Refeeding syndromes encompass 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.3–5 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 inmates3 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
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 PO₄) and venous acid–base indexes (pH, pCO₂, 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. 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

![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).](image)

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
Peripheral hypocaloric fluids were started on day 43. Day 57 was the 13th day of oral diet. replenishment of their depleted body stores.5,16,17 serious or even fatal complications in response to overzealous the Aryan race. Therefore, it is no surprise that refeeding syndrome is a severe condition that 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

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, have become 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, fortuitously 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 myofibrillar degeneration, not just to fluid overload or any other of the classic mechanisms of refeeding syndrome.20

<p>| TABLE I. ANTHROPOMETRIC AND BIOELECTRICAL IMPEDANCE FINDINGS |
|-----------------------------|-----------------------------|-----------------------------|</p>
<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Weight loss (%)</th>
<th>BMI (kg/m²)</th>
<th>Fat weight (kg)</th>
<th>Water volume (L)</th>
<th>Resistance (Ω)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission</td>
<td>80.9 ± 8.2</td>
<td>0</td>
<td>26.1 ± 2.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 31</td>
<td>66.3 ± 5.8*</td>
<td>17.9 ± 2.0</td>
<td>21.4 ± 2.2*</td>
<td>17.6 ± 3.9</td>
<td>35.1 ± 4.5</td>
</tr>
<tr>
<td>Day 43</td>
<td>66.4 ± 6.6</td>
<td>17.6 ± 2.4</td>
<td>21.5 ± 2.6</td>
<td>12.9 ± 1.8*</td>
<td>38.4 ± 5.2</td>
</tr>
<tr>
<td>Day 57</td>
<td>71.4 ± 7.5†</td>
<td>11.7 ± 4.4*</td>
<td>23.0 ± 2.4</td>
<td>14.5 ± 1.8†</td>
<td>41.0 ± 6.1</td>
</tr>
</tbody>
</table>

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.

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 electrolyte 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-
neously with the first dextrose infusions.\textsuperscript{12,13} Amounts should be increased the least rapidly in the sickest patients.\textsuperscript{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,\textsuperscript{12,13} 1) Initial energy prescription of 20 kcal \(\cdot\) kg\(^{-1}\) \(\cdot\) d\(^{-1}\), including a generous protein allowance (1.2–1.5 g \(\cdot\) kg\(^{-1}\) \(\cdot\) 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.\textsuperscript{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;\textsuperscript{2,22} 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\textsuperscript{1–3} or hunger strikes,\textsuperscript{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.,\textsuperscript{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.\textsuperscript{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.\textsuperscript{12,13} This program could be interpreted as unusual care, especially given the lack of evidence of significant undernutrition and

\[
\begin{array}{ccc}
\text{PROFILE OF PRINCIPAL LIPID FRACTIONS} & \text{Normal range} \\
\hline
\text{Day 36} & \text{Day 53} & \\
\text{Total cholesterol (mM/L)} & 3.0 \pm 0.7 & 3.9 \pm 1.0 <5.2 \\
\text{Triacylglycerols (mM/L)} & 0.9 \pm 0.1 & 4.2 \pm 2.6* & 0.5–1.8 \\
\hline
\end{array}
\]

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.
because the conventional exchange rate between the intravascular and extravascular space exceeds the synthesis rate by a factor of 10.\textsuperscript{27} As a marasmic condition, uncomplicated starvation should be associated with a slow decrease of serum albumin concentrations over many weeks,\textsuperscript{6,13,18,26} as shown in the historic publication of Keys et al.\textsuperscript{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.\textsuperscript{25,26} This should effectively mask even mild degrees of albumin consumption or reduced synthesis during fasting.\textsuperscript{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.\textsuperscript{28} In rats, the strong activity of sympathetic nerves in white adipose tissue was shown to contribute to fasting lipolysis.\textsuperscript{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.\textsuperscript{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.\textsuperscript{31}

Prolonged fasting reduces concentrations of intestinal brush border enzymes and the protein and DNA content of the mucosa,\textsuperscript{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.\textsuperscript{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.\textsuperscript{33} 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.

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