Implementing high energy liquid nutrition, omega-3 fatty acids and nutritional supplements for the treatment of anorexia nervosa

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Short running title: Refeeding anorexia nervosa patients

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Abstract

Objective: To examine the effects of two different treatment approaches on the course of anorexia nervosa (AN) over time.

Methods: The subjects were 27 hospitalized AN patients (mean age: 14.91 years; mean BMI: 14.58; mean height: 163.56) . In our retrospective analysis we compared weight gain in two groups. While one group was treated with a standard oral refeeding protocol (historical control) through January 2013 (N=16), the second group (highly standardized refeeding protocol) received a high energy liquid nutrition and nutritional supplements including omega-3 fatty acids (N=11).

Results: On admission, the two groups were comparable in terms of height, weight, age and heart rate. At the end of our monitoring time frame of 25 days, weight gain was 121.4% higher in the highly standardized refeeding protocol group than in the historical control group (66.5 ±52.4 vs 147.3 ±55.7 grams/day; t-Test p=0.004; CI95%: 29.3-132.2). About 45% of our patients stated they were vegetarians at admission. However, we could not identify a vegetarian diet as a statistically significant negative prognostic factor for weight gain.

Discussion: The highly standardized refeeding protocol seems to be helpful in malnourished AN patients to improve weight gain without enhancing the risk of a refeeding syndrome. Because of an increasing energy turnover, caloric intake should be adjusted during refeeding.

Keywords: Anorexia nervosa; refeeding syndrome; vegetarians

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AN is a serious illness leading to substantial morbidity and mortality. The standard mortality ratios for patients with AN and a psychiatric comorbidity are 5.4 (95% confidence interval [CI 95%]: 4.6-6.4) and 18.1 (CI 95%: 15.2-21.3) for natural and unnatural causes of death, respectively (Kask et al., 2016). The treatment of AN is often protracted with repeated hospitalizations. Nutritional refeeding is the first therapeutic step to recovery. In case and cohort studies different low and high-calorie diet protocols exist (Garber et al., 2016; Redgrave et al., 2015). There are well known major complications during weight-restauration, called refeeding syndrome: a shift of electrolytes and fluid can occur in malnourished patients leading to (potentially fatal) cardiovascular, respiratory and neurological symptoms. However, prospective and retrospective studies showed that higher calorie diets instituted at admission predicted faster weight gain and less hospitalization in patients with AN (Kohn, Madden, & Clarke, 2011; Madden et al., 2015; O'Connor, Nicholls, Hudson, & Singhal, 2016; Parker et al., 2016; Smith et al., 2016). Such a rapid refeeding protocol was well tolerated with no indicators of refeeding syndrome. Particularly tube refeeding proves to be the most effective method for gaining weight (Born et al., 2015; Rigaud, Brondel, Poupard, Talonneau, & Brun, 2007). However, nasogastric tube insertion requires high patient compliance levels and side effects have been reported.

In this study, we examined the effects of two non-invasive treatment approaches over the course of AN. We stepwise changed our treatment protocol by introducing high liquid energy nutrition, omega-3 fatty acids and nutritional supplements according to the NICE protocol. To our knowledge until now no study has examined the effect of omega-3 fatty acids on the course of AN. Even so studies with heart disease and cancer patients have shown an improved weight gain or a decrease in weight loss under supplementation of omega-3 fatty acids (Bayram, Erbey, Celik, Nelson, & Tanyeli, 2009; Mehra, Lavie, Ventura, & Milani, 2006; Pappalardo, Almeida, & Ravasco, 2015).

Methods and Patients:

We retrospectively analyzed the clinical charts of all consecutive patients admitted for hospital refeeding due to AN (all patients met DSM criteria for restricting subtype) between 2009-2013 (N=16) and in 2016 (N=11) who had at least one 24 hour Holter electrocardiogram (ECG). Based on our recently published model of the impact of nutrition on the autonomic nervous system measured by 24 hour heart rate variability, our refeeding protocol was changed in January 2013 (Dippacher, Willaschek, & Buchhorn, 2014). In May 2016 we introduced a highly standardized written refeeding protocol based on a supervision process. Because the treatment of AN was not standardized between January 2013 and May 2016 we excluded all data from this period for the comparison between the two groups. However, we decided to include the data from January 2013 until May 2016 to compare the effect of different nutritional compositions on weight gain.

Standard oral refeeding protocol up to January 2013 (historical control; group 1; N=16): Three meals and two snacks were served based upon the patient’s choice according to a daily consultation with a dietician. Physicians prescribed diets starting around 5 024 kJ (1 200 kcal) per day increased by 837 kJ (200 kcal) per day up to a normal caloric intake between 10 467 kJ (2500 kcal) and 12 560 kJ (3000 kcal) according to patients weight gain. Only two patients received high-energy liquid supplements or nasogastric tube feeding due to insufficient weight gain. Room sitters – mostly nurses – were assigned to observe patients during all meals and snacks, and for 30 minutes after consumption. The weight of each patient was measured each morning using the same weight balance under standardized conditions These conditions included consistent clothing and weighing before the patient visited the bathroom. Fluid balance, blood counts, and serum electrolytes were measured at admission and later according to the doctor's orders. Nutritional supplements were not routinely given. We performed at least one Holter ECG in this historical control group (Pathfinder ™, Reynolds, Germany).

In May 2016 we introduced a highly standardized written refeeding protocol based upon a supervision process (group 2; N=11): In 2015 we realized a better therapeutic success after introduction of the modified NICE protocol[3] with omega-3-fatty acid supplements. Our model about the effect of nutrition on the autonomic nervous system was published (Clancy et al., 2014). For further implementation of the new protocol we performed supervision by an experienced psychologist in which all professional groups participated. The results were published in an internal written protocol: All patients received a high energy liquid nutrition (Fresubin high energy[4]) at admission starting with 42 kJ/kg/day (10 kcal/kg/day) which continuously increased within one week to reach a significant weight gain. In addition to the NICE protocol, we supplemented 2g omega-3-fatty acids per day (2 x 2Tbl Espricot ™) in all patients. Most patients received nutritional supplements: Thiamin 200-400 mg/day, vitamin B complex (Freka Vit ™), multi vitamins (Multivitamin Liechtenstein ™), Zinc, Potassium, Calcium Glycero phosphate and Magnesium. We performed a Holter at admission and before discharge. For better visualization of heart rate variability we introduced a new Holter ECG system (Medilog Darwin ™, Schiller, Switzerland). The observation program was not changed but we realized an unconscious liberalization of our surveillance routines in response to the better weight gain of our patients.

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[3] https://www.nice.org.uk/guidance/cg9/chapter/1-guidance#anorexia-nervosa

[4] Per 100ml Fresubin Energy DRINK: 150kcal (630kJ), 5.8g fat, 0.4g saturated fatty acids, 3.8g monounsaturated fatty acids, 1.6g polyunsaturated fatty acids, w6 : w3 = 2.6:1, 5.6g protein, 18.8g carbohydrates

Statistics

All patients who were admitted in our unit and agreed to the current protocol contributed data to our statistical analysis. Our primary end goal was weight gain. We also measured diet composition, energy intake, body composition and HRV-parameters. Due to staff shortage, the data for these secondary outcomes were partly fragmented. Moreover we could only capture the exact amount of calories eaten by AN patients who were in our hospital between June 2014 and January 2016 (N=22). We checked the assumption of normality by using the Kolmogorov-Smirnov-Test and viewing boxplots and q-q diagrams. We compared our two groups using unpaired student t-test. The statistical significance threshold accounted for p=0.05. All statistical analyses were performed using SPSS 23 for Windows. Due to different courses of disease, the length of admission of our patients varied. The in-patient care time averaged out to 30 days (as seen in Table 1). As for the major component of our statistical analysis, weight gain, we decided to make a cut after 25 days. Choosing a later moment would have shrunk the number of patients for statistical analysis, whereas an earlier moment might not have shown different impacts of our treatment regimens.

Table 1: Characteristics

Characteristics at Baseline	Historical control N=16 Group 1	Highly standardized refeeding protocol N= 11 Group 2	All
Age (y)	15.47 ±2.03(12.48-20.38)	14.08 ±1.22 (12.39-16.56)	14.91 ±1.86 (12.39-20.38)
Child´s gender			
Male	2 (12.50%)	0 (0%)	2 (7.41%)
Female	14 (87.50%)	11 (100%)	25 (92.59%)
Height (cm)	165.36 ±7.12 (153.50-180.00)	160.95 ±8.12 (141.40-174.00)	163.56 ±7.71 (141.40-180.00)
Percentile	53.25 ±31.98 (10.00-99.00)	43.27 ±28.28(3.00-92.00)	49.19 ±30.38 (3.00-99.00)
Weight at admission (kg)	40.12 ±5.06 (28.00-51.00)	37.77 ±5.59(23.70-44.60)	39.16 ±5.31 (23.70-51.00)
Percentile	7.44 ±11.01 (0.00-31.00)	6.00 ±8.83 (0.00-24.00)	6.85 ±10.03 (0-31)
BMI (kg/m^2)	14.62 ± 1.05 (11.90-16.20)	14.52 ±1.40 (11.90-16.80)	14.58 ±1.18 (11.90-16.80)
Weight before disease (kg)	52.18 ±8.79 (36.00-65.00) N=13	53.25 ±4.50 (50.00-60.00) N=8	52.59 ±7.33 (36.00-65.00)
Disease length (months)	10.13 ±5.16 (4.00-24.00)	10.09 ±9.76 (1.00-36.00)	10.11 ±7.21 (1.00-36.00)
Vegetarian/vegan	8(50%)	4 (36.36%)	12 (44.44%)
HR [bpm]	66.13 ± 12.48 (38.00-86.00)	62.52 ±13.11 (30.00-81.00)	64.66 ±12.62 (30.40-86.00)
SDNN [ms]	248.63 ±64.03 (156.00-362.00)	242.78 ±85.45 (144.60-419.10)	246.24 ±71.99 (144.60-419.10)
RMSSD [ms]	57.00 ±19.93 (32.00-105.00)	74.02 ±24.46 (47.30-109.70)	63.93 ±23.06 (32.00-109.70)
Length of stay (d)	24.00 ±8.91 (11,00-40.00)	38.91 ±17.44 (23.00-85.00)	30.07 ±14.78 (11.00-85.00)

(±SD; range in brackets) SDNN: standard deviation of NN intervals; RMSSD: quare root of the mean of the sum of squares of differences between adjacent NN-intervals

Results

During in-patient care neither refeeding syndrome nor other severe complications such as hypophosphatemia or hypokalemia were observed in any patient.

All ratio variables shown in table 1 except ‘length of stay’ ‘RMSSD’ and ‘disease length’ were normally distributed. When we compared vegetarians versus carnivores all major baseline variables were normally distributed.

Table 2: Weight history

Characteristics	Historical control N=16 Group 1	Highly standardized refeeding protocol N= 11 Group 2
Weight at admission (kg)	40.12 ±5.06 (28.00-51.00)	37.77 ±5.59(23.70-44.60)
Percentile	7.44 ±11.01 (0.00-31.00)	6.00 ±8.83 (0.00-24.00)
BMI at admission (kg/m^2)	14.62 ± 1.05 (11.90-16.20)	14.52 ±1.40 (11.90-16.80)
Weight at discharge (kg)	42.17 ±4.84(31.70-53.10)	42.31 ±6.07 (27.75-49.15)
BMI at discharge (kg/m^2)	15.38 ±.95 (13.45-17.07)	16.25 ±1.40 (13.88-18.84)
Weight at discharge/Weight at admission	1.05 ±0 .03 (0.99-1.13)	1.12 ±0.07 (1.04-1.28)
Caloric intake (kcal/d)	-	2413.86 ±445.90 kcal N=11 10106 kJ
Calories (g/d/kg)	-	62.86 ±15.83 kcal N=11 263 kJ
Weight gain total (kg)	2.05 ±1.13 (-0.20-3.70)	4.54 ±2.55 (1.50-10.50)
Weight gain day 25 (kg)	1.66 ±1.31 (-0.60-3.70) N=12	3.68 ±1.51 (1.70-5.70) N=8
Weight gain day 25 (g/d)	66.50 ±52.36 (-24.00-148.00) N=12	147.25 ±55.71 (68.00-228.00) N=8

(±SD; range in brackets)

At the end of our chosen monitoring time frame of 25 days, weight gain was 121.4% higher in the highly standardized refeeding group than in the historical control group (table 2). Beyond that mean caloric intake per day of group 2 patients was 26.4% higher than in group 1 patients (10 106 vs 7 996 kJ / 2 413.9 vs 1 909.9 kcal). In order to visualize and make our study groups more comparable in spite of different baseline values, we studied weight during different days in relation to weight at admission (as seen in table 3). On day 12 we observed a significant difference between the historical control and the highly standardized refeeding group using unpaired student t-test (p=0.04 CI95%: 0.2-4.9). Over the course of time the p-value decreased.

Table 3: Changes in body weight (percentage of baseline weight)

Days	Historical control Group 1	Highly standardized refeeding Group 2	Sig.	CI95%
Day 1	100 ±0.00 N=16	100 ±0.00 N=11	-	-
Day 3	99.18 ±2.17 N=14	98.65 ±2.46 N=11	.857	-2.09-1.75
Day 8	101.38 ±2.44 N=15	103.08 ±3.16 N=11	.134	0.56-0.70
Day 15	102.85 ±2.90 N=13	106.07 ±3.61 N=11	.024	0.46-5.97
Day 22	104.81 ±2.94 N=14	108.08 ±4.13 N=11	.030	0.35-6.20
Day 29	103.28 ±3.53 N=6	111.79±4.13 N=3	.014	2.31-14.72

(±SD)

Based on anamnesis the weight before disease could be determined for 21 out of the 27 AN patients. At discharge, group 2 patients had reached 84.1% (SD: ±4.4) of their original weight compared to 82.3% (SD±10.0) by group 1 patients despite group 2 patients having a lower baseline value (74.4% ±6.3 vs 78.1% ±10.0). Nevertheless, only a single Phase 2 reached a BMI at discharge higher than 18.5 kg/m^2.

In accordance with Bardone-Cone et al we observed a high rate of AN patients were vegetarian. About 45% of our patients stated eating some form of vegetarian diet. One patient out of the 27 patients ate meat products irregularly and two AN patients were pesco-vegetarian. During refeeding at our hospital unit there was no attempt to convince patients of a meat diet. Using student t-test we found a significant difference in the length of disease between vegetarians and carnivores (14.63 ±9.81 versus 7.70 ±3.37 months). Although we could only detect small differences in mean calorie intake/kg/day and mean calories/day, we found that vegetarians gained less weight on average than carnivores (1.35 ±2.37 versus 1.81 ±1.42 kg). However, this incongruence was not statistically significant (unpaired student t-test).

In contrast we found a strong correlation between daily mean calorie intake and weight gain until day 20 (Pearson r=0.44 p=0.04). As seen in figure 1 many patients initially lost weight. Over time our patients gained weight more rapidly. However, at some point most patients stopped gaining weight as rapidly. This occurred especially from day 15-20 when we observed a very low rate of weight gain per kcal compared to day 5-10 (0.02 g/kcal vs 0.11 g/kcal; paired student t-test p=0.00).

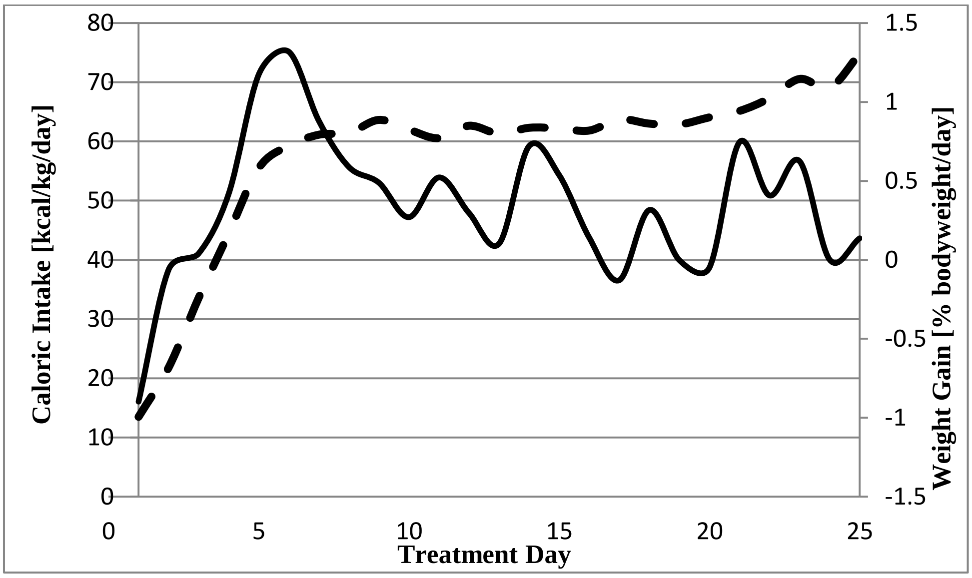

Fig. 1 Necessary caloric intake for weight gain rises during refeeding. Dashed line depicts caloric intake in kcal/kg/day while solid line shows weight gain per day in % of bodyweight

Moreover, we observed a significant better weight gain in 21 patients who received a high-carbohydrate diet with more than 50% carbohydrates and concomitantly lower fat as shown in figure 2. The better weight gain starts after two weeks, at a time when high energy liquid nutrition was replaced by a diet according the patient's wishes.

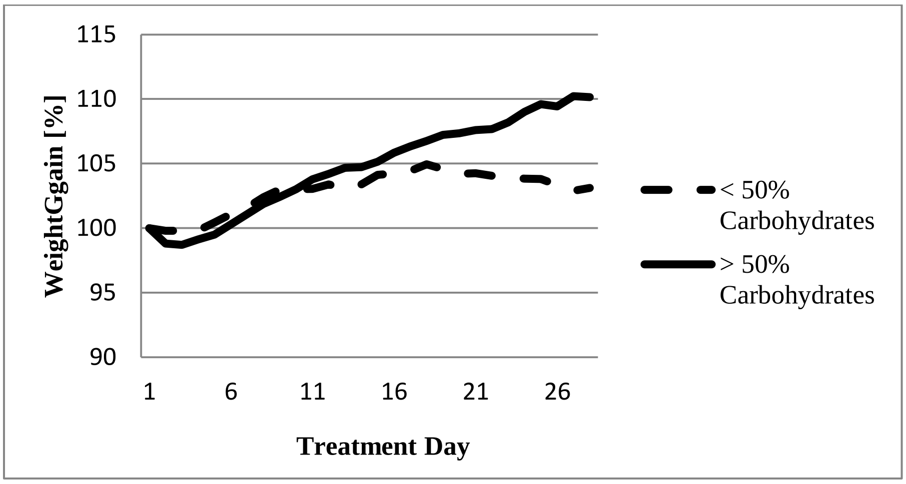

Fig. 2 A carbohydrate rich diet improves weight gain Weight gain in 21 patients with a carbohydrate rich diet > 50% and in 16 patients with < 50% carbohydrates according the patient's own wishes. Daily caloric intake is comparable (9 931 ±251 versus 9 416±247 kJ / 2 372 ± 60 versus 2 249 ± 59 kcal). Unpaired student t-test: *p*=0.03 for day 20 and *p*=0.01 for day 25)

Carbohydrate rich diet: 14.93% (±2.83) protein, 24.13% (±8.32) fat, 58.38% (±6.85) carbohydrates

Carbohydrate poor diet: 14.97% (±3.89) protein, 34.02% (±11.94) fat, 41.19% (±3.35) carbohydrates

Discussion

This retrospective analysis is result of an internal quality management process of in hospital weight restitution in adolescents suffering from AN. As we were dissatisfied with the weight gain of our patients using a standard refeeding protocol we decided to introduce additional nutritional interventions beginning in January 2013. Our first analysis in 2015 showed a clear trend of improved weight gain but the therapy was still heterogeneous since the entire team did not stick to the changes of the new treatment plan. As a consequence, we implemented supervision by an experienced psychologist in which all professional groups participated. Our team now agreed on a standardization of the treatment protocol and a re-examination of the therapeutic results after one year. Indeed, we were then able to show a significantly improved weight gain in eleven consecutive patients with AN who were treated with our new refeeding protocol. We did not need a nasogastric tube or anxiolytic medications in ten of the eleven patients. Together with the liberalization of our surveillance routines our refeeding protocol is extremely comfortable for the patients. For methodological reasons it must be stressed that in the past six years there have been no relevant personnel changes in the team.

The following considerations have contributed to the changes of our refeeding protocol:

1) Vitamin B, Zinc, Potassium, Calcium Glycero phosphate and magnesium supplementation:

This point is based upon a standard for the prevention and management of the refeeding syndrome published from UK's Institute for clinical Excellence (NICE) published in 2004.

In several studies prophylactic phosphate supplementation was linked to a lower risk of refeeding syndrome, even though patients started on a higher caloric intake (Leitner, Burstein, & Agostino, 2016; Madden et al., 2015). Parker et al. concluded that 'Withholding phosphate supplementation until hypophosphatemia is observed may have the potential of increasing the risk of RFS[5] and slowing down increases in caloric intake required to promote adequate weight restoration during the admission.'(Parker et al., 2016)

2) High energy liquid nutrition

Rigaud et al. published a randomized trial which evaluates the long term effects of tube refeeding with a relatively high number of patients (n=41)(Rigaud, Brondel, et al., 2007). Compared to other refeeding protocols the study conducted by Rigaud et al showed the best weight gain. We proved that oral high energy liquid nutrition can have a comparable benefit (Figure 3). At day eight the Rigaud refeeding group only achieved a 0.08 percent point higher weight gain (103.16 vs 103.08) than the highly standardized refeeding group. Over time the gap increased steadily. At day 15 the difference accounted for 1.40 percent points (107.47 vs 106.07). At day 29 the Rigaud tube feeding group reached 116.67% of their admission weight compared to 111.79% by the highly standardized refeeding group.

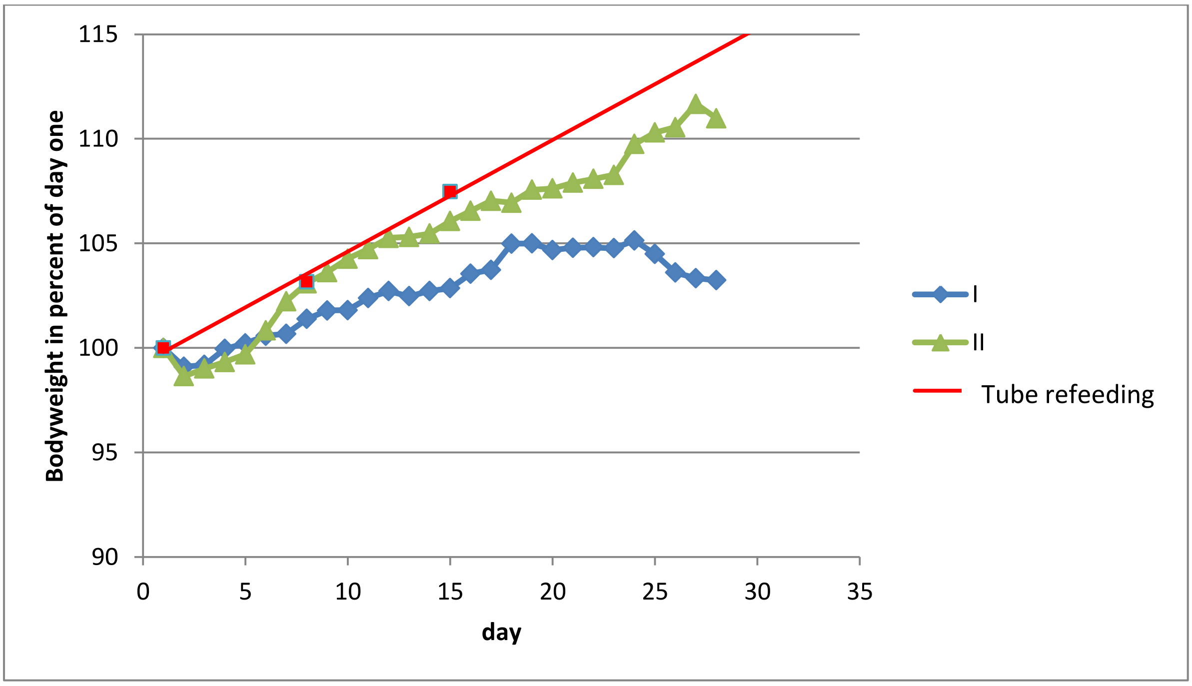

Fig. 1: Similar weight gain in highly standardized refeeding group and tube refeeding patients. Comparison of bodyweight in % of day one between highly standardized refeeding group, historical control and the Rigaud et al. refeeding group.

[5] Refeeding syndrome

However, it should be taken into account that the groups compared here are very heterogeneous. Most of all, the Rigaud tube feeding group had a higher age (22.5±4.5 vs 14.74±1.93) and a lower BMI at admission (12.1±1.5 vs 14.53±1.37) than the patients admitted in our hospital unit. It should also be noted that data from another study, in which a comparable group of children were treated according to a standard refeeding protocol, was in harmony with our historical control (Robb et al., 2002). However, we agree with Rigaud et al. who also showed that infused gastric loads triggered a dose-dependent increase in the thermic effect of food (Rigaud, Verges, et al., 2007). Our data now confirms in a clinical setting that we need a higher caloric intake after ten days of refeeding to reach the same weight gain as within the early refeeding. The reason behind the difficulties for AN patients in gaining weight could be an increase in plasma cortisol, ACTH and catecholamine's after caloric intake (Rigaud, Verges, et al., 2007).

Further, our data clearly showed a better weight gain in patients with a carbohydrate rich nutrition. We are aware of a higher risk of a refeeding syndrome in patients with a carbohydrate rich diet as recently proved by Gilles et al. in an animal model (Giles, Hagman, Pan, MacLean, & Higgins, 2016). Therefore we routinely controll electrolyte levels but did not observe any predicators of a refeeding syndrome in our patients. Possibly we were able to minimize the risk of a refeeding syndrome by supplementing minerals and omega-3 fatty acids.

Surprisingly we could not find a significant difference in weight gain between vegetarians and carnivores. Presumably we were able to compensate nutritional deficiencies in vegetarians which would have worsened the course of disease.

3) Omega-3-fatty acid supplementation

A deficit in membrane long chain poly-unsaturated fatty acids appeared in patients with AN (Caspar-Bauguil et al., 2012). Moreover omega-3 fatty acid supplementation decreases hepatic expression of lipogenic genes in a high-carbohydrate refeeding model in rats and has shown to have HRV-normalizing and neurophysiological properties (Barbadoro et al., 2013; Christensen, 2011; Goncalves, Ramos, Suzuki, & Meguid, 2005; Keenan, Hipwell, Bortner, Hoffmann, & McAloon, 2014; Prior & Galduroz, 2012). This observations may explain the beneficial effect of omega-3 fatty acid supplementation during refeeding (Ayton, Azaz, & Horrobin, 2004). We implemented omega-3 fatty acid supplementation in our refeeding protocol for all patients in group 2.

Limitations

We were not able to prove which therapeutic change was the most important. This question must be proven by a prospective randomized trial. Moreover, our study had three major limitations: 1) The study group was too small to draw general conclusions and we had missing data 2) We did not examine the long term effects of our therapy, therefore we could not make any assertion about the relapse rate. 3) The groups were partly heterogeneous regarding 'length of disease', 'RMSSD' and 'length of stay'. In our analysis we bypassed the problem of the differences in 'length of stay' by making a cut after 25 days. Considering the fact that most patients do not even approximately reach their weight before disease during refeeding, longer hospital stays should be contemplated. For the variable 'length of disease' it is conceivable that the statements of patients also depended on the examiner.

Conclusions

In summary, we recommend introducing high energy liquid nutrition with a sufficient share of carbohydrates and nutritional supplements including omega-3 fatty acids for an improved weight gain during refeeding. Because of an increasing energy turnover during refeeding, caloric intake should be adjusted. In terms of a rapid weight gain nasogastric tube refeeding remains the benchmark. Nevertheless, regarding the disagreeableness accompanied by tube refeeding, the pros and cons should always be studied for each patient before inserting a nasogastric tube. To get a better understanding of AN pathophysiology we are now analyzing the 24 hour ECGs of our patients.

Abbreviations

AN = anorexia nervosa

bpm = beats per minute

cm = centimeter

d= day

g = gram

HRV = heart rate variability

kilogram = kg

kJ = kilojoule

m = meter

ms =milliseconds

y = year

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Conflict of interest

This study was carried out independently and approved by the committee for Medical Ethics of the University of Würzburg (No 143/16-mk). The authors had no conflict of interest and did not receive any funding for the conduction of the study.

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