

Clinical Use of a Protein-Sparing Modified Fast

Bruce R. Bistrian, MD, PhD

OBESITY is notoriously resistant to treatment. Short-term weight reduction of greater than 18 kg occurs in fewer than 5% of outpatients.¹ Possible explanations for noncompliance and ineffectiveness of conventional diet therapy include hunger and the disappointingly slow rate of weight loss. Total fasting reduces hunger and induces rapid weight loss,² but half the weight loss in the first month and one fourth to one third thereafter is from muscle tissue,³ and hepatic, renal, and endocrine function is affected.⁴ For these reasons fasting regimens are generally recommended only for inpatients.

Long-term follow-up of persons who previously fasted has demonstrated a high rate of recidivism⁵ due to obligate regain of lean tissue or the lack of a weight-maintenance program or both. When a fast is supplemented by small amounts of protein in the form of egg albumin,⁶ casein,⁷ casein with glucose,⁸ or amino acids with glucose,⁹ body protein losses are reduced without a return of hunger. If larger amounts of protein (1.2 to 1.5 g/kg ideal body weight) as egg albumin¹⁰ or meat protein,^{4,11,12} along with other essential nutrients, are provided, nitrogen equilibrium is achieved, and physiological function improves. The addition of protein, fat, or carbohydrate to such a regimen does not improve protein sparing¹⁰ in the semistarvation range of fewer than 1,000 kcal but will eliminate ketosis if more than 100 g of carbohydrate is added. These semistarvation ketogenic regimens are effective. Weight loss in excess of 18 kg has occurred in the majority of patients in several large series of studies conducted among outpatients.^{8,11,13}

In light of these results, the limit-

From the Nutrition and Metabolism Laboratory, Cancer Research Institute, New England Deaconess Hospital, Boston, Department of Nutrition and Food Science, Massachusetts Institute of Technology, Cambridge, and Harvard Medical School, Boston.

Reprint requests to Department of Medicine, Harvard Medical School, New England Deaconess Hospital, Boston, MA 02215 (Dr Bistrian).

ing factor in the successful management of obesity is maintenance of weight loss. The separation of obesity treatment into weight loss and weight-loss-maintenance components made possible by modified fasting regimens has important therapeutic implications, since many of the techniques suitable for one purpose are inappropriate for the other purpose. For example, a diet designed to reduce weight must be hypocaloric, which renders it inappropriate for weight maintenance. Moreover, given the restrictive composition of present semistarvation regimens, simply increasing the allowed amounts of a limited variety of nutrients is not desirable. Similarly the benefits of behavior modification techniques for weight loss have proved illusory, but such techniques do help in preventing regaining weight.¹⁴

The appropriate use of behavior modification may be as a weight-maintenance tool when the rapid weight loss induced by modified fasting is no longer serving as a positive reinforcer. Preliminary results with such a program, using a semistarvation regimen for weight reduction accompanied by instruction in behavior modification, nutrition, and exercise for maintenance of weight loss, have been recently reported.¹⁵ In 36 patients followed up for one to 4½ years, maintained weight loss greater than 9 kg occurred in more than half the patients; loss greater than 18 kg occurred in one third of the patients.

Protein-Sparing Modified Fast

The semistarvation regimen used by our group^{4,11,12} has been designated the protein-sparing modified fast (PSMF). To minimize misconceptions regarding this regimen, however, many points require clarification. The protein used in a PSMF must be of the high biologic value found in animal sources (meat, fish, and fowl), which also contain approximately 1 g of potassium (half the potassium requirement) and other micronu-

trients, including magnesium and phosphorus. The daily protein allowance is 1.5 g/kg of ideal body weight. Other components of the daily PSMF diet are One-A-Day Vitamins Plus Minerals, providing the US recommended dietary allowances for all vitamins and minerals except calcium, phosphorus, and magnesium; 5 g of sodium chloride; 25 mEq of potassium in liquid form as the bicarbonate and citrate; 800 mg of calcium daily as four Tums, usually not available in commercial vitamin and mineral preparation; fluids ad lib but at least 1,500 ml; absent carbohydrate; and meal feeding two to three times daily. Protein content for various meats either in the cooked¹⁶ or uncooked¹⁷ form can be obtained by reference to standard tables. Patients should weigh each portion and consume the protein in two to three meals.

Potassium supplementation is crucial. Although fasting persons may tolerate low potassium regimens, the protein-sparing nature of a PSMF increases potassium requirements over requirements during total fasting. Two grams of potassium, half provided from the protein source and half provided as a supplement (potassium bicarbonate, 25 mEq), will permit potassium balance. Any liquid form of potassium in a sugar-free vehicle can be used, although potassium provided with the metabolizable anion (gluconate, citrate) or as bicarbonate will tend to counteract the mild ketoacidemia of modified fasting. Potassium chloride in slow-release tablets should not be used because of reduced gut motility in semistarved patients. Salt restriction is not desirable because of the obligate natriuresis of fasting; salt intakes of at least 5 g/day should be maintained. If symptoms of postural hypotension or muscle cramping occur, it is safer and just as effective to increase salt intake without changing the level of potassium supplementation.

The vitamin and mineral supplements meet the recommended daily dietary allowances except possibly for magnesium. Certain protein sources such as seafood (particularly crab, oyster, lobster, and shrimp) contain substantial amounts of magnesium. In addition, recommended daily dietary allowances are intended to exceed minimum daily requirements. Vitamin K is not routinely provided, although an oral form of vitamin K is available. During treatment periods of as long as a year, nutrient deficiencies have not been found.

PSMF vs Liquid Protein Diets

Recently controversy regarding the PSMF and other semistarvation regimens has developed in relation to the liquid protein diet. Ten deaths have resulted in otherwise healthy women, aged 25 to 44 years, who had experienced substantial weight loss (mean, 41 kg).¹⁸ Since this liquid protein diet contains protein and is low in calories, it bears a superficial resemblance to the PSMF. However, there are major differences. Liquid protein is hydrolyzed collagen fortified with one of the limiting essential amino acids, tryptophan, but it remains a protein source of poor biologic value. The exclusive use of a poor-quality protein is contrary to extensive evidence demonstrating the necessity for adequate daily quantities of the eight essential amino acids.¹⁹ This is not to imply that there is anything inherently wrong with this protein, ie, that it is toxic. Gelatin is a widely used foodstuff that may have an additional role as a concentrated supplemental protein in hospitalized patients. However, it should never be used as the sole source of protein in any diet whether for a hypocaloric or maintenance regimen.

Liquid protein also contains only minor amounts of potassium, phosphorus, and magnesium. Thus, three of the essential nutrients for maintenance of lean tissue—nitrogen, potassium, and phosphorus²⁰—are inadequate in either quantity or quality. Potassium deficiency is of particular concern given the presumed cardiac nature of the unexplained deaths attributed to the liquid protein diet²¹ and the extensive evidence in animals linking potassium depletion to myocardial degeneration.²² It is particularly unfortunate that by limitation

of dietary carbohydrate (liquid protein contains 1 g of carbohydrate for each 5 g of protein), hunger is ameliorated, permitting adherence to such a diet for extended periods.

Deaths have also occurred in the series of 1,300 patients studied by Vertes et al,²³ but none of these four deaths were considered unexplained. We have not had any deaths in the more than 800 patients using the PSMF, but we do accept the likelihood that unrelated deaths will occur at some time in this high-risk population. It is not totally unfortunate that the liquid protein diet has focused attention on all semistarvation regimens. Recognition of the potent nature of all such diets and their inappropriate use as a do-it-yourself program or if handled in a casual manner by physicians unfamiliar with their use is sorely needed.

Biochemical Aspects of PSMF

The PSMF is characterized by a fall in serum insulin and glucose concentrations, a rise in free fatty acid and ketone levels, and the appearance of ketonuria,⁴ similar to what happens in a total fast. Ketone bodies are important to protein sparing in total and semistarvation, substituting for protein-derived glucose as a fuel for the brain. In the early weeks of a PSMF, there may be a transient fall in total protein, albumin, polymorphonuclear leukocyte levels, and total WBC count, but these reductions are slight and do not exceed the limits of normal variation in adults. Presumably, the changes reflect the negative nitrogen balance in the early period while adaptation to fasting is taking place. Serum uric acid levels initially rise above baseline values but after several months fall to the baseline level or even below as the modified fast is continued. The initial rise is due to a competition of urates with ketones for renal tubular excretion²⁴; the later fall is due to the increased reabsorption of ketone bodies as the starvation period is extended.²⁵ Usually serum cholesterol levels fall; serum triglyceride levels always drop. There may be a transient increase in serum cholesterol levels after substantial weight loss in patients who are initially hypercholesterolemic, but the values return to baseline or below within several days after weight loss is discontinued.

Thyroid function, as measured by total triiodothyronine is reduced. Natriuresis, kaluresis, and diuresis develop but are not as severe as in total fasting. This loss of water and electrolytes is best explained by urinary ketone-body excretion²⁶ and is less pronounced in a PSMF.

Clinical Aspects of PSMF

Weight loss ranges from 1 to 3 kg weekly, depending on the patient's age, height, weight, sex, and level of activity. During the first two weeks of a PSMF, substantially more weight is lost due to diuresis, which may also produce mild symptoms of a transient postural hypotension. Patients who are more obese have fewer symptoms than those who are less obese. Patients who are only minimally obese have the highest serum ketone levels and are also most likely to experience the signs and symptoms of postural hypotension and electrolyte disturbances in the early phase of modified fasting. Systolic and diastolic blood pressures (BPs) fall, particularly in hypertensive patients. Complaints of cold intolerance, indicating functional hypothyroidism, are common but mild. Bowel movements become less frequent and may lead to constipation or even obstipation.

Hair loss (a telogen effluvium) is occasionally seen after substantial weight loss.²⁷ The loss is temporary; normal hair growth resumes after the weight loss is discontinued. A normal hair pattern returns after several months of a weight-maintenance diet.

Alteration of menstrual function occurs in a limited number of patients. Three patterns are seen: (1) Morbidly obese patients who are amenorrheic often have spontaneous return of menses during weight loss. (2) Irregularity such as menorrhagia or irregular cycle length after weight loss greater than 18 kg may develop in patients with moderate degrees of overweight and a normal menstrual pattern. (3) Minimally obese women may experience irregularity or even amenorrhea with even mild degrees of weight loss. Except for the return of function in the morbidly obese person, these patterns are reversed when weight loss is discontinued, although the minimally obese person may need to regain to their initial weight.

As assessed by delayed hypersensitivity skin testing, cellular immune function is not impaired, even after major weight loss.²⁸

Respiratory function can show a distinct improvement as a result of the weight loss and the effect of ketone bodies, which improve the cerebral response to carbon dioxide.²⁹

Exercise tolerance is increased during weight loss in untrained subjects and is maintained reasonably well in well-trained persons who are not clinically obese.³⁰

Medical Management of PSMF

Postural hypotensive symptoms are minimized by giving salt and potassium; in addition, a balanced-deficit diet limited in refined carbohydrate and simple sugars is provided prior to the PSMF to produce a more gradual diuresis. Plateauing of weight loss does not occur for periods longer than several days. Dietary carbohydrate does depress ketonuria and cause some reaccumulation of water, which remits with redevelopment of ketonuria.

Constipation is minimized by increased fluid intake; by bulk-producing agents low in carbohydrate, eg, bran; by mild laxatives, eg, milk of magnesia; and by reducing calcium intake when necessary. Bowel movements should occur at least weekly to prevent abdominal cramping or fecal impaction.

Complaints of hair loss can be managed by assuring the patient of its temporary nature. Amenorrhea can be similarly managed with one important exception. Pregnant patients should not be consuming a PSMF, nor should the diet be continued if pregnancy occurs. The implications of maternal weight loss on fetal development are disturbing. If the possibility for pregnancy exists, patients should be informed of this contraindication; if amenorrhea develops during the course of a PSMF, a pregnancy test must be done.

Exercise limited by previous exercise tolerance and fatigue should be encouraged after the first week. A walking program should be encouraged, since such exercise is more likely to be continued. Patients should be cautioned about hot showers or baths immediately after exercise owing to the potential for hypotensive symptoms. There may also be reduced abil-

ity to tolerate swimming in cold water.

The development of mild intercurrent illness need not interfere with continuation of the PSMF. The nitrogen-sparing of a PSMF persists during infection.³¹⁻³³ In patients needing surgery, parenteral administration of amino acids³⁴⁻³⁶ can be substituted for oral feeding, or the PSMF can be temporarily discontinued. Glucocorticoids may also be less catabolic in patients consuming a PSMF.³¹

There are few absolute known contraindications to medications while consuming a PSMF. Drugs in a carbohydrate-containing vehicle should be avoided. Diuretic drug therapy, whether used for water retention or hypertension, should be discontinued when the PSMF is begun or within several days if the initial doses were large. In the latter case, this should be done while the patient is in the hospital. The diuretic effect of a PSMF acts synergistically with such medications, and notable postural hypotension can occur. More important, serious potassium depletion can result. Other antihypertensive drug therapy can be continued, with its reduction and elimination determined by subsequent BP response. In maturity-onset diabetes in obese patients, therapy with oral hypoglycemic agents can be discontinued coincident with the PSMF. Such patients who require insulin injection can have this drug therapy withdrawn immediately if total daily requirements of isophane insulin suspension and regular insulin are 35 units or less. With higher requirements, the dose is initially reduced by half. When the blood glucose level stabilizes below 150 mg/dl, therapy with insulin injections is further reduced to 30 to 35 units/day and then discontinued after stabilization of the blood glucose level. Such weaning regimens should be initiated only with inpatients.⁴

Patients with gout who take allopurinol or probenecid can continue receiving the medication. Those with asymptomatic hyperuricemia less than 10 mg/dl need not, in our experience, receive premedication with allopurinol before commencing the PSMF. Precipitation of gout by a PSMF is rare. If it does occur, standard treatment can be used. In our experience, colchicine is effective although somewhat more likely to

produce diarrhea.

Although there is little medical necessity for follow-up of this intensity, there does appear to be a reinforcing aspect of weekly visits that helps to maintain patient compliance. Some aspects of the program can be managed by a clinical psychologist trained in behavior modification techniques, but the physician must assume overall responsibility. Generally, at least weight, BP, and urinary ketone levels should be measured at each visit; and the patient should be queried regarding untoward symptoms.

Refeeding should be extended during a four- to six-week period to minimize the abrupt weight gain that can result from the antidiuresis induced by dietary carbohydrate. Simple sugars should be avoided, for they are most likely to aggravate this problem. The addition of 3% to 6% carbohydrate-containing vegetables and skim milk, progressing to higher carbohydrate-containing vegetables, fruits, and cereals seems to work well. Potassium supplementation is discontinued early in the feeding program after ketonuria is eliminated, but vitamin supplementation should be maintained. Because of the lingering hypometabolism, estimated caloric needs often exceed actual requirements and quickly lead to weight gain during this phase. The deficit in lean tissue should be minimal after a PSMF. Thus, one does not see the substantial gains reflecting protein repletion that routinely occur after total fasting. However, weight regain secondary to a return to former inappropriate eating patterns can and does occur after a PSMF.

Contraindications

Patients with marginally compensated cerebrovascular and cardiovascular disease should have their therapy individualized. Balanced against the risk that mild postural hypotension imposes should be the potential benefit from weight loss. For this reason, patients with symptomatic cerebrovascular insufficiency, who can expect little benefit from weight loss, should probably not undergo a PSMF. Those with cardiac disease, particularly those with severe degrees of obesity, usually can reap major benefits in terms of improved cardiac function with weight loss. According-

ly, the benefits of a PSMF often exceed the risks in such patients. The PSMF is contraindicated in the presence of a recent myocardial infarction, although there is no good evidence that free fatty-acid elevation of the degree seen with a PSMF predisposes to cardiac arrhythmia. Patients with juvenile-type diabetes, even those who become moderately obese after the development of diabetes, should never be considered as candidates for a PSMF, since insulin therapy cannot be withdrawn in such patients.

Other relative contraindications for a PSMF would be the adolescent (except on an experimental basis), the child, and the aged, due to the limited information about their response and greater potential for harm with any stringent weight-reducing regimen. It would be inappropriate to lose weight purposefully by any means when there is serious illness complicating obesity in which severe weight loss is anticipated and the prognosis is poor. Many malignant conditions would be in this category. Patients with severe liver and renal disease in whom protein intakes must be limited should also be excluded from the PSMF.

The morbidly obese person whose weight exceeds 200% ideal body weight is resistant to balanced-deficit dieting. Although substantial weight loss can be achieved by semistarvation, ketogenic regimens, the ability of most severely obese persons to maintain body weight is minimal. For this reason the PSMF should be used in morbidly obese persons with short-term goals such as medical emergencies like the Pickwickian syndrome, in preparation for surgery, or as the final attempt at medical therapy before bypass surgery. Gastric bypass surgery³⁷ will probably become the procedure of choice in morbidly obese persons who are suitable candidates.

Summary

Concerned primary-care physicians armed with some basic knowledge in metabolism can confidently handle the PSMF as a weight-reduction regimen. However, the PSMF should be considered investigational; informed consent is desirable. Unlike balanced-deficit dieting, the PSMF is a potent clinical tool that has definite risks

and indications and contraindications for clinical use similar to other efficacious clinical procedures. The PSMF should not be used for trivial reasons or small amounts of weight loss. It should be restricted to those persons who are at least 30% over desirable body weight; for such persons there is an increased risk of morbidity and mortality attributable to obesity,³⁸ and the PSMF is best tolerated. As developed in detail elsewhere, a comprehensive obesity treatment program should also be combined to optimize the results of treatment.^{11,13,39}

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Nonproprietary Name and Trademark of Drug

Allopurinol—Zyloprim.

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