Ann. Rev. Nutr. 1987. 7:465–84

STARVATION AND SEMISTARVATION DIETS IN THE MANAGEMENT OF OBESITY[1,2]

Janis S. Fisler

Department of Medicine, University of Southern California, Los Angeles, California 90033

Ernst J. Drenick

Medical Service, West Los Angeles Veterans Administration Medical Center, Wadsworth Division, Los Angeles, California 90073; and Department of Medicine, University of California, Los Angeles, California 90024

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[1]Send reprint requests to Janis S. Fisler, Ph.D., Division of Diabetes and Clinical Nutrition, USC School of Medicine, 2025 Zonal Avenue, Los Angeles, CA 90033.

INTRODUCTION

An important advance in the treatment of obesity in recent years has been the development of very low calorie diets. The use of these diets has grown from the initial reports of 20 years ago using supplements during therapeutic fasting for weight reduction to the many commercial weight loss programs now available in this country and in Europe. For a series of papers on various aspects of the management of obesity by severe caloric restriction, the reader is referred to a book edited by Blackburn & Bray (9).

This paper addresses four questions. What is a "semistarvation" or "very low calorie diet"? Is a semistarvation diet nutritionally adequate? Is it safe? Who should use such a diet? In attempting to answer these questions, we discuss the historical development of semistarvation diets; evaluate the risks attendant to both starvation and semistarvation diets, i.e. the loss of body protein and minerals and what factors modify these losses; examine the potential complications; and conclude by suggesting the appropriate target population.

HISTORICAL DEVELOPMENT

Total fasting for weight reduction became popular about 25 years ago (10, 32, 33). Weight loss was spectacular. By the early 1970s, however, it was evident that weight reduction by total fasting was not without hazards. The main concern to many investigators was the loss of body protein: during the first month of starvation in the obese, approximately 6.5 kg of lean tissue are catabolized; during the second month, this is reduced to 3.5 kg, and this rate of loss continues with more prolonged fasting (93).

The "protein-supplemented fast" was evolved to reduce the loss of body protein that occurs during starvation. Initially, periods of food intake (160–600 kcal, 0.67–2.51 J) were interspersed with periods of total fasting (13, 99) or were used as realimentation after a prolonged fast (83, 93). In 1970, Apfelbaum and associates (2) reported using a protein-supplemented fast abruptly after normal food intake and found that the mean nitrogen balance was positive by the third week. Thereafter, two groups independently evaluated very low calorie, protein-supplemented dieting, and two types of diets evolved. Blackburn and associates (8) found that, on the average, nitrogen equilibrium was attained with 1.4 g protein/kg ideal body weight (IBW)/day in males and 1.2 g protein/kg IBW/day in females consuming 300–600 kcal (1.26–2.51 J) diets composed solely of meat or egg. Genuth & coworkers (46) reported favorable clinical results in an outpatient population with diets composed of 35–45 g casein with glucose added to bring the energy intake to 300 kcal (1.26 J) per day. A slightly negative mean nitrogen balance persisted

even after an extended diet period. There is still some debate as to the advantage or disadvantage of carbohydrate in the semistarvation diet, and both high-protein, natural food diets and mixed protein-carbohydrate formula diets are used. In recent years, the term "very low calorie diet" has been used to refer to diets that have less than 600–800 kcal (2.51–3.35 J) and from 30 to more than 100 g protein.

WEIGHT LOSS

Tables 1 and 2 give weight loss data taken from the literature on starvation and semistarvation diets. For the first five to ten days of starvation, weight loss for males is as much as 1.1 kg/24 hr. Weight loss decreases with the duration of the fast and stabilizes at 0.36 to 0.47 kg/24 hr at the end of one month. Weight loss on semistarvation diets is only 50–80% as great as in a total fast. The pattern of weight loss is, however, the same for both starvation and semistarvation regimens. Males lose approximately 30% more weight per

Table 1 Selected studies of weight and nitrogen loss during starvation

Ref.	Subjects no., sex	Age (yr)	Initial weight (kg)	Time on fast	Weight loss (kg/24 hr)	Nitrogen balance (g/24 hr)
32	1F, 10M	33–71	108–204	Day 1–10	0.82	—
				Month 1	0.36	−4.0[a]
				Month 2	0.32	−2.4[a]
93	1F, 12M	33–49	107–206	Month 1	0.58	−6.7
				Month 2	0.38	−3.4
				Month 3	0.38	−3.1
81	58F	14–71	75–153	Day 1	—	−9.4[a]
				Day 1–14	0.55	—
				Day 23–30	0.27	−4.2[a]
81	18M	22–66	76–199	Day 1	—	−11.7[a]
				Day 1–14	0.73	—
				Day 22–30	0.36	−3.6[a]
39	7M	27–55	134–207	Day 1–5	1.1	−10.2[b]
				Day 6–15	0.68	−8.1[b]
				Day 16–40	0.47	−5.0[b]
39	15M	26–57	103–225	Day 1–5	1.1	−11.9
				Day 6–15	0.73	−8.9
				Day 16–40	0.47	−6.1

[a] Apparent balance calculated from urinary nitrogen only.
[b] KCl supplement during fast.

Table 2 Selected studies of weight and nitrogen losses during semistarvation[a]

Ref.	Subjects no., sex	Age (yr)	Initial weight (kg)	Protein intake (g)	Energy intake (kcal)	Diet duration	Weight loss (kg)	Nitrogen balance (g/24 hr)	Nitrogen balance (#Pos/Tot)
2	26F	14–56	--	55 casein	220	Week 1	0.69	−1.6	—
						Week 2	0.34	−0.2	—
						Week 3	0.28	+1.6	
21	6F, 1M	23–38	120–169	100 meat	400	Week 1	—	−4.9	—
						Week 3–5	—	−1.6	—
				50 meat	400	Week 1	—	−4.6	—
						Week 3–5	—	−1.0	—
6	5F	21–28	72–108	46 meat	394–505	Week 1	—	−4.8	—
						Week 2	—	−2.9	—
						Week 3	0.30	−2.1	—
39	10M	37–57	115–173	100 soy or collagen	400	Day 1–5	1.1	−7.4	0/10
						Day 6–15	0.46	−5.6	0/10
						Day 16–40	0.36	−2.7	4/10
39	6M	38–70	114–171	55 mixed food	500	Day 1–5	0.83	−6.8	0/6
						Day 6–15	0.44	−4.8	0/6
						Day 16–20	0.36	−4.5	0/6

110	6M	19–33	135–178	68–120	700	Day 1–16	0.51	–5.7	—
				SUPRO 630®[b]		Day 17–32	0.29	–2.9	—
						Day 33–64	0.28	–1.3	2/6
52	9F	25	84	85	559	Week 1	—	–4.0	—
				meat		Week 2–3	0.2	–0.5	—
						Week 4–8	0.2	+0.1	4/9
52	8F	26	87	44	501	Week 1	—	–4.8	—
				meat		Week 2–3	0.2	–2.7	—
						Week 4–8	0.2	–2.0	0/7
107	9M	39	138	50–53	655–789	Day 5–28	0.37	–5.0	—
						Day 29–68	0.33	–2.8	—
107	16F	38	99	50–53	655–789	Day 5–28	0.23	–2.5	—
						Day 29–68	0.21	–1.8	—
51	3F, 2M	43	126	30	300	Day 1–4	—	–10.8	—
				milk & soy		Day 5–16	—	–7.4	—
						Day 17–36	—	–5.2	0/5

[a] All diets contained potassium and all nitrogen balance data are calculated from urinary and fecal nitrogen losses.
[b] Soy isolate 75%, casein 18%, albumin 2%; J. B. Williams, Crantford, New Jersey.

day than females, and heavier individuals lose more weight than lighter individuals.

Composition of the weight loss can be attributed to protein, fat, or water losses by means of the energy-nitrogen balance method (38, 47, 73, 110) or the fluid-nitrogen balance method (51, 107). The strengths and limitations of these methods have been reviewed (35). During the initial two weeks of total fasting when water losses are high, protein and fat losses as a percentage of weight loss are low, 6–10% as protein and 30–50% as fat (24, 47). After one month of fasting, protein losses stabilize at 5–10% of weight loss and fat losses at about 70% of weight loss (24, 38, 47), although fat loss has been estimated to be as high as 96% of the weight loss in prolonged starvation (81). Passmore et al (73) maintained two men and five women on mixed diets providing 400 kcal (1.68 J) and 25 g protein for six weeks. Fat loss varied from 73 to 83%, protein loss from 4 to 7%, and water loss from 10 to 23% of the total weight loss in representative patients. There were no differences between the sexes. The time course of the change in the composition of weight loss has been reported for subjects consuming 600–800 kcal (2.51–3.35 J) diets containing either 68 or 121 g protein for 64 days (110) and in subjects given 300 kcal (1.26 J), 30 g protein diets for 36 days (51). In these two studies the composition of weight loss during the first two weeks ranged from 46 to 57% water, 35 to 48% fat, and 5.9 to 9.8% protein. During the third and fourth weeks the composition of the weight loss was 16–36% water, 55–77% fat, and 5.5–9.2% protein. Thereafter, water and protein losses, as a percentage of weight loss, stabilize at about 20% and 2–10%, respectively. Fat losses tend to remain at 60–70% of weight loss beyond one month of dieting in subjects consuming 300–700 kcal (1.26–2.93 J) diets (38, 51, 110), although in one study of subjects consuming 700 kcal (2.93 J) diets after 68 days 93% of the weight loss was fat (107).

NUTRITIONAL ADEQUACY

The question of the nutritional adequacy of very low calorie diets has focussed primarily on the ability of these diets to conserve body protein, the standard measure of which has been nitrogen balance, although some studies have also used more complex measures of body composition change (see above) or have measured blood protein levels. Much less is known regarding the adequacy of mineral and vitamin nutrition during starvation and semistarvation diets. Again, the balance method has been the primary tool for examining mineral status during these diets.

This section focuses primarily on protein and mineral nutrition, as determined by total body balance and by blood protein and mineral levels during starvation and semistarvation, and on the factors that determine conservation

or loss. For other discussions of protein nutrition during semistarvation diets, the reader is referred to reviews by Wadden and associates (103) and Felig (34); for a review of individual variability and metabolic adaptation to low intakes of energy and protein, see the recent paper by Waterlow (104); and for discussions of water, electrolyte and mineral metabolism, and acid-base changes during starvation, the reader is referred to reviews by Drenick (24) and Kerndt et al (58).

Protein Losses

Table 1 presents selected studies of nitrogen loss reported for subjects totally fasted for up to three months. Losses vary from 4 to 12 g nitrogen (25 to 75 g protein)/24 hr during the first 5–10 days of total fasting, depending on the prior protein intake (47), to approximately 3 to 5 g nitrogen (19 to 31 g protein)/24 hr after two to three months when protein conservation mechanisms are functioning maximally. Short-term studies of abrupt-onset starvation show large negative nitrogen balances (5, 109), whereas longer periods of fast, or those preceded by a calorically restricted diet, show reduced nitrogen losses (88, 99).

The protein requirement of patients on very low calorie diets has been examined by many investigators and selected studies are presented in Table 2. As with total fasting, nitrogen losses are greatest early in the diet, diminishing over time. Nitrogen retention may occur in some subjects after two to three weeks on the diet. The loss of body protein is, however, quite variable among subjects. Daily nitrogen balance may range from −15 g to −4 g (−94 to −25 g protein) during the initial days of the diet and from −6 g to +1 g (−38 to +6 g protein) after three to four weeks when protein conservation mechanisms are fully active. Differences in total nitrogen loss have been reported to be as great as threefold in subjects on identical diets (39, 108).

Measurements of nitrogen loss can be converted to the amount of lean tissue degraded by defining lean tissue as 25% protein and 75% water (59) and by assuming that 1 kg of lean tissue will yield 40 g of nitrogen (1 g of nitrogen is equivalent to 6.25 g of protein). Comparison of lean tissue losses throughout seven weeks of very low calorie diets or total fasting is presented in Figure 1. The total seven-week loss of lean tissue averaged 3.57 kg and 4.41 kg in men consuming 400 kcal diets composed exclusively of good and poor quality protein, respectively (39). The subjects, both men and women, given 320 kcal, 31 g protein diets lost 66% more lean tissue (6.56 kg) during an equivalent time period (51) than did the subjects receiving higher levels of protein and energy (39). By comparison, the men who were totally fasted lost 6.41 kg of lean tissue if they were given potassium supplements and 7.63 kg if they were not (39).

What causes the variability in protein loss and how protein conservation is

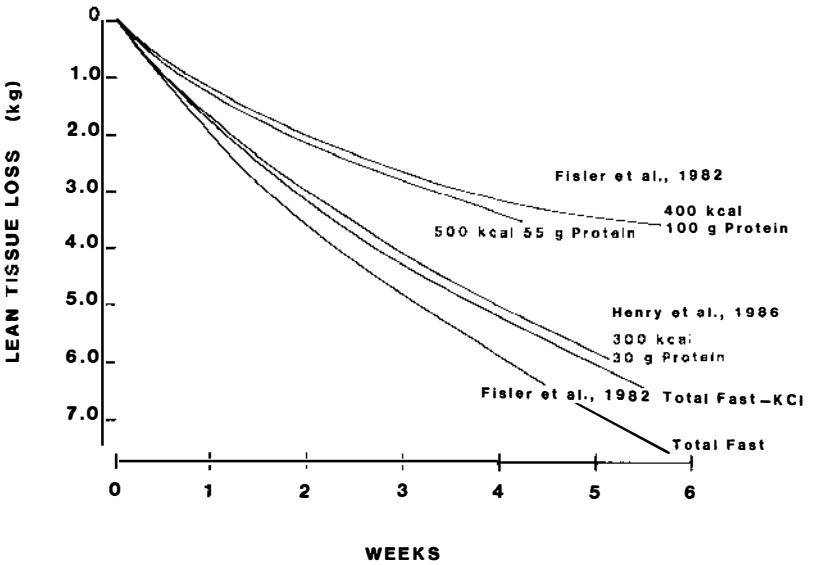

Figure 1 Comparison of lean tissue losses during seven weeks of very low calorie diets or total fasting. Data are adapted from (39, 51).

regulated are not entirely clear. Women consistently have a less negative nitrogen balance and attain nitrogen equilibrium during a very low calorie diet more readily than do men (8, 46). The relationship between nitrogen loss and creatinine excretion suggests that nitrogen loss is greater in subjects with greater muscle mass (51), which may explain the higher protein losses in men. During starvation heavier subjects have greater total nitrogen loss than lighter subjects (29). Weight loss, however, is also greater in the heavier subjects. In an analysis of changes in body weight and nitrogen during extended total fasting, Forbes & Drenick (41) found that the obese individual who fasts loses weight and nitrogen at a slower relative rate than the nonobese and that the ratio of nitrogen loss to weight loss is inversely related to body fat content: it is about 20 g/kg in the nonobese and about 10 g/kg in those overweight by 50 kg or more. These estimates are consistent with the calculation made by Garrow (45) that 10.5 g nitrogen were lost per kg of weight lost in obese women.

One of the primary determinants of protein-sparing may be the protein supply itself (68). At each level of protein intake from 0 to 12 g of protein nitrogen (0 to 75 g protein), an increase in energy intake leads to a corresponding improvement in nitrogen balance in lean subjects (18). Likewise, at a given energy intake, increasing the protein intake improves nitrogen balance (18). There are, however, conflicting data as to whether nitrogen retention will differ between groups given equal energy but variable protein-containing

very low calorie diets. Comparisons of 400 kcal (1.68 J), 100 g protein or 700 kcal (2.93 J), 120 g protein diets with equicaloric diets in which one half of the protein was replaced with carbohydrate found no difference in nitrogen balance (21, 110). On the other hand, in comparisons of diets containing 480 or 500–550 kcal (2.0 J), subjects ingesting 66 or 85 g protein per day had significantly better nitrogen retention than subjects given 33 or 44 g protein per day, respectively (52, 72). This suggests that 33 to 44 g of high quality protein is inadequate. If the protein intake is high, e.g. 100 g, a poor quality protein will permit nitrogen retention (39). Nitrogen balance studies include relatively few subjects, and individual variability may partially explain the difference among these studies. After adaptation to a 400 kcal (1.68 J) diet, a reduced nitrogen intake with isocaloric glucose substitution resulted in worsening nitrogen balance in some subjects but not in others (39).

Another determinant of protein-sparing may be the magnitude of the decrease in net endogenous protein catabolism (68). Nitrogen losses appear to be related to the fall of triiodothyronine (T3) during very low calorie diets (40, 61, 110). This finding supports the conclusion that, during severe caloric restriction, the decrease in circulating serum T3 levels may allow the adaptational decrease in body protein loss (17), perhaps through adjustment of the balance between protein synthesis and degradation (40). Exogenous thyroid hormone, which is sometimes administered to obese patients who are energy deprived to facilitate weight loss (15, 61, 70, 72), abolishes this metabolic adaptation (15, 61), although the negative nitrogen balance appears to improve with time despite continuing T3 administration (15).

The adequacy of potassium intake also affects nitrogen loss. Ammonia production and potassium homeostasis are linked in a feedback regulatory system (95, 96), in which potassium deficiency results in increased, and regular potassium supplementation in decreased, ammoniagenesis. Administration of potassium chloride to fasting subjects reduces their daily urinary ammonium and 3-hydroxybutyrate excretion by one third (49, 82) and results in a conservation of 1.3 g nitrogen/24 hr (39). In a study of 41 obese females given 55 g of protein as the exclusive diet, Apfelbaum et al (2) observed that a potassium intake of 1525 mg (39 meq) resulted in positive potassium and nitrogen balances. In contrast, a potassium intake of 508 mg was associated with a 19-day cumulative deficit of 4868 mg (124 meq) of potassium and 21.9 g of nitrogen.

It is difficult to predict which subjects will be at risk for losing excessive body protein during severely hypocaloric diets. Fisler and associates (40) developed an equation that uses baseline plasma valine and urinary N^t-methylhistidine concentrations and the decrease in plasma T3 to predict nitrogen balance during a very low calorie diet. Whether this approach will be useful remains to be proven.

Short of measuring nitrogen balance, it is also difficult to determine how much protein any given individual has lost. Plasma protein levels are generally insensitive to the body protein deficit in fasting. Total protein, albumin, the globulins, and transferrin generally remain constant during both starvation and semistarvation diets (4, 39, 46, 53, 57), but reductions in these blood proteins have been observed in some subjects (39, 57, 79). Proteins with a more rapid turnover rate, such as thyroxine-binding prealbumin (39, 53, 57, 62), retinol-binding protein (53, 57, 62), and complement C3 (39), are frequently reduced during very low calorie dieting. These changes in plasma proteins have not shown a relationship to nitrogen balance except for decreases in complement C3 that correlated positively ($r = 0.87$, $n = 9$) with nitrogen deficit (39).

Electrolyte and Mineral Losses

In the absence of sodium or potassium supplementation, urinary sodium excretion increases during the first two to six days of fasting to maximum levels of 2000–5700 mg (87–248 meq)/24 hr (12, 76, 80), then falls to 25–350 mg (1.1–15 meq)/24 hr by day ten, remaining at that level throughout prolonged fasting (32, 76, 80, 91). Sodium excretion during a very low calorie diet follows a similar pattern but levels are higher depending on sodium intake. Sodium balance is negative during the initial days of the diet when the diuresis and natriuresis of fasting occur (1, 21, 51). Fasting natriuresis is increased by potassium supplementation (24) and is inhibited by the addition of carbohydrate (11, 21, 56, 101) and, to a lesser extent, protein (56, 101) to the diet. Individual differences in the magnitude of sodium loss are very likely the result of differences in stores of sodium and water (24). Because of the ample sodium stores in most obese subjects and the limited period of sodium loss, the appearance of the clinical depletion syndrome is unusual, even without sodium supplementation during fasting. When a sodium supplement of 1.4–3.9 g (61 to 170 meq) is given, a net positive sodium balance results (1, 11, 51, 107).

With the abrupt onset of fasting, the initial urinary potassium excretion of 1400–1800 mg (36–46 meq)/24 hr (12, 26, 81) rises by the fifth or sixth day to 2700 mg (69 meq)/24 hr (76, 88), then exhibits a linear fall to ~400–700 mg (10–18 meq)/24 hr by one month of fasting (26, 32, 76, 80, 81, 88). Potassium supplementation (2 g KCl, 36 meq K) during the fast results in positive potassium balance within 15 days (26). The data on potassium balance during semistarvation diets are less consistent. Subjects consuming 400 kcal (1.68 J) diets containing 1251 or 2652 mg (32 or 68 meq) potassium achieved positive potassium balance (1, 21), whereas subjects consuming 1720 mg (44 meq) potassium in a 300 kcal (1.26 J) diet lost an average of 805 mg (21 meq) potassium/24 hr (51). In subjects consuming 650–700 kcal

(2.72–2.93 J) diets containing 1911–2574 mg (49–66 meq) potassium, potassium balance during the first month was −398 mg (−10 meq)/24 hr in males and −140 mg (−3.6 meq)/24 hr in females. These negative balances were improved during the second month to −152 and −55 mg (−3.9 and −1.4 meq)/24 hr for males and females, respectively (107). The source of the net potassium loss is primarily lean tissue. The apparent very negative potassium balances of the latter two studies may be due, therefore, to the larger lean tissue losses observed. Carbohydrate refeeding induced a rapid antidiuresis of potassium in fasting subjects (101), but chronic supplementation of a semistarvation diet with carbohydrate had little effect on total potassium losses (21).

Urinary calcium excretion is 50–125 mg/24 hr early in starvation or with a very low calorie diet, rises to 80–350 mg at the end of two weeks, and gradually falls, but after one month remains above the early fast level (37, 77, 88). These high urinary levels may produce markedly negative calcium balances: during a two-month fast as much as 1.5% of body calcium can be lost. The pattern of rising calcium excretion seen in subjects on starvation or semistarvation diets has been associated with the onset of ketosis (90) and acidosis (77). Exogenous potassium, through reduction of ammoniagenesis, exaggerates the acidosis of fasting and increases calcium losses, whereas energy or bicarbonate supplementation reduces the acidosis of fasting and reduces calcium losses. A high phosphorus intake reduces renal calcium loss during a semistarvation diet (37). A calcium intake of less than 300 mg/24 hr is consistently associated with a negative calcium balance (13, 21, 37). In subjects given 800–1000 mg calcium/24 hr, calcium balance was slightly negative in one study (51), but markedly positive in another (13).

The urinary excretion of magnesium is highest early in the starvation or semistarvation regimen, then gradually declines toward pre-diet levels by one month (30, 37). In fasting a marked excess of magnesium loss beyond the amount released by catabolism of lean tissue is evident in some studies; the net loss after fasting can range from 10 to 20% of body stores (30, 37, 65). Urinary magnesium excretion is not affected by magnesium or potassium supplementation during fasting but is suppressed by a high phosphorus intake (37). Fecal magnesium losses are increased with potassium supplementation (37). During very low calorie dieting, magnesium balance is directly related to magnesium intake. Ingestion of 7–116 mg magnesium/24 hr resulted in losses of 48 to 0.6 mg/24 hr, respectively (21, 37, 65). Intakes of 364 or 449 mg magnesium per day, on the other hand, resulted in a positive daily magnesium balance of 64 or 135 mg, respectively (1, 51).

In fasting, urinary phosphate increases until day five or six, after which it decreases to baseline (30, 88) or below (77) by one month. This pattern parallels the increase in urine titratable acidity, of which phosphate is the

primary buffer. There is an early markedly negative phosphorus balance that becomes less negative as the fast progresses. During very low calorie dieting, phosphorus balance is directly related to phosphorus intake, with intakes of 88 to 991 mg/24 hr resulting in phosphate balances of −490 to −35 mg/24 hr (1, 21, 37, 51, 65). In studies of starvation or semistarvation diets to date, with one exception (1), phosphorus balance remains negative, even when the phosphorus intake meets or exceeds the Recommended Dietary Allowance (19).

During very low calorie (400 kcal, 100 g protein) diets urinary zinc excretion increased until about day 20, then leveled off (67). The pattern of urinary zinc excretion was similar to the pattern of urinary calcium excretion, which suggests that the rise was due to the increased acid load during the diet. Zinc excretion was reduced in subjects with a high phosphate intake in a manner similar to calcium and magnesium excretions. Average daily zinc balance was −4.8 mg in subjects consuming either 6.81 or 0.32 mg zinc/24 hr. Urinary copper excretion is negligible and is independent of copper intake. Copper balance, therefore, is primarily determined by fecal excretion. During a very low calorie diet, balance was +1.9 mg/24 hr when the daily copper intake was 3.1 mg and −0.28 mg/24 hr when the copper intake was 0.54 mg (67).

The mineral balance data given above are averaged over 21–40-day studies and are not corrected for the contribution of minerals released by lean tissue breakdown. The balances of sodium, potassium, magnesium, phosphate, and copper all become progressively less negative (or more positive) as the duration of the diet increases. Calcium and zinc balances, on the other hand, become increasingly more negative, at least through the first four weeks, after which time calcium losses diminish. Because of the high potassium, magnesium, phosphate, and zinc contents of cells, the corresponding balances should be corrected for the contribution of lean tissue catabolism. When so corrected, magnesium balance will be 20–60 mg/24 hr less negative, phosphate balance will be 400–600 mg/24 hr less negative, and zinc balance will be 8–13 mg/24 hr less negative during the early phase of the diet when nitrogen losses are high (37, 67). Once protein conservation is maximal at three to four weeks on the diet, there is little contribution of lean tissue catabolism to mineral balance in many subjects consuming very low calorie diets, but lean tissue may remain an important contributor to the mineral losses of totally fasting subjects. The mineral losses reported above may, therefore, be erroneously high when, in fact, conservation of minerals is adequate. Unmeasured losses of some minerals, especially potassium (42) and magnesium (20), however, can result in significant underestimation of losses in balance studies.

Serum mineral and electrolyte levels do not reflect electrolyte or mineral

deficit. Serum or plasma electrolyte levels generally remain within normal limits throughout the starvation or semistarvation period and severe mineral disturbances are generally not observed (2–4, 30, 32, 77, 97, 99, 106). Serum potassium levels tend not to decrease below low-normal levels even after three to four months of total fasting, although significant hypokalemia may be noted in a few subjects given no mineral supplements (26, 32). Even with potassium supplementation, 980 mg (25 meq)/24 hr, the low-normal serum potassium during semistarvation may not be increased (23, 46). Serum chloride and iron also decrease despite supplementation of a 240 kcal, 33 g protein diet with 0.8 g (23 meq) chloride and 25 mg iron daily (23). In three studies that compared the changes in serum minerals to mineral balance, variations in serum calcium, magnesium, phosphorus, zinc, and copper were unrelated to either loss or retention of the respective minerals (37, 65, 67).

Vitamin Nutritional Status

The B vitamins, such as pantothenic acid (94), biotin (94), riboflavin (20, 94), pyridoxic acid (20, 94), thiamine (20, 102), and niacin (20) continue to be excreted throughout a period of fasting. However, riboflavin and thiamine excretions diminished markedly in the early phases of fasting, while the other B vitamins tended to decrease more slowly. Only biotin excretion failed to decline (94). The decreasing quantities of vitamins in urine reflected vitamin deficiencies that actually resulted in impaired metabolic performance (102). Clinically significant vitamin deficiencies, such as Wernicke's syndrome, have been reported after as little as 30 days of semistarvation without vitamin supplements in an obese subject (31) and in 40 days of total fasting in nonobese subjects (22, 43). Vitamin B_{12} absorption decreases with fasting (64); however, body stores should be adequate to maintain vitamin B_{12} functions. Serum levels of folic acid were shown to fall within four weeks and a macrocytic anemia developed in obese men after four months fasting in the absence of folate supplementation (50). Consumption of 330 kcal (1.38 J), 33 g protein diets for four weeks did not result in a fall in the blood ascorbic acid concentration when the daily intake of the vitamin was 80 mg (54).

CLINICAL PROBLEMS

The marked diuresis and natriuresis following severe caloric restriction, with a resultant decrease in blood volume, can lead to potentially dangerous postural hypotension (32, 76, 97). The fall in blood pressure is not prevented by maintaining sodium intake (60, 69, 78), but may be reduced by carbohydrate intake through maintenance of sympathetic nervous system activity (21). Without supplementation, potassium losses can lead to frank hypokalemia (26). Hyperuricemia can lead to acute gouty arthritis (32), but this

complication can generally be managed with drug therapy (28). After a fast of two or more months, a refractory normochromic and normocytic anemia (32) and neutropenia have been observed (25). Subjective complaints in patients on starvation diets include cold intolerance, fatigue, light-headedness, nervousness, and euphoria (97). The most common side effects reported for the very low calorie diets are postural hypotension (46, 100), cold intolerance (100, 106), euphoria (4, 100), constipation or diarrhea (4, 8, 106), dry skin and thinning, reddening hair (4, 8, 100), anemia (4, 46), menstrual irregularities (8, 100), and a tendency to sleep longer (106). These are the same side effects reported in total fasting but generally are of less severity during semistarvation.

A major concern over the use of semistarvation or starvation regimens for weight reduction arises from the reports of fatal cardiac dysrhythmias. The Centers for Disease Control and the Federal Drug Administration have investigated 17 individuals who suffered sudden death or death due to intractable ventricular arrhythmia while (or shortly after) consuming very low calorie diets for at least two months, and who had lost a large amount of weight (55, 87). Their review of electrocardiograms (ECGs) and pathological specimens revealed a pattern of cardiac changes similar to those previously described in starvation. Consistent ECG findings were an increased incidence of prolonged QT_c intervals (QT interval corrected for heart rate) and diminished amplitude of the QRS complexes. Many factors have been postulated as culprits in these deaths, including toxic substances in the diet, deficiency of electrolytes or minerals, inadequate intake of good quality protein, distortion of the physiological pattern of plasma amino acids, high weight loss rates, and protein depletion of the heart despite persisting obesity. Both excess or deficiency of many mineral nutrients, including sodium, potassium, calcium, magnesium, phosphorus, iron, zinc, and copper, are known to disturb cardiac function (16, 36, 71, 84, 92, 98). Although hypokalemia has been suspected as a factor in cardiac dysrhythmias, an etiological role for potassium depletion in the sudden deaths occurring during severe weight reduction has been questioned (55). Tissue depletion of other minerals, or disproportionate concentrations of several intracellular minerals, as well as losses of myofibrillar protein, could also be implicated in the conduction disturbances observed.

The question of arrhythmias developing during very low calorie dieting remains controversial. Prolongation of the QT interval, progressive reduction in QRS voltage, and ventricular arrhythmias have been reported during total fasting (44, 75, 89), during very low calorie dieting (55, 63), and during the refeeding period (55). This has been observed when protein of both low (55, 63) and high (55) biological quality was used. Arrhythmias occurred with

inadequate mineral supplements in one study (63) but not in another (39). In several reports no significant arrhythmias developed during semistarvation diets (1, 39, 66, 74, 86). Lantigua et al (63) found that the arrhythmias occurring during semistarvation were not associated with the loss of potassium, sodium, calcium, magnesium, or phosphorus, nor with blood potassium, magnesium, or calcium levels. In a similar study (27), seven of ten subjects demonstrated prolonged QT_c intervals prior to the initiation of the diet. With weight loss seven of nine subjects showed shortening of the QT_c interval, while the QT_c interval became more prolonged in two subjects. These changes in QT_c intervals were not related to changes in the plasma amino acid patterns, to the blood concentrations of potassium, magnesium, calcium, zinc, or copper, nor to the cumulative balances of potassium, calcium, magnesium, phosphate, or zinc. A negative copper balance and a fall in serum phosphate, however, were associated with prolongation of the QT_c interval. No arrhythmias occurred, however, during six weeks on the diet. The cause of the sudden deaths during very low calorie dieting remains unsolved and may be multifactorial, possibly resulting from a combination of protein depletion, electrolyte and mineral imbalances, and neurohumoral factors (85).

APPROPRIATE TARGET POPULATION

The relationship between obesity, as measured by the Body Mass Index (BMI, kg/m^2), and medical complications describes a J-shaped curve (14). A BMI between 25 and 30 kg/m^2 places an individual in the "low risk" category, between 30 and 40 kg/m^2 in the "moderate risk" category, and above 40 kg/m^2 in the "high risk" category.

The risk incurred by energy restriction for weight reduction can increase as the risk of maintaining the elevated body weight increases. With this in mind, Bray (14) suggested that individuals at moderate or high risk because of obesity (BMI of > 30 kg/m^2) could appropriately undergo more vigorous, and hence more risky, therapy. Very low calorie diets are, therefore, appropriate therapy for the population at moderate or high risk. Healthy subjects with BMI less than 30 are at low risk and, since this group may lose proportionately more body protein during severe caloric restriction than heavier individuals (41), are not appropriately treated with semistarvation diets. Gray & Bray (48) have argued that diseases concurrent with obesity, such as diabetes, hypertension, or sleep apnea, place a person in a higher risk category than indicated by BMI alone. Therefore, individuals with a BMI between 25 and 30 who have concurrent illnesses that can be corrected by weight loss may also be appropriate candidates for very low calorie diets.

SUMMARY AND RECOMMENDATIONS

Although starvation is no longer an accepted modality for weight reduction, semistarvation diets are widely used. Currently utilized diets generally contain at least 70 g protein and 400–600 kcal (1.68–2.51 J) energy per day. Even with diets containing 70 g protein, lean tissue loss of up to 2 kg can occur in the first two weeks of the semistarvation diet. Thereafter, some individuals will conserve, while others will continue to lose, lean tissue. Experimental data are not available to allow us to conclude whether semistarvation diets will maintain adequate vitamin and mineral nutritional status. It appears likely, however, that supplementation of the diet with vitamins and minerals to the Recommended Dietary Allowance level (19) will prevent major deficiencies from occurring.

In essence, the use of very low calorie diets in the treatment of severe obesity requires appropriate patient selection, careful monitoring of the clinical course, and attention to maintenance of an overall adequate nutrient intake, other than calories. Although not proven, a diet composed of natural foods may be preferable to semisynthetic preparations because of the potential for inclusion of essential micronutrients not available in commercial semisynthetic preparations. To avoid potential hazards it appears reasonable that very low calorie diet periods not be extended beyond two months, a time period that has been demonstrated to be reasonably safe. For a discussion of guidelines for professional weight control programs, the reader is referred to the paper by Weinsier et al (105).

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