Received: 21 June 2021 | Revised: 16 November 2021 | Accepted: 21 November 2021

DOI: 10.1002/erv.2877

WILEY

RESEARCH ARTICLE

Rapid renutrition improves health status in severely malnourished inpatients with AN - score-based evaluation of a high caloric refeeding protocol in severely malnourished inpatients with anorexia nervosa in an intermediate care unit

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Abstract

Objective: Refeeding syndrome is a feared complication of refeeding patients with anorexia nervosa. There are now a number of controlled studies showing that refeeding with an initial high calorie count is more beneficial than cautious refeeding and is safe under continuous monitoring. However, there have yet not been studies in severe anorexia nervosa.

Method: We present an observational study in two different samples. The first sample consists of those 1075 out of a total of 3230 patients with anorexia nervosa treated in our hospital within 4 years for whom a complete admission laboratory was available and who had an age of at least 18 years at admission. A risk score was calculated from the number of pathological laboratory values out of 12 parameters indicating either refeeding syndrome or health hazards related to malnutrition. The second sample was obtained from a special ward for patients with eating disorders medically at-risk. During the period in question, 410 patients with anorexia nervosa were treated there. 142 patients had a BMI of 13 or less and at the same time a complete data set with the mentioned 12 laboratory parameters at admission and weekly in the following 4 weeks after admission.

Results: The risk represented by the laboratory parameters is significantly and negatively correlated to BMI and much higher for the group of patients with a BMI below 13 than for those with a higher BMI (χ^2 sig < 0.000). The 142 patients in the special care unit gain an average of more than 4.1 kg within 4 weeks on the high-calorie diet. With this rapid weight gain, the risk score

Abbreviations: ALT, alanine aminotransferase; AN, anorexia nervosa; ANOVA, one-way-analysis of variance; AST, aspartate aminotransferase; ATP, adenosine triphosphate; BMI, Body Mass Index; ECG, electro cardiogram; ED, eating disorders; Hb, hemoglobine; kcal, kilocalories; LDH, lactate dehydrogenase; MANOVA, multiple measurements analysis of variance; RFS, refeeding syndrome; RH, refeeding hypophosphatemia; SPSS, Statistical Package for the Social Sciences.

decreases highly significantly. Neither hypophosphatemia nor rhabdomyolysis is found under phosphate substitution. Hyperhydration occurred often, which manifests itself in the drop in haematocrit by the second week.

Discussion: Under thorough medical surveillance, supplementation of phosphate and thiamine, and substitution of electrolytes whenever necessary rapid renutrition appeared to be save even in extremely malnourished inpatients with anorexia nervosa. As measured by the laboratory values, the health status of the severely malnourished patients improves significantly on a high-calorie diet. Except for hyperhydration, there was no evidence of a refeeding syndrome.

KEYWORDS
anorexia nervosa, health status, refeeding syndrome, weight gain

Key points

- The risk, assessed by significant laboratory parameters, increases considerably with increasingly low weight.
- Rapid refeeding under medical supervision leads to rapid stabilization of health.
- Under these conditions, there was no evidence of a threatening refeeding syndrome.
- Even in extremely underweight patients with anorexia nervosa, rapid refeeding appears to significantly improve the risk profile.

1 | INTRODUCTION

Refeeding concepts in anorexia nervosa (AN) starting with low calorie intake at the beginning in order to avoid a potentially dangerous 'refeeding syndrome' have come into doubt. In recent years randomized control studies have demonstrated the safety and effectiveness of higher caloric intake in order to achieve faster weight gain and to stabilize health status (Agostino et al., 2013; Garber et al., 2013; Golden et al., 2013; O'Connor et al., 2016). Based on a systematic review of approaches to refeeding Garber and colleagues (Garber et al., 2016) concluded that:

- In mildly and moderately malnourished patients, lower calorie refeeding is too conservative;
- Both meal-based approaches or combined nasogastric meals can administer higher calories;
- Higher calorie refeeding has not been associated with increased risk for the refeeding syndrome under close medical monitoring with electrolyte correction.

However, there is still insufficient evidence for a change in the current standard of care in severely malnourished inpatients. This group of inpatients has the highest risk of morbidity and mortality (Fichter et al., 2017) and also carries the highest risk of developing a refeeding syndrome (RFS). An initially low BMI seems to be a better predict the occurrence of refeeding problems than the initial calorie intake (Redgrave et al., 2015). As highly malnourished men and women with AN carry the highest mortality risk, rapid weight gain is needed in order to:

- improve nutritional status (weight gain),
- normalize somatic disorders secondary to undernutrition,
- combat the acute somatic effects such as hypoglycaemia, muscle weakness, bradyphrenia, severe hypotension, leucopenia and severe bradycardia,
- improve mental state and therewith improving the possibilities of establishing a psychotherapeutic relationship (Bargiacchi et al., 2019).

This is the group of patients that needs weight gain the most, and delaying weight gain by too cautious nutrition protocols might bear a higher risk than that resulting from a potential RFS.

Since there is no clear-cut definition of 'refeeding syndrome' the best description might be a rapid worsening of health status during renutrition of malnourished subjects. It presents a serious dysregulation of

metabolism with high risk of death (Garber et al., 2012). This entails the metabolic and physiologic consequences of the depletion, repletion, compartmental shifts and interrelationships of phosphorus, potassium, magnesium, glucose metabolism, vitamin deficiency and fluid resuscitation (Skipper, 2012; Solomon & Kirby, 1990).

One core symptom of refeeding is hypophosphatemia along with a consecutive breakdown of cell metabolism and rhabdomyolysis. Involved in this scenario of cell death are furthermore other electrolytes, glucose metabolism and thiamine (Crook et al., 2001). Malnutrition is associated with a drastic depletion of intracellular phosphate concentrations. This is caused by diminished nutritional intake of phosphorus and a latent hyperparathyroidism (Idolazzi et al., 2018). Phosphate is sucked into the cell by an energy consuming sodium-phosphate co-transporter, which is more active in the presence of insulin. Lack of energy might contribute to a decreasing intra-extracellular phosphate gradient with subsequently lowered total body phosphate levels despite of normal serum levels.

During renutrition the shift from katabolic metabolism back to glucose utilization in the citrate cycle boosts the intracellular need for phosphate in order to generate phosphate compounds especially adenosine triphosphate (ATP). The lack of available phosphate can then lead to cellular damage—in the case of damage of muscle cells to increasing levels of creatine kinase. Clinical symptoms are rhabdomyolysis, failure of organs, convulsions or even death. Parallel to phosphate thiamine is needed as a coenzyme in the renutrition carbohydrate metabolism. Markers of ongoing refeeding syndrome are therefore hypophosphatemia and increasing levels of creatine kinase.

Another critical symptom of refeeding is a considerable change in fluid compartments. Hypovolaemia is due to decreased fluid intake—oligodipsia is often seen in AN—and purging behaviour most frequent in AN on admission (Caregaro et al., 2005). On the other hand with ongoing normalization of food and fluid intake it comes to hyperhydration and oedema, which is often referred to as refeeding syndrome (Azumagawa et al., 2007; Rigaud et al., 2010; Tey et al., 2005). Besides oedema low levels of haematocrit indicate hyperhydration. Whether or not the hypervolaemia is normo- or hypoosmolar can be identified by serum sodium levels. Severe hypervolaemia might be threatening due to cardiovascular overload.

Routine laboratory parameters also provide information about the health status threatened by underweight beyond refeeding phenomena. Bone marrow shows a gelatinous transformation in AN containing more fat cells than normal (Ecklund et al., 2017; Fazeli et al., 2018; Fazeli & Klibanski, 2019). It is therefore less productive with less cell turnover with the consequence of thrombocytopaenia, leucopenia and anaemia (Cleary et al., 2010; De Filippo et al., 2016; Hutter et al., 2009). Bone marrow fat content might even increase with short term weight gain (Fazeli et al., 2018). Although there is no evidence for an increased number of bacterial infections due to leucopenia (Słotwińska & Słotwiński, 2017) it remains an indicator of poor immune defence and thus represents a potential lethal risk. Markers for bone marrow function are platelet count, leucocytes and haemoglobin (which recovers last).

Hypovolaemia (due to oligodipsia), hypokalaemia and a permanent lack of available energy compromise renal function. Renal failure is a common sequel of anorexia nervosa (Bouquegneau et al., 2012; Stheneur et al., 2014). Although creatinine in regard of decreased muscle mass might underestimate the degree of renal impairment (Delanaye et al., 2009) it is useful in order to survey the course of renal function.

Autophagy is a cellular process responsible for the degradation of proteins and organelles. During starvation, autophagy is induced in numerous organisms ranging from yeast to mammals, and promotes survival by supplying nutrients and energy (Kheloufi et al., 2014). It causes elevated transaminases and may severely impair liver function in AN (Rosen et al., 2017).

Hypokalaemia may be induced by purging behaviour and hyperaldosteronism both common in AN (Lai et al., 2017). Hypokalaemia is a risk factor for cardiac arrhythmia and can lead to renal damage (Liang & Yeh, 2011). Hypokalaemia and hypomagnesaemia can be induced by the same mechanisms and are often clinically intercorrelated.

The objective of this study has two steps: First to establish a risk estimation based on routine laboratory parameters in order to judge overall health status in AN regarding as well sequelae of a potential refeeding syndrome as well as health in a sample comprising all patients admitted to the institution in the last 4 years and second to use this risk estimation in order to evaluate the course of health status during refeeding using a rapid nutritional recovery protocol in severely malnourished inpatients with AN (<BMI 13 kg/m^2).

2 | METHODS

2.1 | Participants

All participants had been inpatients admitted to Schoen Clinic Roseneck, a hospital specialized for the treatment of mental disorders, which offers 15 specialized wards for patients with eating disorders.

Sample 1: Between 1.5.2016 and 1.5.2020 3230 AN inpatients have been treated [mean age 22.5 years, range 12–73 years; 3097 females; mean BMI 15.4 kg/m^2, range 9.4–26.8 (some of them had been in remission)]. For 1672 out of the total 3097 inpatients a complete data set was available [admission data including weight, age, BMI and relevant laboratory parameters for further analysis (mean age 22.5 years, range 12–73 years; mean BMI 15.3 kg/m^2, range 9.4–25.7)].

The patients from Sample 2 ($n = 520$) were admitted in the same period of time in an intermediate care unit specialized for the treatment of severely ill ED patients. Most of these patients had been transmitted from other hospitals because of medical problems. The ward offers medical treatment comparable to an intermediate care unit with (whenever needed) permanent monitoring of cardiovascular parameters, frequent controls of laboratory parameters and availability of ultrasound, body impedance analysis, ECG and echocardiography. During this 4-year period 410 out of the 520 admitted patients had a AN primary diagnosis.

In order to provide a sufficient observation period for potential RFS occurrence only those inpatients were included who stayed at least 28 days. Standard treatment of these severely malnourished inpatients comprised at least weekly bloodwork, initial monitoring of cardiovascular parameters and weekly multi frequency body impedance measurements. Phosphate (1024 mg/day) and thiamine (200 mg/day) were supplemented routinely. Although weekly measurements are part of standard procedures, the complete data set was not always available. 142 inpatients with a BMI <13 had a data set complete enough to be included (no missing data at admission and after 28 days and at the most one missing in between; see Table 1).

2.2 | Renutrition

All patients receive three meals with an average total energy content of 2000 kcal per day from day 1 after admission to the ward, divided into three main meals with a choice between vegetarian and non-vegetarian meals consisting of approximately 39% carbohydrates, 42% fats and 19% proteins. The caloric intake is adjusted and increased according to weight development to aim for an increase in body weight of 700–1000 g/week. The criterion for a sufficient food intake is weight gain, which should be at least 100 g per day. If the weight gain cannot be achieved, the portion size of one or more main meals is increased, and up to three snacks between meals are added. In addition, liquid food is offered to substitute for energy losses in case of incompletely eaten meals. All meals are therapeutically accompanied by a nurse or therapist in a 1:6 group supervision. Patient adherence to dietary intake is supported through daily therapeutic contacts and medical rounds. Patients eat their meals in a stable group setting and support each other. Peer pressure may play an important role. In weekly eating protocol sessions patients review their progress and commit to new goals related to hitherto avoided food, fears and counteractive behaviour. Patients do not receive nasogastric feeding since normalization of eating behaviour is a general therapeutic goal. Physical restraint or force feeding had never been used in this sample. The average caloric value (data provided by the caterer and controlled in samples) for the non-vegetarian menu is 743, 717 and 704 (total 2164) kcal for breakfast, lunch and dinner; and 743, 737 and 683 (total: 2162 kcal) for the vegetarian option. If patients do not finish their meal (50%–99% eaten) they are asked to drink 1 supplemental drink (400 kcal, Fresubin® 200 ml with 2 kcal/ml). If they eat less than 50% of their respective meal, they are asked to replace the missed-out calories by drinking 2 supplemental drinks (2 × 400 kcal). The group setting and the support from experienced therapists are considered essential for compliance with dietary adherence. Contingency measures are often necessary in order to regulate excessive exercising and slow weight gain. During the first 28 days it is rare that patients require more than 2000 kcal/day but many patients receive liquid food in order to replace unfinished meals. Patients reduce their calorie consumption by limiting their physical activity. Contingency contracts and video surveillance with 24/7 nursing staff presence as well as very moderate exercise therapy play an important role in normalizing exercise behaviour.

In individual cases, energy intake of more than 4000 kcal is necessary to ensure sufficient weight gain. All patients participated in an intensive therapeutic programme adapted to the special needs of the severely underweight women and suitable for therapeutically addressing the considerable anxieties and resistance associated with weight gain.

2.3 | Statistical analysis

Interrelationships between laboratory parameters and BMI were calculated as Pearson correlation. Spearman correlations were calculated for interrelationships between BMI and the scores.

We used One-way-Analysis of variance (ANOVA) in order to test the relationship between BMI-classes and laboratory parameters, respectively the Friedman-test for the relationship between score and BMI-classes.

TABLE 1 Sample characteristics

	Sample 1 All wards for ED	Sample 2 Intermediate care unit
All inpatients 2015–2020		520
Diagnosis anorexia nervosa *F* 50.0	3228	410
Laboratory parameter complete & age >18 years	1075	339
BMI < 13	196	142
Age	27.5 years, SD 10	26.4 years, SD 9.4
	(Range 18–68 years)	(Range 18–62 years)
Female/male	1022/53	142 female
Weight (kg) admission	43.9 kg, SD 7.6	31.5, SD 3.6
	(Range 21.5–78 kg)	(23.5–40.1)
BMI admission	15.7, SD 3.0	11.5, SD 0.85
	(Range 9.5–26.8)	(Range 8.4–13)

TABLE 2 Course of weight gain in 142 inpatients

	Minimum	Maximum	Mean	SD	*t* test
Weight admission 7 days	−2.2	13.2	2.1 kg	2.2	$p < 0.000$
Weight 7–14 days	−1.2	3.4	0.8 kg	0.8	$p < 0.000$
Weight 14–21 days	−0.8	2.8	0.76 kg	0.7	$p < 0.000$
Weight 21–28 days	−1.4	2.6	0.75 kg	0.6	$p < 0.000$
Weight admission 28 days	−2.5	14.6	4.4 kg	2.2	$p < 0.000$
BMI admission to 28 days	−0.8	5.7	1.7	0.9	$p < 0.000$

Multiple measurements analysis of variance (MANOVA) was calculated to analyze the change of parameters within the process of weight gain.

A two-sided *p*-value <0.05 was considered statistically significant. Statistical analyses were performed by using SPSS version 21.0 for Windows (IBM Corp.).

2.4 | Quantitative variables

Refeeding syndrome in the narrower sense is characterized by hypophosphatemia and high levels of creatine kinase as a sign of rhabdomyolysis. Refeeding hypophosphatemia (RH) is the most common complication associated with the refeeding of malnourished patients. Normal values are above 0.75 mmol/L. A critical drop is characterized by serum phosphate below 0.5 mmol/L. (see Table 3)

Creatine kinase in blood tests serves as a marker for muscle damage such as occurs in rhabdomyolysis due to hypophosphatemia. The normal range is below 300 U/L, a critical additional threshold is above 600 U/L.

Hypovolaemia is indicated by a drop in haematocrit below 34%; we consider it critical below 30%. Hypovolaemia can be isoosmolar at the same time as normal serum sodium. Hyponatraemic hypovolaemia can be caused by polydipsia or by elevated adiuretin release (Kanbur & Katzman, 2011). The lower threshold for normal serum sodium is 132 mmol/L.

Bone marrow function is characterized by the three cell lines erythropoiesis, granulopoiesis and thrombopoiesis. The threshold values are summarized in Table 3.

Kidney function is assessed on the basis of creatinine levels. Thresholds derived from normal weight populations may be misleading because creatinine is a breakdown product of creatine phosphate in muscle. Given the low muscle mass in AN as a function of BMI, creatinine overestimates renal function. Since there is no correction formula to adapt to low muscle mass, we followed the standard values that apply to people of normal weight.

We used alanine aminotransferase (AST) and aspartate aminotransferase (ALT) to monitor liver damage and therewith autophagy.

TABLE 3 Pathologic values in the course of weight gain

	Creatin kinase	AST	ALT	Hematokrit	Haemoglobin	Protassium	Creatinin	LDH	Leucocytes	Natrium	Phosphate	Platelets
Normal	<300 U/L	<35 U/L	<35 U/L	>34%	>11.2 g/dl	>3.5 mmol/L	<>1.1 mg/dl	<250 U/L	>3.98 g/L	>132 mmol/L	>0.75 mmol/L	>182 g/L
Pathologic	>300 U/L	>35U/L	>35U/L	<34%	<11.2 g/dl	<3.5 mmol/L	>1.1 mg/dl	>250 U/L	<3.98 g/L	<132 mmol/L	<0.75 mmol/L	<182 g/L
Highly pathologic	>600 U/L	>100 U/L	>100 U/L	<30%	<9 g/dl	<2.5 mmol/L	>1.5 mg/dl	>500 U/L	<2.5 g/L	<125 mmol/L	<0.5 mmol/L	<100 g/L
Admission: mean BMI 11.5												
Valid	142	142	142	141	141	142	142	142	141	142	142	141
Normal	133	64	56	107	110	101	137	73	68	131	126	109
Pathologic	7	52	52	18	23	34	5	60	58	10	11	29
Highly pathologic	2	26	34	16	8	7	0	9	15	1	5	3
7 days, mean BMI 12.3												
Valid	134	135	135	134	134	136	136	135	134	137	135	134
Normal	131	90	54	89	88	118	136	71	64	135	127	109
Pathologic	2	38	61	24	34	18	0	60	58	2	8	24
Highly pathologic	1	7	20	21	12	0	0	4	12	0	0	1
14 days, mean BMI 12.6												
Valid	137	137	137	138	138	138	138	137	138	139	138	138
Normal	136	111	57	82	71	129	138	67	69	137	137	132
Pathologic	1	26	62	34	51	9	0	67	57	2	1	6
Highly pathologic	0	0	18	22	16	0	0	3	12	0	0	0
21 days, mean BMI 12.9												
Valid	127	127	127	128	128	127	128	127	128	128	128	128
Normal	124	107	53	83	74	120	128	53	67	126	127	125
Pathologic	1	20	66	27	41	7	0	70	51	2	1	3
Highly pathologic	2	0	8	18	13	0	0	4	10	0	0	0

(Continues)

TABLE 3 (Continued)

	Creatin kinase	AST	ALT	Hematokrit	Haemoglobin	Protassium	Creatinin	LDH	Leucocytes	Natrium	Phosphate	Platelets
28 days, mean BMI 13.2												
Valid	139	139	139	138	138	138	140	138	138	140	140	138
Normal	136	123	57	95	86	129	140	50	87	139	139	138
Pathologic	3	16	80	29	41	9	0	87	45	1	1	0
Highly pathologic	0	0	2	14	11	0	0	1	6	0	0	0

Hypokalaemia can cause severe cardiac arrhythmias and is therefore particularly threatening in people with eating disorders. It can be caused either by hyperaldosteronism associated with an overactivation of the HPA axis or it can be the result of the purging behaviour of the patients.

If hypokalaemia occurred during hospitalization, potassium chloride was replaced. As potassium and magnesium are highly correlated, we have also supplemented magnesium in such situations. As purging behaviour is closely monitored and prevented whenever possible at the intermediate care ward, supplementation was not often necessary, but there are no exact figures for the frequency and dosage of substitution.

The **risk score** was calculated by summing each of the 12 parameters above or below the defined standard threshold values. Thus, the maximum theoretical risk is a risk of 12 and the minimum risk is 0. In addition, we defined even stricter limits to clarify how many patients were in critical condition at the respective measurement points (see Table 3).

All patients with an admission diagnosis of an eating disorder are asked to answer a series of eating disorder-specific questionnaires. We used the ED-Quest (Fichter et al., 2015) to assess the eating disorder population of the patients. We used subscale 2 'binging and vomiting' with the recommended cut-offs in order to classify purging behaviour.

3 | RESULTS

3.1 | Risk score

The risk score calculated according to the method described above had a mode of 0, a median of 1, a mean of 1.21, and a maximum of 8 for all 1672 persons and correlated highly significant and negative (Spearman correlation 0.41 $p < 0.000$) with the BMI.

Figure 1 clearly shows the correlation between BMI and risk score and five of the most significant parameters.

While 67% of weight normalized AN had no pathological values and another 30% had a maximum of two pathological parameters, only 15% of AN with a BMI below 13 had no pathological parameters and more than 52% had between three and 12 pathological parameters.

Most of the parameters correlated highly significantly with the BMI (in the sense that pathological values are more frequent with lower BMI: AST: −0.300**; $p = 0.000$, ALT: −0.283**, $p = 0.000$, haematocrit: 0.258**; $p = 0.000$, haemoglobin: 0.194**, $p = 0.000$; potassium: 0.119**, $p = 0.000$; creatinine: 0.074*, $p = 0.025$; LDH:

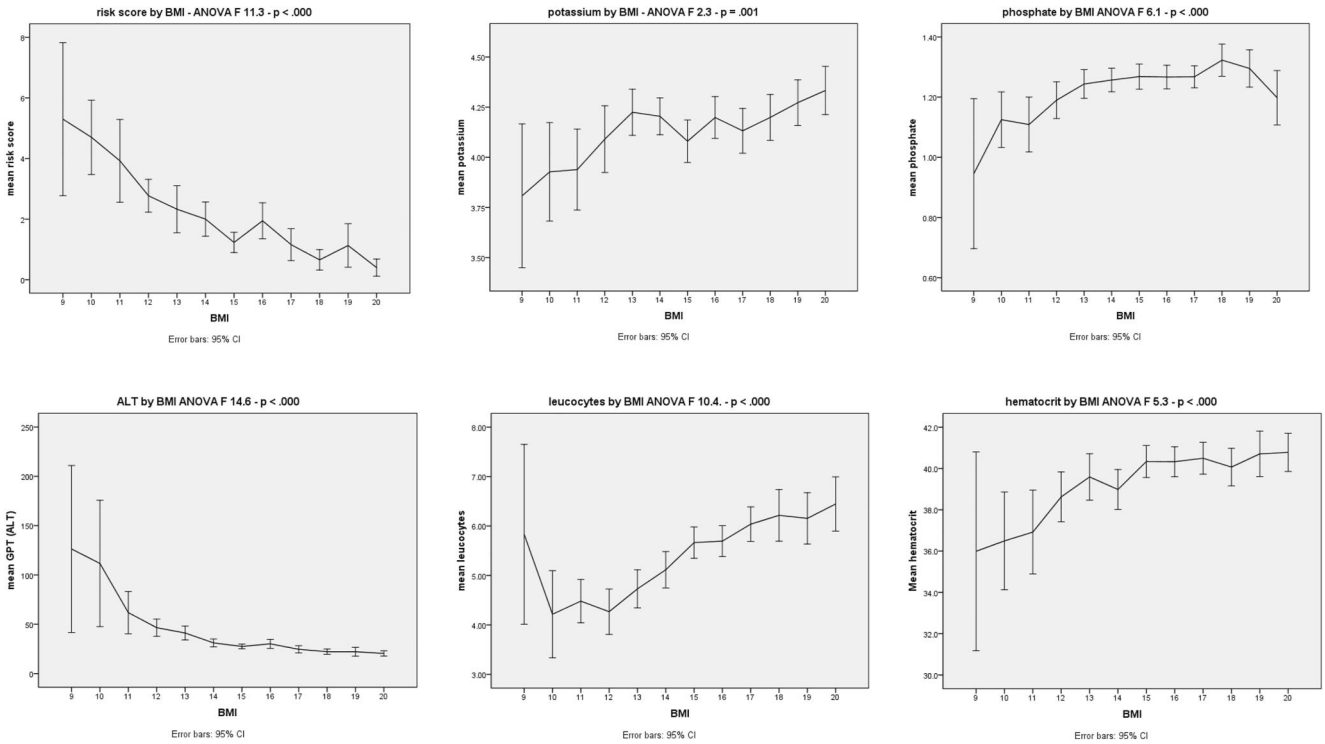

FIGURE 1 Mean risk for classes of BMI: risk score and laboratory parameter of 1075 patients with a diagnosis of AN [until BMI 10: $N = 16$ (1.5%); until 11: 39 (3.6.%), until 12: 53 (4.9%), until 13:78 (7.3%); until 14: 115 (10.7%); until 15: 138 (12.8%); until 16: 156 (14.55%); until 17: 142 (14.5%), until 18: 116 (8.2%), above 18: 134 (13.5%)]

−0.331**, $p = 0.000$; leucocytes: 0.311**, $p = 0.000$; sodium: 0.173**, $p = 0.000$; phosphate: 0.200**, $p = 0.000$; platelets: 0.043, $p = 0.193$). Creatine kinase was not correlated with BMI (CK: −0.061*, $p = 0.022$), creatinine showed a small positive correlation (creatinine: 0.062*, $p = 0.012$) (taking into account that a low BMI means low muscle mass and therefore low creatine response).

ANOVA shows a highly significant relationship between the level of potassium values and the BMI (see Figure 1). While patients of the purging type had significantly lower potassium values (mean 4.18, SD 0.62) than patients of the restricting type (4.37, SD 0.62) (t test $p < 0.000$), there was also a significant difference between patients with a BMI below 13 ($N = 258$, mean = 4.12; SD = 0.68) and patients with a BMI above 13 ($N = 1401$, mean = 4.35, SD = 0.52) (t test $p < 0.000$). This difference between AN below BMI 13 and above BMI 13 remained significant even when comparing only the subtypes of purging or restricting type AN:

Restricting type AN:

below BMI 13 kg/m^2, $N = 145$, mean 4.24, SD 0.58; above BMI 13 kg/m^2, $N = 720$ mean 4.4 SD 0.46—t test $p < 0.001$.

Purging type AN:

below BMI 13 kg/m^2, $N = 64$, mean 3.8, SD 0.81; above BMI 13 kg/m^2, $N = 460$ mean 4.23 SD 0.58—t test $p < 0.000$.

According to laboratory parameters patients in the Intermediate care sample are at even higher risk (mean risk score 3.42) compared to those patients out of the bigger sample with a BMI below 13 (mean risk score 2.7).

3.2 | Weight gain

Patients in the intermediate care nutritional refeeding programme gained rapidly weight especially in the first week (most probably due to hypovolaemia at admission). Mean weight gain in the first week was 2.1 kg followed by at least 700 g in the next 3 weeks (see Table 2), proving the effect of chosen meal sizes. Mean total weight gain was 4.15 ± 1.96 kg.

3.3 | Laboratory parameter changes in the course of weight gain

Serum phosphate increased under supplementation—not a single case of hypophosphatemia occurred except for those with low phosphate levels at admission. After 2 weeks all but one patient was within the normal range. Accordingly, except for those at admission no severe cases of rhabdomyolysis were observed.

Hypervolaemia occurred with increasing frequency until week 3 and the frequency declined to approximately the level at admission after 4 weeks (see Table 3), Hypervolaemia as measured by low haematocrit was present in more than the half of all patients, in contrast to hypervolaemia hyponatremia was only a problem at admission, In the following weeks only one patient had a transient and mild hyponatremia, Elevated transaminases are quite common in severe AN. More than a half of all low weight patients in this sample had elevated transaminases, AST declined by mean from 71 to 26 U/L (MANOVA F 10.7, $p < 0.001$) and ALT from 88 to 41 U/L by mean during 4 weeks ($F = 9.9$, $p < 0.001$), Haemoglobin, with a mean value of 12.4 + 1.8 g/L, is too low in a high proportion of patients at admission and in the course of weight gain the proportion of anaemic patients continues to increase. This drop corresponds to the values for the haematocrit falling in the first weeks. Despite the hypervolaemia, which is evident from the initial drop in haematocrit, the leucocyte count is steadily increasing, as is—and even faster—the number of thrombocytes.

According to clinical impression there had not been any adverse events in this group of patients which could be attributed to a 'refeeding syndrome' in a broader sense (rapid worsening of health status in the course of weight gain). The risk score was highest at admission and declined significantly beginning with the first week of weight gain (see Figure 2). Friedman analysis of variance for multiple measurements showed a highly significant (Chi-square 88, $p < 0.001$) decrease of risk.

4 | DISCUSSION

In recent years, several controlled studies have been conducted comparing low-calorie and higher-calorie refeeding programs, and found that the higher-calorie dietary protocols had the advantage of accelerating weight gain without a higher health risk. However, it is still unclear whether a higher calorie renutrition of extremely underweight patients increase their risk for refeeding syndrome. Our hospital treats more than 300 patients with AN every year, starting with a high calorie refeeding protocol. This has also been applied to patients below BMI 13 kg/m^2 and according to our clinical observations the benefits of rapid weight gain far outweigh the risks. We consistently observed a stabilization of their health status and no case of severe RFS under the conditions described above (Koerner et al., 2020).

Therefore, it seemed unethical to us to test a low-calorie refeeding protocol against the common treatment due to the very high health risk caused by underfeeding of extremely underweight patients. The present retrospective study was conducted to verify the clinical impression that

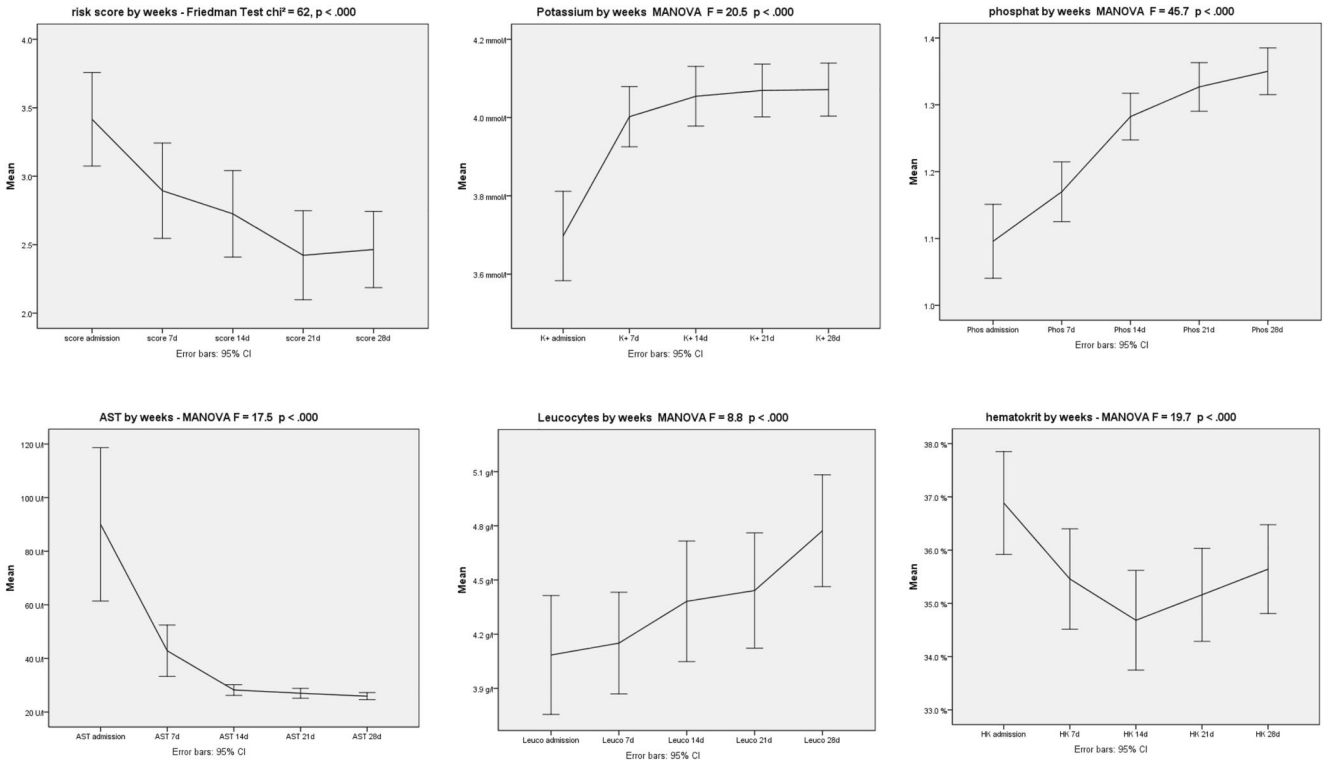

FIGURE 2 Mean risk scores and 95% confidence interval in the course of weight gain

rapid refeeding improves the health status of even severely cachectic patients with multiple health risks rather than exposing these patients to additional risk. It was necessarily limited to the data obtained from the two samples and used only those laboratory parameters that were most likely to reflect the health risk. We used the risk score in order to determine whether rapid refeeding improves or threatens the health of our patients.

Regarding the subject of RFS in terms of hypophosphatemia and rhabdomyolysis, the result is quite clear: no severe hypophosphatemia was observed under phosphate supplementation and initial high levels of creatine kinases decreased in most cases. Hypervolaemia, as documented by a low haematocrit (and clinically by the presence of oedema), is a common concomitant of renutrition. It is questionable whether less weight gain is associated with less oedema. Hypervolaemia is potentially dangerous because it puts a strain on the cardiovascular system due to volume overload, and since hypervolaemia develops slowly, it is possible to intervene medically as appropriate (if necessary, by diuretics) according to fluid balance monitoring.

Creatinine remained unchanged, which underlines that the kidney is not threatened by rapid weight gain.

Transaminases decreased rapidly, which shows that weight gain and improved energy supply to the body are essential to stop cell death in the liver and other vital organs.

Platelet and leucocyte counts are steadily increasing, suggesting that normalization of food intake leads to bone marrow recovery. Since erythropoiesis recovers more slowly, erythrocyte numbers increase slowly and Hb values even decrease initially according to the decreasing haematocrit.

The electrolytes sodium and potassium are regularly monitored and do not show higher degrees of deflection. Potassium is low in extremely underweight patients independent of the type of AN which demonstrates that hypokalaemia in those cases is caused by hyperaldosteronism rather than by purging behaviour.

The risk score indicates that the general state of health improves significantly during the resumption of nutrition. There were no indications of an increased risk of RFS, except for the hypervolaemia which grew over the first 2 weeks of weight gain.

5 | CONCLUSIONS

Extremely underweight women and men with AN (BMI $< 13\ kg/m^2$) are in a very poor state of health, which requires close medical monitoring and appropriate medical interventions.

- The risk score calculated from the relevant laboratory parameters can be easily derived from routine laboratory parameters and reflects the general state of health in case of malnutrition.
- The general state of health, as measured by the risk score, improves significantly when severely malnourished patients are hospitalized and refed,
- With supplementation of phosphate and thiamine, rapid weight gain does not lead to the occurrence of hypophosphatemia or rhabdomyolysis,
- Hypervolaemia is frequently seen in the course of weight gain in AN and may require medical intervention.
- The advantages of rapid refeeding are the rapid recovery of bone marrow. Platelet and leucocyte counts are increasing steadily, suggesting that normalization of food intake leads to bone marrow recovery. Since erythropoiesis recovers more slowly, the erythrocyte numbers increase only slowly and the Hb values even decrease initially according to the decreasing haematocrit.
- The transaminases decreased rapidly, which shows that weight gain and improved energy supply to the body helps to stop the autolysis of cells in the liver and other vital organs.
- There were no indications of an increased risk of RFS, except for the occurrence of increased hypervolaemia. Rapid refeeding seems to be safe even in severely malnourished inpatients with AN when accompanied by thorough medical surveillance, supplementation of thiamine and phosphate and supplementation of electrolytes whenever necessary. The benefits of rapid weight gain under the given circumstances outweighed the risks.

CONFLICT OF INTEREST

All three authors are involved in the treatment of eating disorders, especially in the treatment of severely underweight anorexia nervosa. None of the authors received funding from third parties.

DATA AVAILABILITY STATEMENT

We are prepared to share the data as soon as the paper has been accepted.

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How to cite this article: Cuntz, U., Körner, T., & Voderholzer, U. (2022). Rapid renutrition improves health status in severely malnourished inpatients with AN - score-based evaluation of a high caloric refeeding protocol in severely malnourished inpatients with anorexia nervosa in an intermediate care unit. *European Eating Disorders Review*, *30*(2), 178–189. https://doi.org/10.1002/erv.2877