# Refeeding Procedures After 43 Days of Total Fasting

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Refeeding syndrome encompasses fluid and electrolyte imbalances and metabolic, intestinal, and cardiorespiratory derangements associated with appreciable morbidity and mortality. Although refeeding syndrome has been well documented in concentration-camp subjects, and more recently during parenteral therapy of critically ill patients, little is known about the importance of refeeding syndrome during recovery from a hunger strike. Thus, we studied the response to a four-step dietary replenishment routine in eight hunger strikers who refused food for 43 d. In this retrospective, observational study, we assessed the safety and efficacy of the refeeding procedure and analyzed the clinical and nutritional course of the cohort during both starvation and refeeding, mainly on the basis of clinical as well as a few biochemical determinations. During starvation, average weight loss was about 18% and, with the exception of occasional oral vitamins and electrolytes, the subjects consumed only water. Available body-composition and biochemical profiles showed no clinically significant changes during starvation, but one-half of the group displayed spontaneous diarrhea at some time before refeeding. Stepwise nutritional replenishment lasted for 9 d, after which all patients tolerated a full, unrestricted diet. Only one episode of diarrhea occurred during this phase, and both clinical and biochemical indexes confirmed a favorable clinical course, without any manifestation of refeeding syndrome. In conclusion, we observed the following: 1) Hypophosphatemia and other micronutrient imbalances did not occur, nor was macronutrient intolerance detected. 2) Despite some episodes of diarrhea, nutritional replenishment was not associated with significant enteral dysfunction. 3) There was some fluid retention, but this was mild. 4) Acute-phase markers were abnormally elevated during the refeeding phase, without associated sepsis or inflammation. *Nutrition* 2001;17:100–104. ©Elsevier Science Inc. 2001

Key words: hunger strike, prolonged starvation, total fasting, refeeding syndrome, nutritional therapy, enteral feeding, glutamine

## INTRODUCTION

Although hunger strikes are rare, prolonged subtotal or total food deprivation has been used as a therapy for morbid obesity in many centers over the past four decades.[1–3] Both situations have in common a discontinuation, for weeks up to 1 to 2 months, of the normal energy and protein intake of previously healthy persons. This time frame is commonly perceived as being insufficient for severe tissue damage,[3] especially because metabolic adaptation mechanisms to negative energy balance are assumed to be fully operative.[4]

Subtle but possibly important differences exist between hunger strikes and food deprivation and the advanced, chronic starvation of concentration camp inmates[5] as well as hospital malnutrition,[6] in which, after many months or years of hunger and associated diseases, the anatomy and physiology of organ systems are often compromised and the complex metabolic aberrations create difficulties for therapeutic replenishment.[6] Although acute total fasting is not exempt from dangerous and potentially fatal consequences,[10,11] refeeding syndrome although theoretically possible in any malnourished organism submitted to vigorous nutritional repletion is mostly associated with chronically depleted subjects.[7–9]

Given the theoretical risks of generous food reintroduction in nutritionally debilitated persons, various modifications and precautions for refeeding have been devised.[12,13] However, techniques specific for voluntary fasting or radical weight-losing regimens have not been recommended.[1–4] Such omission could be explained by the rarity of these situations. However, even in the classic studies of prolonged, spontaneous food deprivation conducted by Keys et al.,[14] no special care to prevent intolerance during refeeding was taken, nor were any untoward effects reported. In the present study, we report the routines adopted for nutritional replenishment and the clinical result of these procedures in eight prisoners who refused food for 43 d.

## PATIENTS AND METHODS

The population consisted of eight adult prisoners (seven men and one woman) with a mean age of 43.3 ± 6.2 y (range: 33–52 y). For the first 11 d of the prisoners' hunger strike, they were maintained within the correctional facility, but afterward seven of eight were transferred to Hospital das Clínicas (the eighth patient arrived 1 wk later). The hunger strike lasted for 46 d, but after 43 d of starvation ("absolute hunger"), replenishment of intravenous fluids and micronutrients was started. Otherwise, the patients consumed only water and occasional oral vitamins and electrolytes during the period of food deprivation.

Clinical and laboratory measurements were limited by ethical and legal constraints related to the prisoner status and negative social and psychological conditions of the patients. Each diagnostic and therapeutic intervention had to be individually submitted for approval to the patients, and rejections were frequent. As a result, no prospective investigation or systematic clinical protocol

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could be applied and all findings were analyzed retrospectively. This report was approved by the Ethical Committee of Hospital das Clínicas and São Paulo University Medical School.

Anthropometric measurements included body weight, percentage of weight loss, and body mass index (BMI). Bioelectrical impedance analysis (BIA) was done after the 4th week with use of a standard tetrapolar technique and a single-current apparatus (50 kHz, Biodynamics model 310; Biodynamics, Seattle, WA, USA). To the best of our knowledge this is the first report of BIA assessment in hunger strikers. Thus, reports of validation of the method for this population are not available in the literature, nor could validation be performed within the context of this study. The following variables were documented: body fat, total body water, and resistance.

During the more than 6 wks of food refusal, patients ingested only water. During the last 3 wk patients were prescribed twice-weekly water-soluble vitamin and electrolyte supplements; however, patients often rejected the supplements. The usual prescription included complex B, vitamin C, and approximately 25 mEq potassium, 8 mEq magnesium, 10 mM phosphate, and 50 mEq sodium.

Mean total energy and protein intakes during the various phases of refeeding were calculated and gastrointestinal tolerance and nutritional complications were documented. Nutrient intake data for the prestrike period could not be obtained. However, the menu in the state prison system are supervised by dietitians and the BMIs of all subjects were in the normal range (one patient was overweight) and no patients had chronic or consumptive diseases. Thus, serious nutritional imbalances were deemed unlikely.

Serum electrolytes (Na, K, Mg, Ca, and $PO_4$) and venous acid–base indexes (pH, $pCO_2$, bicarbonate) were assessed on several occasions. Blood glucose and urea, serum creatinine, total bilirubin, cholesterol, triacylglycerols, and albumin were also measured. The inflammatory markers C-reactive protein (CRP) and serum amyloid A (SAA) were measured only after refeeding.

Values are presented as means ± SEMs. Differences between nutritional and biochemical values in the same group were compared by standard paired-sample two-tailed Student's *t* tests in an EXCEL spreadsheet (MICROSOFT OFFICE 97, Microsoft Corp, Redmond, WA) and were confirmed by the small-sample *t* test suggested by Kleinbaum et al.[15] The significance level was 5%.

## RESULTS

Nutritional rehabilitation started with intravenous fluids, electrolytes, and vitamins for approximately 48 h, supplying less than 5% of daily energy needs but between 100% and 200% of the allowances for vitamins and also intracellular electrolytes (potassium, magnesium, and phosphate). This regimen was followed by standard peripheral parenteral nutrition (glucose and amino acids) in combination with modest amounts of a commercial semielemental oral diet enriched with glutamine (mean total energy equivalent of roughly 25% of estimated requirements). Three days later 100% of the planned prescription was well tolerated by mouth in the form of a polymeric diet restricted in fiber and lipids (less than 15% of energy as fat and less than 5 g/d of total fiber) but supplemented with substantial amounts of glutamine (10 to 22 g/d). After another 4 d, or on the ninth day since the start of refeeding, all patients tolerated an unrestricted general diet in the standard amount of 2200 kcal/d (76 g protein, Fig. 1).

After 5 wk of fasting, weight loss was in the range of 18% of initial body weight, but anthropometric and BIA measurements were still within the acceptable range. On day 43, after the start of intravenous fluid therapy, anthropometric variables remained stable, whereas body fat reflected additional energy consumption, body water tended to increase, and resistance significantly decreased. On day 57, after nearly 2 wk of recovery, body weight and fat weight had improved but body water and resistance continued to worsen, although not significantly (Table I).

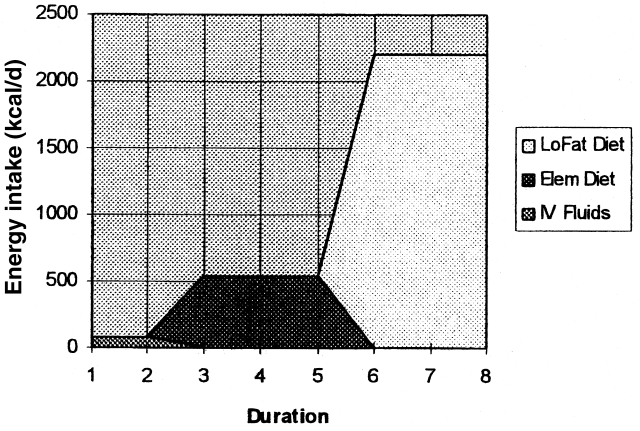


FIG. 1. Refeeding schedule. Days 1 to 2 (days 43 and 44 of hunger strike): intravenous (IV) fluids (83 ± 83 kcal, 3.8 ± 3.8 g amino acids/d); days 2 to 4 (days 44–46): peripheral total parenteral nutrition + semielemental diet (total of 535 ± 206 kcal and 10.3 ± 2.3 g protein/d) enriched with 2 to 7 g glutamine (Elem diet); days 5 to 8 (days 47 to 50): low-fat, low-fiber oral diet (2200 kcal, 68 g protein/d) supplying additional 10 to 22 g glutamine (LoFat diet); day 9 and afterward: full oral diet (2200 kcal, 76 g protein/d, no glutamine).

The serum electrolyte and acid–base profile in the fifth week was acceptable. With the introduction of intravenous hypocaloric feedings, reductions in calcium and phosphate were detected; at the same time, magnesium and venous pH increased. During the period of a normalized oral diet, calcium, phosphate, and pH returned to baseline values, whereas a modest but significant increase in sodium measured (Table II).

Results of standard biochemical tests were in the expected range on day 31, with the exception of low blood glucose and urea, which reflected the zero-calorie regimen (Table III). With the introduction of preliminary intravenous refeeding, total bilirubin decreased, whereas glycemic readings increased rapidly. Serum albumin decreased with the introduction of refeeding. On day 53, few notable changes in biochemical indexes were recorded, except for triacylglycerols, which increased markedly, despite careful modulation of oral intake (Table IV), and urea, which finally became more elevated but stayed within the normal range, in parallel with the introduction of protein-rich meals (Table III).

Acute-phase markers were measured only during the recovery period, when patients were already receiving a full oral diet. All tests were performed in the absence of diarrhea, fever, or any other infectious or inflammatory complication. CRP was moderately increased in two of eight patients (25.0%) and SAA became markedly abnormal in the entire population (Table V).

Four of the eight patients were affected by diarrhea. Only one of these cases occurred during the refeeding phase, in a subject who also had diarrhea during starvation. The other cases of diarrhea were during the phase of absolute hunger. All episodes were mild and responded to symptomatic medications. Edema of the lower limbs was noticed within a few days of refeeding in most of the population (75.0%). Nevertheless, this was also a mild form of swelling that disappeared spontaneously after a few days, without the need for diuretics or sodium restriction.

## DISCUSSION

Chronic hunger is a fact of life in overpopulated, agriculturally challenged, and poor countries and can degenerate to true famine as a result of droughts, floods, and military conflicts. The most

TABLE I.

ANTHROPOMETRIC AND BIOELECTRICAL IMPEDANCE FINDINGS

| | Weight (kg) | Weight loss (%) | BMI (kg/m$^2$) | Fat weight (kg) | Water volume (L) | Resistance (Ω) |
|---|---|---|---|---|---|---|
| Admission | 80.9 ± 8.2 | 0 | 26.1 ± 2.7 | | | |
| Day 31 | 66.3 ± 5.8* | 17.9 ± 2.0 | 21.4 ± 2.2* | 17.6 ± 3.9 | 35.1 ± 4.5 | 639 ± 80 |
| Day 43 | 66.4 ± 6.6 | 17.6 ± 2.4 | 21.5 ± 2.6 | 12.9 ± 1.8* | 38.4 ± 5.2 | 550 ± 78† |
| Day 57 | 71.4 ± 7.5† | 11.7 ± 4.4* | 23.0 ± 2.4 | 14.5 ± 1.8† | 41.0 ± 6.1 | 520 ± 68 |

Peripheral hypocaloric fluids were started on day 43. Day 57 was the 13th day of oral diet.
*,† Significantly different from previous measurement: *$P < 0.01$, †$P < 0.05$.

devastating and widespread occurrence of food deprivation in modern times was precipitated by World War II, which affected millions of persons in industrialized and developing countries alike. Much of the disaster affected civilian populations, either as part of the war effort or in connection with doctrines of purity of the Aryan race. Therefore, it is no surprise that refeeding syndrome was described shortly after the war in victims who displayed serious or even fatal complications in response to overzealous replenishment of their depleted body stores.[5,16,17]

With the popularization of artificial nutrition in more recent decades, particularly parenteral hyperalimentation, subtypes of refeeding syndrome specific to high-glucose regimens, such as acute hypophosphatemia became better known. In our preliminary experience with hospitalized surgical patients,[8,9] serum phosphate concentrations less than 0.1 mM/L were seen on occasion, fortunately not resulting in death but associated with extreme muscle weakness and other neurologic aberrations.[9]

Currently, the concept of the refeeding syndrome is eclectic and encompasses derangements of electrolytes and minerals, vitamins, body fluids, and glucose in susceptible subjects, triggered by food introduction.[7] However, the definition should be broadened to include some modalities of organ failure.[18,19] Indeed, the most frequent intolerance to energetic refeeding by the enteral route is diarrhea, which is not dependent on any of the previously mentioned nutrients, but results from bowel atrophy.[5] By the same token, certain cases of cardiac death observed in connection with obesity-controlling regimens can be traced to heart atrophy and myofibrilar degeneration, not just to fluid overload or any other of the classic mechanisms of refeeding syndrome.[20]

TABLE II.

SERUM ELECTROLYTES AND ACID–BASE BALANCE

| | Day 31 | Day 45 | Day 53 | Normal range |
|---|---|---|---|---|
| Na (mM/L) | 140 ± 1 | 140 ± 2 | 143 ± 4 | 136–146 |
| K (mM/L) | 4.0 ± 0.2 | 4.2 ± 0.2 | 3.8 ± 0.2 | 3.5–5.1 |
| Mg (mEq/L) | 1.6 ± 0.2 | 2.0 ± 0.2 | 2.0 ± 0.3 | 1.3–2.1 |
| Ca (mM/L) | 2.3 ± 0.1 | 1.3 ± 0.2* | 2.1 ± 0.1 | 2.1–2.6 |
| P (nM/L) | 1.1 ± 0.2 | 0.8 ± 0.2 | 1.2 ± 0.2 | 0.9–1.5 |
| $HCO_3$ (mEq/L) (venous) | 25.1 ± 6.0 | 26.3 ± 0.8 | 26.4 ± 1.7 | NA |
| pH (venous) | 7.34 ± 0.05 | 7.38 ± 0.02 | 7.35 ± 0.01 | NA |
| $pCO_2$ (mm Hg) (venous) | 46.1 ± 9.3 | 45.0 ± 2.5 | 49.6 ± 2.8 | NA |

Day 45 was the 3rd day of peripheral intravenous fluids; day 53 was the 9th day of oral diet. NA, not available.
* Measurement outside the 99% confidence interval for normality.

These criticisms notwithstanding, the most frequent derangements attributable to overfeeding can be summarized in just a few categories. Consumption of intracellular electrolytes and minerals such as potassium, magnesium, and principally phosphate is relevant because of accelerated anabolism combined with long-term depletion. Carbohydrate-rich regimens are especially dangerous because glucose tends to drive large amounts of potassium and phosphate intracellularly when it enters body tissues. Hypophosphatemia can be precipitated within a very short time and can result in death.[7–9]

Acute vitamin deficiencies are probably as common as electrolytic imbalances, but life-threatening cases are ordinarily ascribed to thiamine only, in the form of Wernicke encephalopathy.[11,12,18] Interestingly, hunger strikers seem to be especially susceptible to this condition, which can be diagnosed after less than 40 d of food deprivation.[11,21] Glucose metabolism has been implicated in this process and it is prudent to restore body thiamine before even 5% or 10% dextrose infusions are started in high-risk individuals.[12,13]

The risk of diarrhea when the enteral route is elected for nutritional replenishment is well established,[5,17] but references to diarrhea in studies concerning hunger strike or other forms of voluntary starvation by healthy subjects are scarce in the literature.[1–3,11,21] There is no mention of diarrhea in the comparatively large study of self-inflicted total starvation conducted by Frommel et al.[22] nor in the Minnesota experiment on prolonged semistarvation.[14]

Finally, miscellaneous organ failure, notably acute cardiopulmonary insufficiency but also liver damage, has been associated with prescriptions including high loads of carbohydrates as well as excessive water and sodium. Thus, it makes sense to start refeeding with modest volumes of both fluids and energy, emphasizing mostly protein and micronutrients (especially thiamine) simulta-

TABLE III.

GENERAL BLOOD CHEMISTRY INDEXES

| | Day 31 | Day 45 | Day 53 | Normal range |
|---|---|---|---|---|
| Glucose (mM/L) | 2.9 ± 0.6* | 5.3 ± 0.6 | 4.3 ± 0.8 | 3.9–5.8 |
| Urea (mM/L) | 4.5 ± 1.0 | 4.1 ± 1.2 | 7.2 ± 1.8 | 4.9–12.2 |
| Creatinine (μM/L) | 80 ± 18 | 80 ± 1 | 80 ± 9 | 62–115 |
| Total bilirubin (mM/L) | 12.6 ± 1.8 | 9.0 ± 3.6 | 9.0 ± 1.8 | 3.4–17.1 |
| Total protein (g/L) | 56 ± 4 | 54 ± 11 | 54 ± 3 | 64.0–83.0 |
| Serum albumin (g/L) | 41 ± 4 | 34 ± 3 | 32 ± 2* | 35.0–50.0 |

Day 45 was the 3rd day of peripheral intravenous fluids; day 53 was the 9th day of oral diet.
* Measurement outside the 99% confidence interval for normality.

TABLE IV.

PROFILE OF PRINCIPAL LIPID FRACTIONS

| | Day 36 | Day 53 | Normal range |
|---|---|---|---|
| Total cholesterol (mM/L) | 3.0 ± 0.7 | 3.9 ± 1.0 | <5.2 |
| Triacylglycerols (mM/L) | 0.9 ± 0.1 | 4.2 ± 2.6* | 0.5–1.8 |

Day 36 was a day of no food intake; day 53 was the 9th day of oral diet.

* Measurement outside the 99% confidence interval for normality.

TABLE V.

INFLAMMATORY MARKERS

| | CRP (mg/L) | SAA (mg/L) |
|---|---|---|
| Day 53 | 2.8 ± 2.6* | 79 ± 25† |

CRP, c-reactive protein; SAA, serum amyloid A, Day 53 was the 9th day of oral diet.

* Normal < 5 mg/L; elevated values in 2/8 (25.0%).

† Normal < 5 mg/L; all tests markedly abnormal (100%).

neously with the first dextrose infusions.[12,13] Amounts should be increased the least rapidly in the sickest patients.[7–9,12,13]

These and other principles were applied to a basic protocol for refeeding patients hospitalized with marasmus; this protocol has also been adjusted for prophylaxis of the refeeding syndrome in general. The main components of this approach are summarized here.[12,13] 1) Initial energy prescription of 20 kcal · $kg^{-1}$ · $d^{-1}$, including a generous protein allowance (1.2–1.5 g · $kg^{-1}$ · $d^{-1}$). 2) Carbohydrate restriction with preference for lipids, and thiamine supplementation. 3) Slow increase over 10 to 14 d, until a full diet is tolerated. 4) Careful monitoring of clinical and biochemical variables.[12,13]

In the current study, the population did not become markedly depleted by the self-imposed starvation, at least from the viewpoint of anthropometric, BIA, and serum albumin determinations. As shown in Tables I, III, and IV, average body weight losses and fat consumption after more than 6 wk of food refusal were comparatively modest, serum albumin concentrations were not significantly affected, and patients were still apparently well nourished by the end of their hunger strike. Additionally, only minor changes were noted in electrolytes and other biochemical indexes.

Significant findings in the present study concerned blood glucose, which, as expected, tended to progress to asymptomatic hypoglycemia;[1,22] blood urea, which remained at the lower end of the normal range during fasting but recovered when balanced meals were commenced; and calcium, magnesium, phosphate, and pH, which experienced minor changes. Few of these results suggest impending danger for diet introduction or the need for a modified food introduction schedule.

In virtually all publications dealing with therapeutic fasting for morbid obesity[1–3] or hunger strikes,[11,21] no special formulations were considered to be mandatory, monitoring precautions were omitted, and no food category was left out during refeeding. The same can be noted in the study by Keys et al.[14] in which quantitative manipulations during food reintroduction were related to the experimental design, not to suspected or confirmed intolerances. One exception can be found in the report of Frommel et al.[22] but few details are supplied. In this report, three of the four nonobese adults who fasted for about 40 d were given boiled or raw unsalted vegetables during the first week after the discontinuation of fasting. The remaining case, who acquired Wernicke encephalopathy, was managed by intravenous feeding for 3 d before other dietary components were introduced. Nevertheless, the parenteral approach is advocated for all other cases because all patients displayed nausea and some degree of gastric intolerance to fluids during the first days.

In the present study, only by day 43 could electrolytes and vitamins be parenterally initiated in generous amounts and maintained for 48 h before food administration. Refeeding itself was subsequently continued intravenously for a few additional days, but with more modest energy quantities than those cited previously.[12,13] This program could be interpreted as unusual care, especially given the lack of evidence of significant undernutrition and hardly menacing laboratory findings. Nevertheless, Wernicke encephalopathy and acute hypophosphatemia, and more rarely other micronutrient deficiencies, can be precipitated within days and even hours of dietary introduction, and negative clinical and laboratory results may be entirely misleading under these circumstances.[7–9,11,18,19,21,22] Additionally, nausea and vomiting were common in our population,[10] similar to the observations of Frommel et al.,[22] thus justifying our initial use of an extraintestinal route.

Simultaneously with intravenous feeding, we gradually prescribed a semielemental diet supplemented with glutamine. Although this therapy clearly differs from traditional recommendations,[12,13] our choice of a fiber-poor, lipid-poor, and glutamine-rich diet, which continued during the ensuing phase of polymeric natural foods until a total of 8 d (Fig. 1), mimics the protocol adopted for short-bowel syndrome in Hospital das Clínicas.[23]

Fasting, even for limited periods and in previously obese adults, is associated with marked intestinal atrophy, which may persist for a long time after food reintroduction.[2,5] In the specific population reported here, there were additional reasons to believe that the enteral mucosa was not normal: 50% of the population displayed episodes of diarrhea well before oral meals were offered. Thus, a dysfunctional small bowel was assumed and patients were treated accordingly during the first week.

Response to this protocol was excellent, and within a total transition period of not more than 9 d, all patients were tolerating a voluntary unrestricted diet with a single instance of further diarrhea in one patient who had displayed this symptom previously. Time back to work cannot be calculated in prisoners, but given their conditions at discharge less than 1 wk later, they would have been able to resume all of their activities immediately, which is considerably sooner than the 60 to 75 d reported by others.[22]

Because this was not a controlled trial, we cannot rule out that a simpler routine—or perhaps no routine at all, with straight administration of conventional foods—would have given equal or better results. However, all the patients tolerated a full diet before even the conservative 10 to 14 d indicated by DeLegge[12] and nutritional recovery was not unduly delayed, as shown by anthropometric and BIA evidence of progressive body tissue restoration (Table I) and blood glucose and urea elevation (Table III). Perhaps more importantly, electrolyte and mineral metabolism were never endangered (Table II) and the refeeding syndrome was effectively bypassed. Even excessive restoration of body fat[14,24] and water[25,26] which are deemed common and even inevitable side effects of refeeding after long-term food deprivation of previously healthy individuals, were absent or minimal because dietary intake was controlled at 2200 kcal/d.

Serum albumin is a highly regarded biochemical marker in hospital malnutrition and in general health assessment, and should have faithfully reflected both progressive erosion of visceral protein tissues during fasting and their recovery upon refeeding. The fact that albumin remained normal until late in the fasting period and then declined with the start of refeeding is striking (Table III). However, it is known that serum albumin is sensitive to fluid shifts

because the conventional exchange rate between the intravascular and extravascular space exceeds the synthesis rate by a factor of 10.[27] As a marasmic condition, uncomplicated starvation should be associated with a slow decrease of serum albumin concentrations over many weeks,[6,13,18,26] as shown in the historic publication of Keys et al.[14] One difference between the hunger strikers in the present study and Keys's subjects as well as most clinical marasmic subjects is the simultaneous water loss in hunger strikers despite unrestricted fluid ingestion.[25,26] This should effectively mask even mild degrees of albumin consumption or reduced synthesis during fasting[1,2,25,26] and be compatible with strictly normal values as recorded here by the fifth week. The same phenomenon was probably the underlying cause of the noticeable drop in serum albumin when food input coincided with replenishment of body fluids.

It is debated whether hunger is a stressful situation because of the mixed and rather unique milieu of hormones and acute-phase mediators in this setting. Starvation and weight loss partially suppress insulin secretion but may increase counterregulatory hormones. Sympathetic nervous system activity is inhibited, whereas peripheral sympathetic fibers seem to be stimulated.[28] In rats, the strong activity of sympathetic nerves in white adipose tissue was shown to contribute to fasting lipolysis.[29]

In starved children with long-term kwashiorkor, concentrations of cytokines and CRP are elevated, even in the absence of known infections or associated diseases.[30] This is consistent with the elevated measurements of CRP and SAA in the present study on day 53 (9th day of oral diet), in the absence of diarrhea or any demonstrated precipitating factor.[31]

Prolonged fasting reduces concentrations of intestinal brush border enzymes and the protein and DNA content of the mucosa,[2,5,32] whereas malnutrition with weight loss, even minor weight loss, may interfere with the qualitative and quantitative performance of immunologically active cells, including macrophages.[10,30] Similarly, in well-nourished young rats deprived of food for 3 d (which corresponds to several weeks in humans and is associated with weight loss in the same range as in the current study [15–20% reduction]), abnormal intestinal permeability to a dietary macromolecule was found during starvation and did not return to normal with refeeding.[32] Further studies will be essential to shed light on the intriguing finding of an inflammatory process in hunger strikers.

In conclusion, we observed the following in the present study:

1. Hypophosphatemia and other electrolyte imbalances did not occur, nor was Wernicke encephalopathy precipitated by the refeeding protocol.
2. Excessive macronutrient administration was avoided and hyperglycemia, hyperlipidemia, and body fat "overshooting" were prevented.
3. Episodes of diarrhea were diagnosed in part of the group before food introduction, but nutritional replenishment was not associated with significant enteral dysfunction.
4. Some degree of fluid retention was noticed during the first days of refeeding, but this was mild and self-resolving.
5. Acute-phase markers were abnormally elevated during the refeeding phase, without sepsis or other identifiable causes of inflammation.

## REFERENCES


1. Drenick EJ, Swendseid ME, Blahd WH, Tuttle SG. Prolonged starvation as treatment for severe obesity. JAMA 1964;187:100
2. Thomson TJ, Runcie J, Miller V. Treatment of obesity by total fasting for up to 249 days. Lancet 1966;2:992
3. Wadden T. Treatment of obesity by moderate and severe calorie restriction. Results of clinical research trials. Ann Intern Med 1993;119:688
4. Luke A, Schoeller D. Basal metabolic rate, fat-free mass, and body cell mass during energy restriction. Metabolism 1992;41:450
5. Stein J, Fenigstein H. Anatomie pathologique de la maladie de la famine (pathology of hunger disease). In: *Apfelbaum E, ed. Maladie de la famine. Recherches cliniques sur la famine executée dans le guetto de Varsovie en 1942* (Hunger disease: clinical investigations of the famine executed on the Warsaw ghetto in 1942). Warsaw, Poland: American Joint Distribution Committee, 1946:21
6. Chiolero R, Revelly JP, Tappy L. Energy metabolism in sepsis and injury. Nutrition 1997;13(suppl 9):45S
7. Solomon SM, Kirby DF. The refeeding syndrome: a review. JPEN 1990;14:90
8. Faintuch J, Machado MCC, Cunha JC, et al. Hypophosphatemia, paresthesias and severe muscle weakness in a malnourished patient submitted to parenteral alimentation. Rev Hosp Clin Fac Med Sao Paulo 1973;28:153
9. Faintuch J, Machado MCC, Bove P, Raia AA. Hypophosphatemia during parenteral nutrition with hypertonic glucose and amino acids. In: Romieu C, Solassol C, Joyeux H, Astruc B eds. *Proceedings of the International Congress of Parenteral Nutrition, Montpellier (France)*. Montpellier, France: Imprimérie Déhan, 1976:275
10. Ladeira JP, Janiszewski M, Soriano FG, Faintuch J, Velasco IT. Clinical and hematologic abnormalities during prolonged fasting (abstract). Clin Nutr 1999; 18:42
11. Waterston JA, Gilligan BS. Wernicke's encephalopathy after prolonged fasting. Med J Aust 1986;145:154
12. DeLegge MH. Refeeding syndrome: Clinical symptoms and treatment. In: *Proceedings of the 19th Clinical Congress of ASPEN, Miami Beach.* Silver Spring, MD: American Society for the Parenteral and Enteral Nutrition, 1995:226
13. Apovian CV, McMahon MM, Bistrian BR. Guidelines for refeeding the marasmic patient. Crit Care Med 1990;18:1030
14. Keys A, Brozek J, Henschel A, Mickelsen O, Taylor HL. *The biology of human starvation.* Minneapolis: University of Minnesota Press, 1950
15. Kleinbaum DG, Kupper LL, Muller KE. *Applied regression analysis and other multivariate methods.* Boston: PWS-Kent Publishing Co, 1988:78
16. Schnitker MA, Mattman PE, Bliss TL. A clinical study of malnutrition in Japanese prisoners of war. Ann Intern Med 1951;35:69
17. Burger GCE, Drummond JC, Sandstead HER. *Malnutrition and starvation in western Netherlands, September 1944–July 1945, parts 1 and 2.* The Hague: General State Printing Office, 1948
18. Klein CJ, Stanek GS, Wiles CE. Overfeeding macronutrients to critically ill adults: metabolic complications. J Am Diet Assoc 1998;98:795
19. Kohn MR, Golden NH, Shenker IR. Cardiac arrest and delirium: presentations of the refeeding syndrome in severely malnourished adolescents with anorexia nervosa. J Adolesc Health 1998;22:239
20. Sours HE, Fratalli VP, Brand CD, et al. Sudden death associated with very low calorie reduction regimens. Am J Clin Nutr 1981;34:453
21. Falzi G, Ronchi W. Wernicke's lethal encephalopathy after voluntary, total prolonged fasting. Forensic Sci Int 1990;47:17
22. Frommel D, Gautier M, Questiaux E, Schwarzenberg L. Voluntary total fasting: a challenge for the medical community. Lancet 1984;1:1451
23. Dias MCG, Cukier C, Santoro S, et al. Follow-up of patients with short-bowel syndrome managed by oral diet (abstract). Rev Bras Nutr Clin 1997;12:S143
24. Dulloo AG, Jacquet J, Girardier L. Poststarvation hyperphagia and body fat overshooting in humans: a role for feedback signals from lean and fat tissues. Am J Clin Nutr 1997;65:717
25. Weinsier RL. Fasting—a review with emphasis on the electrolytes. Am J Med 1971;50:233
26. Smith R, Drenick EJ. Changes in body water and sodium during prolonged starvation for extreme obesity. Clin Sci 1966;31:437
27. Fleck A. Plasma proteins as nutritional indicators in the perioperative period. Br J Clin Pract 1988;42(suppl 63):20
28. Schwartz MW, Seeley RJ. Seminars in medicine. N Engl J Med 1997;336:1802
29. Migliorini RH, Garofalo MA, Kettelhut IC. Increased sympathetic activity in rat white adipose tissue during prolonged fasting. Am J Physiol 1997;272:R656
30. Sauerwein RW, Mulder JA, Mulder L, et al. Inflammatory mediators in children with protein-energy malnutrition. Am J Clin Nutr 1997;65:1534
31. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. N Engl J Med 1999;340:448
32. Boza J, Martinez O, Baro L, Suarez MD, Gil A. Influence of casein and casein hydrolysate diets on nutritional recovery of starved rats. JPEN 1995;19:216