.

Despite substantial differences in the energy density of fat, carbohydrate, and protein, there is little evidence that differences in daily intake of these macronutrients influence weight loss. The energy density of fat is more than twice that of carbohydrate or protein, but there is little evidence that low-fat diets have any more favorable effects on weight loss than low-carbohydrate diets. Indeed, as low-fat diets have been widely promoted to lower blood cholesterol levels for the prevention of cardiovascular diseases, some experts have expressed concern that individuals on low-fat diets may compensate by increasing their energy intake from carbohydrates. Indeed, there is a perception that low-fat diets are healthy and should reduce the risk of cardiovascular disease. Many low-fat trials have resulted in negligible effects on body weight after a follow-up of ≥1 year. Indeed, the Women’s Health Initiative Dietary Modification Trial, which compared the effect of a low-fat dietary pattern (with 20% of total energy from fat) with usual diet in almost 49,000 postmenopausal women, reported a significant reduction of 2.2 kg at 1 year, but there was no significant difference in body weight between the allocated groups at 7.5 years.

In contrast, allocation to a balanced diet providing an energy deficit of 500 to 750 kcal/d from the participants’ energy requirement, alone or with group exercise sessions for 90 min/wk, was associated with a 10% reduction in body weight at 1 year in a trial of 107 older people. Thus, the available evidence suggests that a reduction in daily caloric intake is the chief dietary determinant of weight loss.

Recently, the Diet, Obesity, and Genes (DIOGenes) trial reported the effects of experimental diets that differed in their...
protein content and glycemic index on weight regain after weight loss. The trial was carried out in 8 European countries and randomly allocated 773 overweight individuals who had successfully completed a weight-reducing diet to 1 of 5 experimental diets; 548 (71%) completed the intervention. The high-protein diet achieved a 5.4% higher intake of energy from protein than the low-protein diet, and the low-glycemic-index diet had 4.7 unit lower glycemic index than the high-glycemic-index diet. Compared with the control diet, the mean initial weight loss with low-calorie diets was 11 kg. Only the low-protein/high-glycemic-index diet was associated with significant weight regain. The low-glycemic-index diet was associated with about a 1-kg-lower weight regain compared with the high-glycemic-index diet. Similarly, the high-protein diet was associated with about a 1-kg-lower weight regain compared with the low-protein diet. This trial was highly informative, and the results highlight the relevance of carbohydrate quality and protein content for maintenance of weight loss.

In a further report from the DIOGenes trial in this issue of Circulation, Gögebakan and colleagues examined the effects of weight loss and long-term weight maintenance of these experimental diets varying in protein and glycemic index on cardiovascular risk factors, including plasma levels of CRP. After the 8-week low-calorie diet, individuals were randomly allocated to 1 of 5 groups comparing diets with moderately high or low protein content and moderate differences in glycemic index for weight loss maintenance. Blood and anthropometric measures were recorded after the 8-week initial low-calorie diet and after the 26-week interventions to prevent weight regain after weight loss. Among the 487 adults with complete data, levels of blood pressure, blood lipids, and CRP improved significantly during the weight-loss period. Blood levels of CRP declined by $-0.85 \text{ mg/L} (95\% \text{ confidence interval}, -1.30 \text{ to } -0.41)$ during the initial weight loss period and by a further $-0.46 \text{ mg/L} (95\% \text{ confidence interval}, -0.79 \text{ to } -0.13)$ among those allocated to a low- versus a high-glycemic diet, consistent with the effects on weight reduction. Paradoxically, CRP levels declined by $-0.25 \text{ mg/L} (95\% \text{ confidence interval}, -0.59 \text{ to } -0.17 \text{ mg/L})$ among those assigned to a low-versus high-protein diet, which was not consistent with their effects on body weight after the initial weight loss.

The favorable reduction in CRP levels associated with weight loss and prevention of weight regain after weight loss reinforces the value of the low-glycemic-index diet. The paradoxical effects of the modest adverse effects on plasma CRP levels of a high-versus low-protein diet warrant replication to exclude the effects of chance in the assessment of multiple comparisons in a relatively modest number of individuals.

The DIOGenes trial reinforces the scientific rationale underlying the current 2010 Dietary Guidelines for Americans. These guidelines outline practical strategies to balance calories to control body weight and to increase physical activity. In addition to limiting portion sizes, using small plates, avoiding sugar-sweetened drinks, and reducing intake of alcohol and energy-dense foods, the dietary guidelines include practical recommendations on selected foods to increase or decrease. The recommendations include increasing intake of fruit and vegetables (especially dark green, red, or orange vegetables, beans, and peas); replacing refined grains by whole grains; choosing low-fat or fat-free milk, low-fat spreads, and yogurt; selecting lean meat and poultry; and substituting fish for meat. The results of the DIOGenes trial highlight the importance for cardiovascular risk factors of even modest differences in glycemic index and protein content of low-calorie diets for long-term maintenance of weight loss.

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Robert Clarke

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