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Complete List of Authors:	Rio, Alan; King's College Hospital, Nutrition and Dietetics Whelan, Kevin; Kings College Lonodn, Diabetes and Nutritional Sciences Goff, Louise; Kings College Lonodn, Diabetes and Nutritional Sciences Reidlinger, Dianne; Kings College Lonodn, Diabetes and Nutritional Sciences Smeeton, Nigel; Kings College London, Imaging Sciences & Biomedical Engineering
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Title. Occurrence of refeeding syndrome in adults commenced on artificial nutrition and hydration: prospective cohort study.

Alan Rio, Kevin Whelan, Louise Goff, Dianne Reidlinger, Nigel Smeeton.

Alan Rio, Nutrition and Dietetic Department, King's College Hospital, Denmark Hill, London, SE5 9RS, UK. Kevin Whelan, King's College London, School of Medicine, Diabetes and Nutritional Sciences Division, London, SE1 9NH, UK. Louise Goff, King's College London, School of Medicine, Diabetes and Nutritional Sciences Division, London, SE1 9NH, UK. Dianne Reidlinger, King's College London, School of Medicine, Diabetes and Nutritional Sciences Division, London, SE1 9NH, UK, Nigel Smeeton, King's College London, Division of Imaging Sciences & Biomedical Engineering, London, SE1 7EH, UK.

Correspondence to: A Rio, Alan.Rio.1@city.ac.uk

Article Summary

Article focus

Hypothesis: The risk factors for the refeeding syndrome are weak and cause unnecessary delay of nutrition.

Research question: Which risk factors reliably predict development of the refeeding syndrome?

Key messages

- Refeeding syndrome is a complex constellation of major characteristics which requires a multi-facet diagnostic criteria.
- Refeeding syndrome is a rare, survivable phenomena that can occur despite identification of risk and hypocaloric nutritional treatment.
- Intravenous dextrose infusion prior to artificial nutrition can precipitate the refeeding syndrome.
- Starvation is the most reliable predictor for onset of the syndrome.

Strengths and limitations of this study

The authors were not involved in the nutritional treatment, electrolyte supplementation or diagnosis of the refeeding syndrome. The diagnostic criteria enabled the authors to authenticate positive cases and omit borderline results. The main source of data loss was the excluded group which may potentially have contained participants who went on to develop the refeeding syndrome.

Abstract

Background Refeeding syndrome is the metabolic response to excess nutrition in starved individuals characterised by severe intracellular electrolyte shifts, acute circulatory fluid overload and organ failure. It can occur during enteral, parenteral or oral feeding.

Objective To determine the occurrence of refeeding syndrome in adults commenced on artificial nutrition and hydration.

Design Prospective cohort study.

Setting Large, single site university teaching hospital. Recruitment period 2007-2009.

Participants 243 adults commenced on artificial nutrition and hydration for the first time during that admission recruited from wards and intensive care.

Main outcome measures Primary outcome: Occurrence of the refeeding syndrome. Secondary outcome: Sensitivity and specificity of the risk factors for predicting refeeding syndrome. Tertiary outcome: Mortality due to refeeding syndrome and all cause mortality.

Results 133 participants had risk factors and (2% 3/243) participants were diagnosed with the refeeding syndrome. Poor nutritional intake for more than 10 days, weight loss >15% prior to recruitment and a low serum magnesium level at baseline had sensitivity values of 66.7%. Specificity of risk factors for refeeding syndrome were >80% apart from weight loss of >15% which had a specificity of 59.1%. Only low baseline serum magnesium (p=0.021) predicted refeeding syndrome; other independent variables were not significantly associated. There were no deaths attributable to the refeeding syndrome but (5.3% 13/243) participants died during the feeding period and (28% 68/243) died during the hospital admission.

Conclusion

Refeeding syndrome was a rare, survivable phenomenon that occurred during hypocaloric feeding in participants identified at risk. Predictors for refeeding syndrome were starvation and low serum magnesium concentration. Intravenous carbohydrate infusion prior to artificial nutrition and hydration may have precipitated the onset of refeeding syndrome. The risk factors for predicting the syndrome were weak and may inadvertently have contributed to malnutrition.

Introduction

Refeeding syndrome has been defined as severe fluid and electrolyte shifts in malnourished patients during oral, enteral or parenteral refeeding.[1] The key prerequisite for the syndrome is starvation with the earliest documented cases being prisoners of war.[2] In recent times refeeding syndrome has been confirmed in hunger strikers, individuals with anorexic nervosa and chronic alcoholics. The modern definition of refeeding syndrome is life threatening acute micronutrient deficiencies, fluid and electrolyte imbalance and disturbance of organ function and metabolic regulation resulting from over rapid or unbalanced nutrition support.[3] However, this definition is imprecise and lacks definitive electrolyte threshold values to confidently diagnose the refeeding syndrome.

The metabolic shift from starvation to feeding increases cellular uptake of glucose, potassium, phosphate and magnesium which lowers the serum concentration of these electrolytes.[4] The early signs of the refeeding syndrome are non specific but include severely low concentrations of serum phosphate, potassium and magnesium and if untreated can progress to acute circulatory fluid overload, respiratory compromise and cardiac failure.[5] Severe hypophosphataemia has been described as the hallmark of refeeding syndrome.

Guidelines for the prevention and treatment of refeeding syndrome advise identification of individuals at risk, controlled hypocaloric nutritional treatment and supplementary electrolytes.[3] However, not all individuals with risk factors for refeeding syndrome develop symptoms during nutritional repletion.[6] A potential consequence of adherence to these untested guidelines is the delay of adequate nutrition to undernourished individuals. We conducted a prospective cohort study to determine the occurrence of refeeding syndrome in adults commenced on artificial nutrition and hydration. Refeeding syndrome was confirmed using a three facet diagnostic criteria of severely low electrolyte concentrations, acute circulatory fluid overload and organ dysfunction.

Methods

Study design

This was a prospective cohort study conducted at a large, single site university teaching hospital. Criteria to determine risk of refeeding syndrome is displayed in Box 1. The risk factors were Body Mass Index (BMI) < 16 (kg/m^2), unintentional weight loss >15% in the preceding three – six months, very little or no nutritional intake for more than 10 days and low levels of serum potassium, phosphate or magnesium prior to artificial nutrition and hydration. The three facet diagnostic criteria to confirm refeeding syndrome is displayed in Box 2. The criteria of severely low electrolytes, acute circulatory fluid overload and organ dysfunction included the major features of the syndrome. All three major characteristics occurring from the commencement of artificial nutrition and hydration were required to diagnose the syndrome. To avoid any potential bias the authors were not involved in nutritional treatment, electrolyte supplementation or the initial diagnosis of refeeding syndrome during the study period. The schematic for participant exclusion, recruitment and analysis is displayed in Flow chart 1.

Sample size

The sample size was estimated from the reported prevalence of refeeding syndrome, defined as hypophosphataemia <0.4 mmol/L, to be 1 - 10%. [7-8] A cohort of 240 participants was anticipated to produce between 2 - 24 positive refeeding syndrome cases.

Participants

Researchers were alerted of potential new participants by the medical teams who referred to the nutrition and dietetic department for commencement of artificial nutrition and hydration. Inclusion criteria were; adults >18 years of age commenced on artificial nutrition and hydration for the first time during that hospital admission. Exclusion criteria were; previous artificial nutrition and hydration during that admission, participants <18 years of age or failure to obtain consent/assent. Study participation was for the duration of artificial nutrition and hydration to a maximum of 15 consecutive days. Informed consent was obtained from participants or next of kin prior to recruitment. All participants were recruited within 48 hours of the commencement of artificial nutrition and hydration which included enteral and parenteral

tube feeding. Energy prescriptions for each participant were estimated by the dietetic speciality who used stress related factors[9] or by body weight[10] calculations. The hospital nutrition policy for adults with risk factors for refeeding syndrome was 800 kcal day or 50% of estimated adult energy requirements.

Outcome measures

The primary outcome of interest in this study was the occurrence of refeeding syndrome. The medical team for each participant diagnosed refeeding syndrome based on severe serum electrolyte shifts of potassium, phosphate and magnesium. Severe shifts in serum electrolytes triggered an automatic electronic response on each participant's blood results. The normal hospital reference ranges were; potassium 3.5 – 5.0 mmol/L, phosphate 0.8 – 1.4 mmol/L and magnesium 0.7 – 1.00 mmol/L. The research team investigated each case and using the criteria shown in Box 2 confirmed the diagnosis. The secondary outcome was the sensitivity and specificity of the risk factors at predicting refeeding syndrome. The tertiary outcome measure was mortality; due to refeeding syndrome and all cause mortality.

Data Collection

Baseline serum electrolyte concentrations were recorded within 24 hours of study enrolment then every third day for a maximum of 15 days during the period of artificial nutrition and hydration. Serum electrolytes were not recorded when artificial nutrition and hydration was stopped. Serum electrolyte concentrations were obtained from the hospital electronic in-patient system (iSoft, v1.0 Oxon, England). The normal hospital adult serum reference ranges were potassium 3.5 – 5.0 mmol/L, phosphate 0.8 – 1.4 mmol/L and magnesium 0.7 – 1.00 mmol/L. Body weight (kg) was measured using balance and digital scales accurate to within 0.1kg (Seca, 22089 Hamburg, Germany) wearing light indoor clothing. Body weight was not recorded in participants who were sedated or unconscious. Height (m) was recorded using measured or recalled data as appropriate. Body mass index (kg/m^2) and percentage weight loss (normal body weight - current body weight/normal body weight x 100) were calculated. To determine which participants had poor nutritional intake prior to artificial nutrition and hydration, dietary caloric intake was calculated by a research assistant. Participants unable to provide a diet history the next of kin was interviewed, failing this retrospective food intake records were used.

Data Analysis

Descriptive statistics were performed on the cohort of 243 participants. All participants were classified at risk of refeeding syndrome risk or not at risk according to the diagnostic criteria displayed in Box 2. Predictor variables were transformed to binary categories representing whether or not refeeding syndrome was diagnosed. Sensitivity and specificity values for refeeding syndrome were calculated for each predictor based on the 243 participants with precision set at 70%. The refeeding syndrome outcomes were assessed using Fisher's exact test at the $p<0.05$ level. Participants with risk factors for refeeding syndrome were analysed as a subgroup of 133 participants. This subgroup was stratified dependent on baseline energy intake as; Group 1 <800 kcal at baseline versus Group 2 >800 kcal at baseline, Flow chart 1. There was no further analysis of the 110 participants who did not have risk factors for the syndrome. All data analysis was performed using SPSS version 17 (Chicago, Il, US).

Results

Four hundred and eighty four participants were eligible to be recruited, displayed in Flow chart 1. A total of 243 participants were recruited median age 57.0 years (interquartile range 44.0 – 69.0), sex 130 (53.5%) men. There were 133 participants with risk factors for refeeding syndrome of which 68 were men. Recruitment locations were wards 153 (63.0%), high dependency unit 46 (18.9%) and intensive care 44 (18.1%), see Table 1. In total 212 (87.2%) participants received enteral, 23 (9.5%) participants parenteral and 8 (3.3%) received enteral/parenteral tube feeding. There were 2615 total feed days, median duration 13 days (interquartile range 6-15). A total of 2765 serum electrolyte results were recorded, 1014 for potassium, 1006 for phosphate and 745 for magnesium. Potassium was the most frequently supplemented electrolyte followed by magnesium. The total number of participants who received electrolyte supplementation were potassium 71, phosphate 49 and magnesium 52. Occurrence of moderate and severely low serum electrolyte concentration with mortality is displayed in Table 2. Mortality was not attributed to refeeding syndrome either during feeding (5.3%, 13/243) or hospital admission (28% 68/243). Cause of death in these participants was due to underlying disease with mortality by location; ward 45/153, high dependency unit 14/46 and intensive care 9/44.

Three participants were diagnosed with refeeding syndrome, two participants developed borderline electrolyte depletion without acute circulatory fluid overload or organ dysfunction and 238 participants did not develop refeeding syndrome. The sensitivity and specificity values for the predictors of refeeding syndrome are shown in Table 3. Poor nutritional intake for more than 10 days, weight loss >15% prior to recruitment and a low serum magnesium level at baseline had sensitivity values of 66.7%. By contrast, all specificity values were high (>80%) apart from weight loss >15%, which had a specificity of 59.1%. Only low baseline serum magnesium (p=0.021) predicted refeeding syndrome; other independent variables were not significantly associated. The pre-existing risk factors for refeeding syndrome for Groups one and two are displayed in Table 4. Daily energy intake from artificial nutrition and hydration from baseline to day nine for Groups one and two are displayed in Table 5. Characteristics of the three participants diagnosed with refeeding syndrome are displayed in Table 6.

Participant diagnosed with refeeding syndrome

Participant X, a 48 year female who presented with confusion, bilateral leg weakness, alcohol withdrawal, poor nutritional intake with repeat vomiting for seven days, C2 fracture, translocation at C2/3 and high urinary ketones. The participant received two doses of intravenous Pabrinex® in 0.9% sodium chloride followed by 100 mg oral thiamine. Day two the patient received one litre of intravenous potassium chloride and two litres of 5% dextrose followed by enteral tube feeding. Day three serum phosphate was recorded at 0.33 mol/L and 500 ml intravenous polyfusor providing 50 mmol/L phosphate was infused over 12 hours. At day four the participant developed peripheral oedema with tachycardia and was transferred to the intensive care unit due to respiratory failure and acute circulatory fluid overload.

Participant Y, a 23 year old female, with Crohn's disease and subtotal bowel colectomy presented with frontal occipital headaches radiating to neck with history of nausea, vomiting and weight loss of 26kg. At day 117 of admission a nasogastric tube was inserted due to poor nutritional intake. Nutrition was stopped within two hours due to vomiting and abdominal pain. The participant collapsed 24 hours later due to hypotension, hypothermia, dehydration and pseudo-bowel obstruction. The participant was transferred to

the high dependency unit for fluid resuscitation. Intravenous 10% dextrose was commenced and a 16Fr wide bore nasogastric tube was inserted for gastric drainage. Day two serum electrolytes levels were potassium 3.2 mmol/L, phosphate 0.26 mmol/L, magnesium 0.55 mmol/L. Intravenous Polyfusor 500 ml providing 100 mmol/l phosphate was commenced. The participant was transferred to the intensive care unit, intubated and commenced on haemofiltration due to multi-organ failure.

Participant Z, a 31 year old female, with decompensated liver cirrhosis secondary to alcohol, with existing chronic pancreatitis and opiate dependency with a weekly alcohol intake of 56 units was admitted to the hepatology unit with abdominal pain, vomiting and dehydration. Usual body weight was 48kg, admission dry weight was 40kg. Intravenous Pabrinex® was infused followed by one litre of 5% dextrose containing 20mmol/L potassium chloride. Oral thiamine 100 mg and vitamin B compound strong were prescribed. The participant had a nasogastric tube inserted and artificial nutrition and hydration was commenced. At day three serum electrolytes were potassium 2.5 mmol/L, phosphate 0.37 mmol/L, magnesium 0.56 mmol/L. The participant developed acute circulatory fluid overload, symptoms of tachycardia and pneumonia. The participant was infused with Polyfusor 500 ml containing 100 mmol/L phosphate, a litre of 5% glucose, 25mmol magnesium and repeat Pabrinex®.

Discussion

This study applied a three facet diagnostic criteria to confirm the occurrence of refeeding syndrome in adults commenced on artificial nutrition and hydration. The three facet criteria provided unequivocal confirmation of the major clinical characteristics in those participants who developed the essential features of the syndrome. Occurrence of refeeding syndrome in participants with risk factors was 2% and was not associated with mortality. The three major facets of the diagnostic criteria; severe serum electrolyte shifts, acute circulatory fluid overload and organ dysfunction occurred in the three participants within 72 hours of hypocaloric tube feeding. Two of these participants who developed respiratory failure and multi-organ failure required admission to the intensive care unit whilst the third participant, who developed acute circulatory fluid overload and tachycardia, was treated on the ward. The survival of these three

participants represents advances in the medical management of severely malnourished individuals since the first cases of refeeding syndrome were reported.[2, 5] This study does not support previous reports that refeeding syndrome can be prevented by identification of risk and treatment with hypocaloric feeding. In this study refeeding syndrome occurred in three participants who had been identified at risk and treated with hypocaloric feeding. Factors distinct to the three refeeding cases were starvation and low baseline serum magnesium concentration. Two of the three cases received intravenous pabrinex and B vitamins prior to artificial nutrition and hydration which may have prevented Wernicke's encephalopathy but did not prevent refeeding syndrome. The small number of refeeding cases in this study may have been due to the medical teams having a policy of early electrolyte replacement. However, we suspect that the most compelling reason for the low occurrence of refeeding syndrome in this study was that starvation was a characteristic of only three participants. The analysis of the two subgroups showed strikingly similar malnutrition profiles but substantially different energy intakes which exceeded guideline recommendations. We interpret this to suggest that for refeeding syndrome to occur a predisposing factor was required. The predisposing characteristic of the three confirmed cases in this study was starvation. This interpretation is supported by our analysis of those participants who reported a short period of fasting prior to artificial nutrition and experienced moderate falls in their serum electrolyte concentrations.

Strengths and weaknesses of the study

The results of this study should be interpreted with caution. The study was not designed to assess the mechanism of refeeding syndrome. The main strengths of the study were the cohort design, the diagnostic criteria and the analysis of the risk factors. The results are applicable to an adult population who received artificial nutrition and hydration. The occurrence of the syndrome in a general adult hospital population treated with oral nutrition may produce different results. The most notable weakness of this study was that only three cases of the syndrome occurred. This small number of refeeding cases limited the statistical analyses that we could perform. The sensitivity values are thus limited to the three cases of the cohort and to some extent the diagnostic criteria applied by the research team. The small number of refeeding syndrome cases may have been due to the medical teams taking preventative actions to avoid the

syndrome. The electrolyte threshold values could be interpreted as too low to capture all cases. The severely low electrolyte threshold values were obtained from a review of the evidence to enable unequivocal confirmation of positive cases. This discreet approach was taken to avoid falsely including participants with single, abnormal electrolyte concentrations. Whilst the evidence review was consistent for severely low serum electrolyte concentrations we identified a lack of consensus on the electrolyte threshold values to diagnose the syndrome. To avoid bias the authors were not involved in nutritional treatment, electrolyte supplementation or the initial diagnosis of the syndrome. The most obvious source of data loss was the excluded group which contained potentially 157 participants. We acknowledge that this group may have contained participants who went on to develop the major characteristics of the syndrome.

Interpretation

Occurrence of serum phosphate <0.5 mmol/L in this study was 3% at day one and 6% at day three which was higher than that reported in a general adult hospital population of 0.2% to 2%.[7,8,11] The higher occurrence of hypophosphataemia in this study may have been due to the cohort containing participants recruited from the high dependency and intensive care units. Very few participants developed severe electrolyte shifts although moderate serum concentrations of potassium, phosphate and magnesium occurred. The interpretation of the moderate electrolyte shifts, without symptoms of the syndrome, was cellular uptake of electrolytes in response to nutritional input. The subgroup analysis identified many participants with risk factors for the syndrome. Hypocaloric nutritional treatment may have prevented refeeding syndrome in some of these participants. However, the subgroup analysis revealed one group received more energy sooner and for longer but did not develop symptoms. This finding supports our interpretation that the risk factors[3] for predicting the syndrome are weak and the practice of hypocaloric feeding may contribute to malnutrition.

The impact of intravenous dextrose infusion as a precipitating factor for refeeding syndrome in the three cases cannot be under estimated. In starved individuals gluconeogenesis is the predominant metabolic

pathway for energy production. Infusion of intravenous dextrose in the three participants caused suppression of gluconeogenesis and an instant switch to glycolysis. This switch caused insulin to be released causing rapid cellular uptake of serum phosphate, potassium and magnesium electrolytes. We propose that the initial infusion of dextrose in the three starved participants was the causal agent that triggered the refeeding syndrome. Hypocaloric feeding failed to prevent refeeding syndrome in these three cases for one important reason, it continued the input of simple carbohydrates causing more insulin to be released. This explanation is supported by other studies where intravenous dextrose infusion was attributed to hypophosphataemia of <0.7 mmol/L[12] which progressed to respiratory failure at serum phosphate concentration 0.2 mmol/L - 0.36 mmol/L.[15-16] The results of the present study indicate that dextrose infusion should be avoided in starved individuals who require fluid replacement and nutritional treatment. This finding that intravenous dextrose infusion acts as a precipitator for the refeeding syndrome requires further research.

Comparison with other studies

The era of hypercaloric feeding in cachectic individuals was associated with cardiac abnormalities,[17] respiratory failure and death.[5] Two decades later controlled hypocaloric nutritional treatment and electrolyte supplementation prevented refeeding syndrome in eight prisoners who had been on hunger strike for 43 days.[18] Under controlled conditions hypocaloric nutritional treatment and intravenous Polfusor phosphate (25 mmol/L) over 12 hours and effervescent oral phosphate (16mmol) twice daily prevented serious complications associated with refeeding syndrome in a 30 year old male who endured 44 days of self imposed starvation.[19] Refeeding syndrome was prevented in 29 anorexic nervosa participants given 500 to 2,000 mg phosphate daily.[20] The energy prescription was 1,900 kcal at day one and 2,200 kcal at day three yet moderate hypophosphataemia (0.31 - 0.8 mmol/L) did not occur. These varied studies reflect the increased awareness of the syndrome where serious complications and mortality can be avoided.[21-22] In the present study refeeding syndrome was a rare, survivable phenomenon that occurred in starved individuals who crucially were identified at risk and treated with hypocaloric nutrition.[23] However, intravenous dextrose infusion prior to artificial nutrition and hydration was a causal,

precipitating factor for the onset of the syndrome.

Other information

Funding; none declared.

Contributors: AR was responsible for the conception, design, initiation and overall co-ordination of the study: AR drafted the paper, is responsible for its intellectual content, interpretation and analysis of the results. KW was involved in the design of the study, interpretation of results and writing the manuscript. NS conducted statistical analysis, interpretation of results and editing of the manuscript. DR and LG assisted with data collection and interpretation of the results; AR is the guarantor.

Competing interests: All authors declare that the answer to the questions on your competing interests form are all no and therefore have nothing to declare. All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) they have no relationships with any companies that might have an interest in the submitted work in the previous 3 years; (2) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work; and (3) have no specified or non-financial interests that may be relevant to the submitted work.

Ethical approval. King's College Hospital Research Ethics Committee (06/Q0703/131).

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Flow chart 1. Flow chart showing number of participants at each stage of the study and stratification.

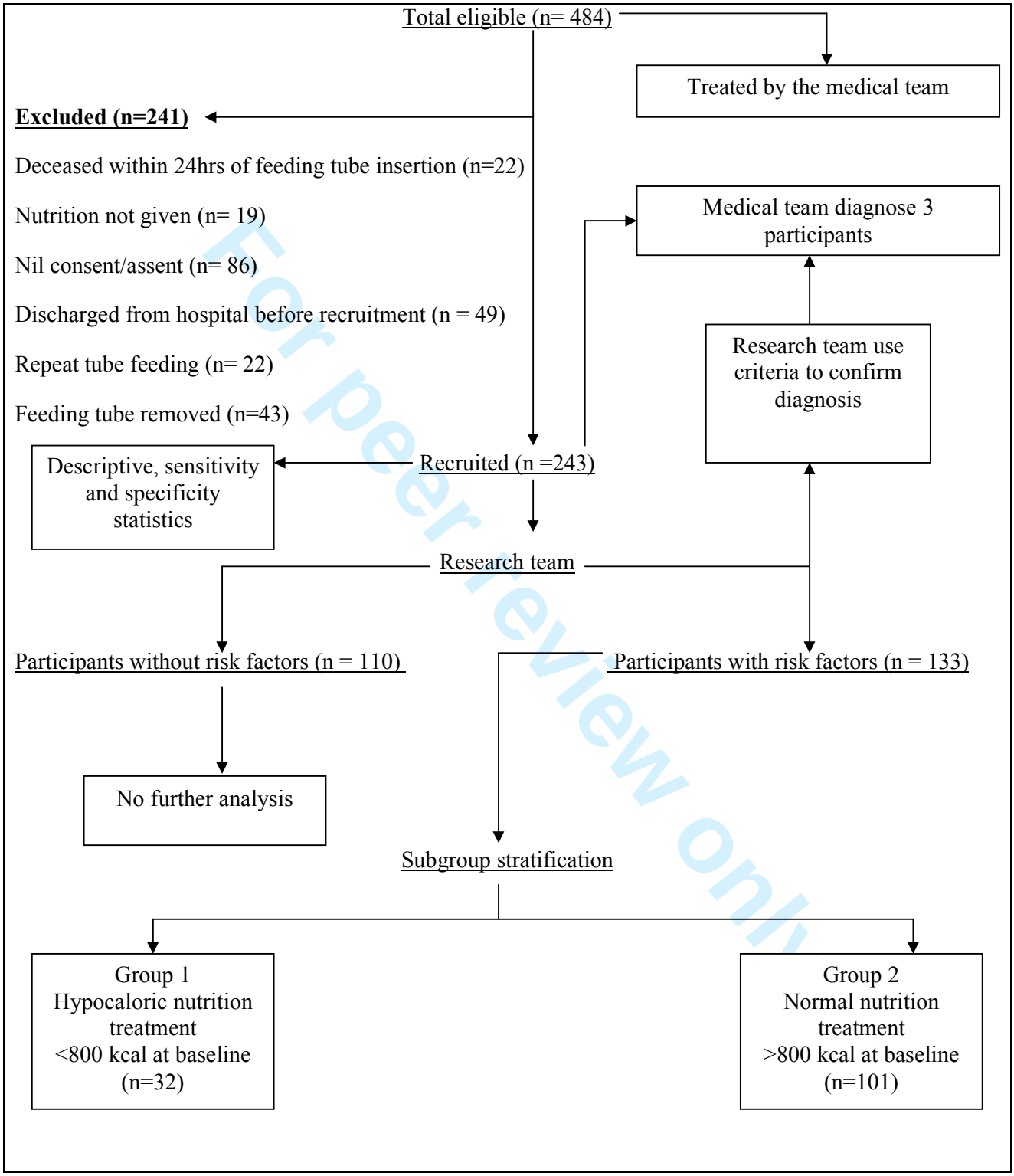

Table 1. Cohort information, diagnostic data, supplementation totals and energy intake. (n= 243)

Factor	**Location**		
	Ward (n= 153)	**HDU (n= 46)**	**ICU (n= 44)**
Male	78	25	27
Female	75	21	17
Age			
Median	62.00	53.00	52.50
95% CI	56.23 – 62.13	48.11 – 58.43	47.05 – 56.00
IQR	47.00 – 73.00	39.00 – 67.50	41.00 – 61.75
Diagnostic categories			
Neurological	39	20	16
Respiratory	6	5	2
Trauma	6	0	0
Medicine	9	0	0
Hepatology	25	2	10
Renal	8	1	0
Pancrease	9	0	1
Gastroenterology	6	3	4
Cancer	13	2	0
Cardiovascular	22	9	4
Surgical	7	1	5
Sepsis	3	3	2
Length of stay (days)			
Median	28.50	38.00	29.50
95% CI	32.99 – 44.95	37.81 – 73.52	28.52 – 39.98
IQR	17.00 – 47.50	17.00 – 67.50	20.50 – 42.75
Electrolyte supplementation totals			
Potassium	72	29	37
Phosphate	48	24	21
Magnesium	46	28	35
B vitamin supplementation totals	43	10	8
Duration of artificial nutrition (days)			
Median	10.50	15.00	15.00
95% CI	8.86 – 10.50	11.27 – 13.62	11.78 – 14.00
IQR	5.00 – 15.00	9.50 – 15.00	12.25 – 15.00
Energy intake kcal/day 95% CI			
Baseline	547.43 – 937.03	515.13- 1023.79	751.75 – 1560.98
Day 3	844.91 – 1173.42	1122.88 – 1537.43	1088.76 – 1864.51
Day 6	1099.98 – 1535.26	1238.85 – 1792.07	1136.19 – 1997.63
Day 9	1063.29 – 1490.58	1007.95 – 1738.51	1099.97 – 2017.30

CI = confidence interval

IQR = inter quartile range at 25th and 75th centiles.

Table 2. Moderately and severely low serum electrolyte values with mortality (participants n = 243).

	Number of moderately low values	Mortality	Number of severely low values	Mortality
Potassium	<3.4 mmol/L		<2.5 mmol/L	
Day 1	20	0	1	0
Day 3	22	0	3	0
Day 6	11	0	0	0
Day 9	7	1	1	0
Phosphate	<0.5 mmol/L		<0.32 mmol/L	
Day 1	7	1	3	0
Day 3	15	3	1	0
Day 6	4	0	0	0
Day 9	2	0	0	0
Magnesium	<0.6 mmol/L		<0.5 mmol/L	
Day 1	14	0	5	0
Day 3	5	0	2	0
Day 6	4	0	2	0
Day 9	5	0	3	0

Normal hospital reference ranges potassium 3.5 – 5.0 mmol/L, phosphate 0.8 – 1.4 mmol/L and magnesium 0.7 – 1.00 mmol/L.

Table 3. Confidence interval, sensitivity and specificity analysis for the refeeding syndrome. (n = 243).

	95% CI	Sensitivity (%)	Specificity (%)
BMI < 16 (kg/m^2)	22.95 - 24.40	0.0*	93.1
Poor intake for > 10 days	†	66.7	84.5
Unintentional weight loss > 15% in the preceding three - six months	10.04 – 13.77	66.7	59.1
Serum potassium at baseline < 2.6mmol/L	4.01 – 4.18	0.0	99.6
Serum phosphate at baseline < 0.33mmol/L	1.04 – 1.16	33.3	99.1
Serum magnesium at baseline < 0.6mmol/L	0.81 – 0.88	66.7	93.3

†Categorical data not applicable.
*BMI uses height and weight to calculate score therefore sensitivity analysis was not applicable.
CI= confidence interval.

Table 4. Malnutrition profiles of the two groups. Figures are totals within each group.

Risk factors	Group 1	Group 2	Totals
BMI < (16kg/m^2)	6	4	10
BMI < (14kg/m^2)	1	1	2
Wt loss > 15% within the previous 3-6 months	16	9	25
Poor nutritional intake > 10 days	20	15	35
Low baseline serum electrolyte concentrations			
Potassium <3.5 mmol/L	14	6	20
Phosphate <0.8 mmol/L	20	14	34
Magnesium <0.7 mmol/L	11	10	21

Table 5. Energy intake of the two groups (participants n=133). .

	Group 1	Group 2
Baseline		
Median intake	380.00	862.50
95% CI	250.76 – 594.99	837.57 – 1174.22
IQR	206.00 – 552.50	821.25 – 1300.0
Mean kcal/kg	7.12	15.60
Day 3		
Median intake	845.00	1315.00
95% CI	598.98 – 899.77	1220.21 – 1507.16
IQR	468.75 – 1000.00	1030 – 1584.25
Mean kcal/kg	12.59	21.35
Day 6		
Median intake	1312.50	1500.00
95% CI	935.83 – 1538.54	1306.40 – 1675.54
IQR	675.00 – 1575.00	1257.50 – 1837.00
Mean kcal/kg	20.79	23.35
Day 9		
Median intake	1462.50	1482.50
95% CI	983.15 – 1644.98	1178.32 – 1573.26
IQR	843.75 – 1750.00	939.50 – 1700.00
Mean kcal/kg	23.13	21.54

CI= Confidence Interval for mean.
IQR = Inter Quartile Range 25th and 75th centiles.

Table 6. Characteristics of the three participants confirmed with refeeding syndrome.

	Participant x	Participant y	Participant z
Age years	48	23	31
Diagnostic group	trauma	gastroenterology	hepatology
Chronic condition	alcoholism	malnutrition	alcoholism
Route of artificial nutrition and hydration	enteral	enteral	enteral
Baseline received energy kcal day	800	294	325
Baseline energy kcal kg	12.7	6.3	8.1
Body weight kg	63	47	40
BMI (kg/m/$^{-2}$)	20	16	16
Intravenous carbohydrate	yes	yes	yes
Survival outcome	survived	survived	survived

Box 1. Criteria for the determination of refeeding syndrome risk.[3]

One of the following:	**Two of the following:**
• BMI < 16 (kg/m^2) • Unintentional weight loss >15% in the preceding three – six months • Very little or no nutritional intake for more than 10 days • Low levels of serum potassium, phosphate or magnesium prior to feed	• BMI < 18.5 (kg/m^2) • Unintentional weight loss >10% in the preceding three – six months • Very little or no nutritional intake for more than 5 days • History of alcohol or drug abuse

Box 2. Criteria for confirmation of refeeding syndrome from the commencement of artificial nutrition and hydration.

1. Electrolytes. • Potassium • Phosphate • Magnesium 2. Peripheral oedema or acute circulatory fluid overload. 3. Disturbance to organ function including respiratory failure, cardiac failure, pulmonary oedema.	Severely low electrolyte concentrations[4] < 2.5 mmol/L* < 0.32 mmol/L < 0.5 mmol/L

*King's College Hospital severely low serum potassium concentration value requiring replacement.

Data sharing statement No additional data is available.

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Response to reviewers.

Reviewer 1. Professor M Hiesmayr.

1. Reviewer Comment

Description of participants: there is no table describing the population according to some major clinical categories (before or after surgery, internal medicine, geriatrics, ...) diagnostic categories (ICD10 or similar) and length of stay before inclusion. Age, gender and location in the hospital is given.

1. Author Response

The authors have included this information in Table 1.

2. Reviewer Comment

There is only minimal use of statistics. Level of association between degree of refeeding syndrome and predictors was tested once with fisher's exact test, but multiple testing was probably done.

2. Author Response

We accept the weakness of only three positive cases for statistical analysis. This small number of positive cases prevented us from performing regression analysis. We include this in the strength and weaknesses section.

3. Reviewer Comment

The consort checklist is the original from the website but does not contain any information related to the actual manuscript.

3. Author Response

The STROBE checklist is fully completed and included in the resubmission. We have included the STROBE checklist as it is applicable to the cohort study design.

4. Reviewer Comment

Presenting sensitivity and specificity based on 3 cases is misleading giving the number of cases in each category would be more informative, measures of precision are missing.

4. Author Response

The authors have addressed this in the strengths and weaknesses section and given more detail in the discussion. We have added the confidence intervals to provide the reader with more detail. Precision was set at 70%.

5. Reviewer Comment

The consort statement is included as a raw file without reference to the current work. Exposure and outcome are well defined (box 1 and 2) but how and whether all cases could be identified. The problem is also partially addressed in the paper. Confounding (e.g. by preventive clinical interventions) is not addressed and numbers are not systematically given.

5. Author Response

The CONSORT statement is included with complete reference to the current work. The confounding factor of preventative interventions by the medical team has been added to the manuscript. The total participants who received electrolytes has also been added.

6. Reviewer Comment

This paper has an interesting research approach to an important question: Do published reports from NICE on the prevention of refeeding syndrome correctly identify the population at risk? (a reference to the Clinical Review Refeeding syndrome: what it is, and how to prevent and treat it BMJ 2008; 336 doi: 10.1136/bmj.a301 (Published 26 June 2008) Cite this as: BMJ 2008;336:149) should also be considered).

6. Author Response

This paper has been cited and is now included in the discussion.

7. Reviewer Comment

Based on this reference the definition of refeeding syndrome is not generally accepted and a major reference is to hypophosphatemia with incidences between 0.4% in hospitalised and, between 18-100% in ICU depending on phosphate policies. Thus any systematic contribution to this field is important. The authors have used a definition for refeeding syndrome with a clinical perspective to confirm the diagnosis but this has added difficulties to the project that need to be clearly addressed to guide potential reader.

7. Author Response

We have clarified the recruitment process, how the diagnosis was confirmed, added a heading to the flow chart which we anticipate clarifies the reading of the manuscript for potential readers.

8. Reviewer Comment

The derivation of criteria used to identify cases needs to be explained with the sources used.

8. Author Response

We have added the derivation of criteria used in Box 2 sourced from NICE 2006 which is reference number three in the references section.

9. Reviewer Comment

The application of these criteria in practice needs clarification. If I understand well only those having a diagnosis of refeeding syndrome were assessed for the presence of the "confirmed refeeding syndrome". Probably there should be a step also the flow chart of "suspected refeeding syndrome".

9. Author Response

A new step in the flow chart has been added, group totals have been simplified and the subgroup analysis we hope is clearer. The authors have made reference to this in the STROBE document.

10. Reviewer Comment

Degree of refeeding syndrome is indicated in statistical methods and results but not explained (1/2/3 facets?)

10. Author Response

The authors have amended the manuscript for clarity.

11. Reviewer Comment

Patient identification was done only in those patients referred for artificial nutrition. Thus the incidence estimate may depend on the artificial nutrition use practice of the institution.

11. Author Response

The results are applicable to an adult population who received artificial nutrition and hydration with careful monitoring of serum electrolyte values. We do not have data on the use of artificial nutrition in the organization. However, we accept the reviewer's comments as being valid and have added more detail to the discussion section. We accept and include that the occurrence of refeeding syndrome in a general adult hospital population treated with oral feeding may produce different results.

12. Reviewer Comment

Many patients died in the relatively large group not included (especially early after feeding tube insertion). This issue is correctly addressed by the authors.

12. Author Response

The reason for early mortality post feeding tube insertion is discussed in the manuscript.

13. Reviewer Comment

Many patients especially in the surgical patients develop severe hypophosphatemia within the first 24 hours after surgery and a second peak is around day 3. If as in this case patients are included after 48 hours and assessed 24 hours later the syndrome may already have occurred.

13. Author Response

Recruitment into the study was within 48 hours of commencement of enteral or parenteral tube feeding. Baseline serum electrolytes were measured within 24 hours of recruitment. Electronic serum electrolyte results were available for retrospective review. These three factors enabled the research team to capture all cases of the refeeding syndrome and not miss any due to the syndrome having already occurred. Use of the three facet criteria which required electrolyte, fluid shifts and organ dysfunction provided the researcher team an element of certainty to rule out falsely diagnosing single electrolyte shifts due to other reasons.

14. Reviewer Comment

Confounding by nutritional interventions or location of patients (ward, hdu, icu) probably should be considered.

14. Author Response

The preventative confounding actions of the medical teams has been included in the discussion.

15. Reviewer Comment

A more detailed description of the patients is needed. Type of patient, location, diagnostic category, before or after surgery, internal medicine.

15. Author Response

The authors have added Table 1 which contains more detail of patient type, location and diagnostic category. Duration of stay prior to recruitment was not available to the researchers.

16. Reviewer Comment

Nice to address that moderately diminished electrolytes were associated with more risk of death than severe disturbance. Could admission to an ICU be the positive confounder whereas remaining on the ward with moderate values may be a risk factor because appropriate treatment and recognition of symptoms may be delayed.

16. Author Response

The authors have included this and the positive confounder of admission to the ICU. The reviewer highlights an important development and the medical progress of severely malnourished individuals has been included. We are grateful to the reviewers insight for this aspect of survival.

17. Reviewer Comment

I discourage using sensitivity when only 3 cases are identified.

17. Author Response

The authors have maintained the sensitivity analysis in Table 3 to identify to readers the low sensitivity of the risk factors when determining risk and treatment of fasted and starved individuals. The authors maintain this part of the research which they hope will stimulate further research into reliable predictors. However, the authors address the reviewers concerns on the limitations of the sensitivity analyses in the strengths and weaknesses section of the paper.

18. Reviewer Comment

Table 4: The risk profile in the reduced intake (to prevent refeeding syndrome) is nearly identical to the normal intake group. Does this indicate that the clinical pathway is confounded by some other factor affecting the nutrition decision process.

18. Author Response

The malnutrition profiles in Table 4 are almost identical not because the clinical pathway and nutrition decisions are different but because the risk factors are weak predictors irrespective of energy intake. The weakness of the risk factors is they capture too many variables. The analysis and interpretation has been developed and discussed in much more detail now.

19. Reviewer Comment

Table 5: may be unnecessary for the actual question but shows that nutrition is not advanced after a few days on very low intake. This should be compared to the recommendations.

19. Author Response

Table 5 is maintained to highlight to the target audience, dietitians and nutrition teams, that prescription of hypocaloric feeding may be unnecessary in many individuals and may inadvertently contribute to malnutrition. The authors thank the reviewer for this insight which has been expanded in the discussion.

20. Reviewer Comment

The most important finding is that 2/3 cases had received the "preventive nutrition regimen". All 3 survived possibly because admitted to an ICU.

20. Author Response

The authors agree that the most important finding was that despite treatment with a preventative nutrition regimen it did not prevent life threatening symptoms of refeeding syndrome. The participants survived because they were admitted to an ICU highlighting the developments of medicine since the first reported cases of refeeding syndrome. This has been added to the manuscript.

21. Reviewer Comment

The low incidence in the risk group needs to be discussed in view of all selection and measurement bias and possible confounding by treatments during the 3 days before evaluation.

21. Author Response

We have added the following for clarity, “The small number of refeeding syndrome cases may have been due to the medical teams taking preventative actions to avoid the syndrome. The electrolyte threshold values could be interpreted as too low to capture all cases. The severely low electrolyte threshold values were obtained from a review of the evidence to enable unequivocal confirmation of positive cases. This discreet approach was taken to avoid inclusion of borderline cases or falsely including participants with single, abnormal electrolyte concentrations.”

The authors clarify that there was no 3 day period before evaluation. Participants were recruited within 48hrs of commencing artificial nutrition and therefore all cases were captured.

22. Reviewer Comment

The generalisability is probably limited because this is not general population of hospitalised patients but "those referred for nutrition treatment". a clarification is possible.

22. Author Response

The authors accept the generalisability is limited to adults commenced on artificial nutrition and hydration. However, many dietitians and nutrition teams prescribe feeds and this detail of the manuscript provides evidence for practice change. The authors have addressed the reviewers comments in the manuscript.

23. Reviewer Comment

The important finding that preventive measures may not work needs emphasis.

23. Author Response

The authors have addressed this in the paper and included it into the abstract and key message of the paper.

Reviewer 2. Dr Stephen Taylor.

1. Reviewer Comment
Capital letter after colon.

1. Author Response
The authors have made this grammar change.

2. Reviewer Comment
Key messages: Bullet point

2. Author Response
The authors have made this change.

3. Reviewer Comment
Replace 'authenticated' with 'diagnosed'.

3. Author Response
The authors have made this change.

4. Reviewer Comment
'risk factors'? Readers won't know what these are at this point, tell them.

4. Author Response
The authors have made this change.

5. Reviewer Comment
I'd rather try: Mortality was not attributed to refeeding syndrome either during feeding (5.3%, 13/243) or hospital admission (28.0%, 68/243).

5. Author Response
The authors have changed this sentence.

6. Reviewer Comment
Overall: Needs to be more emphasis that refeeding could not be accurately predicted, occurred in spite of hypocaloric feeding and treatable and that this evidence questions the merit of current guidelines that advise slow introduction of feeding and therby increase risk of malnutrition.

6. Author Response
The authors have addressed these points.

7. Reviewer Comment
Instead of: refeeding orally, enterally or parenterally..... Try: oral, enteral or parenteral refeeding.

7. Author Response
The authors have made this change.

8. Reviewer Comment
Systematic literature review': Do you give details?

8. Author Response
The authors have changed this to evidence review.

9. Reviewer Comment
How were energy prescriptions calculated, eg. BMR + stress factors and their reference.

9. Author Response
The details of the energy prescriptions and references have been included.

10. Reviewer Comment
Nutritionist' or really a dietitian; many of the former are not adequately qualified.

10. Author Response
This has been changed to research assistant.

11. Reviewer Comment
Positive refeeding syndrome' Readers would find 'refeeding syndrome risk' clearer.

11. Author Response
The authors have changed this

12. Reviewer Comments
After “)” insert “,” participants, of participants

12. Author Response
The authors have made these grammar and punctuation changes.

13. Reviewer Comments
Is there a reason for such high mortality on wards relative to HDU/ICU areas where you would expected it to be higher.

13. Author Response
The authors interpret the higher mortality on the wards, compared to ICU/HDU, as organizational factors which were predominantly neurological and stroke orientated population and a tendency to feed close to death. There is the possibility that participants initially recruited on the ICU were transferred to the wards and subsequently died in that location.

14. Reviewer Comments
Try instead: Only low baseline magnesium significantly ($p = 0.021$) predicted refeeding syndrome; other independent variables were not significantly associated.

14. Author Response
The authors have made this change.

15. Reviewer Comments
Just to be clear, were these single IV and oral doses: state.
State Pabrinex 1+2 as it comes in two separate parts.
Infused over how long?
Unless it's a different polyfusor, our provides 50mmol per 500mL.

15. Author Response
The authors have clarified the formulation, dose, infusion duration and concentration.

16. Reviewer Comments
IV dextrose...' This sentence isn't clear. Are you saying IV glucose may help precipitate PO4 levels <0.7mM and has been associated with resp failure when PO4 levels fell to between 0.2-0.36mM?
• Please clarify.

16. Author Response
The authors have clarified this important aspect of the manuscript analysis and interpretation. The authors have included a revised and extended section on glucose metabolism and its role as precursor to refeeding symptoms in the three cases.

17. Reviewer Comments
100mmol/L, oral/enteral phosphate sandoz is 16mmol/tablet.

17. Author Response
The authors have made this change.

18. Reviewer Comments
Bullet point to make each point stand out separately.

18. Author Response
The authors have made this change.

STROBE checklist.

	Item No	Recommendation
Title and abstract	1	Occurrence of the refeeding syndrome in adults commenced on artificial nutrition and hydration: prospective cohort study.
		Background Refeeding syndrome is the metabolic response to excess nutrition in starved individuals characterised by severe intracellular electrolyte shifts, acute circulatory fluid overload and organ failure. It can occur during enteral, parenteral or oral feeding. **Objective** To determine the occurrence of refeeding syndrome in adults commenced on artificial nutrition and hydration. **Design** Prospective cohort study. **Setting** Large, single site university teaching hospital. Recruitment period 2007-2009. **Participants** 243 adults commenced on artificial nutrition and hydration for the first time during that admission recruited from wards and intensive care. **Main outcome measures** Primary outcome: Occurrence of the refeeding syndrome. Secondary outcome: Sensitivity and specificity of the risk factors for predicting refeeding syndrome. Tertiary outcome: Mortality due to refeeding syndrome and all cause mortality. **Results** 133 participants had risk factors and 3 participants (2%) were diagnosed with the refeeding syndrome. Poor nutritional intake for more than 10 days, weight loss >15% prior to recruitment and a low serum magnesium level at baseline had sensitivity values of 66.7%. Specificity of risk factors for refeeding syndrome were >80% apart from weight loss of >15% which had a specificity of 59.1%. Only low baseline serum magnesium (p=0.021) predicted refeeding syndrome; other independent variables were not significantly associated. There were no deaths attributable to the refeeding syndrome but (5.3%13/243) participants died during the feeding period and (28.0% 68/243) died during the hospital admission. **Conclusion** Refeeding syndrome was a rare, survivable phenomenon that occurred during hypocaloric feeding in participants identified at risk. Predictors for refeeding syndrome were starvation and low serum magnesium concentration. Intravenous carbohydrate infusion prior to artificial nutrition and hydration may have precipitated the onset of refeeding syndrome. The risk factors for predicting the syndrome were weak and may inadvertently have contributed to malnutrition.
Introduction		
Background/rationale	2	Refeeding syndrome is the metabolic response to excess carbohydrate or nutrition in starved individuals characterised by severe intracellular electrolyte shifts, acute circulatory fluid overload and organ failure. It can occur during enteral, parenteral or oral feeding. However, a precise diagnostic criteria is lacking. The accuracy of risk factors for predicting refeeding syndrome are unknown.
Objectives	3	Primary outcome: Occurrence of the refeeding syndrome. Secondary outcome: Sensitivity and specificity of the risk factors for

		predicting refeeding syndrome. Tertiary outcome: Mortality due to refeeding syndrome.
Methods		
Study design	4	Prospective cohort study which recruited adults referred for artificial nutrition and hydration. Recruitment was within 48 hours of commencing artificial nutrition and hydration. Serum electrolyte concentration levels were recorded at baseline then every third day for the duration of study participation at day 15. A three facet diagnostic criteria was used to confirm positive cases of refeeding syndrome. Symptoms of the refeeding syndrome were severely low electrolyte concentrations, acute circulatory fluid overload and organ dysfunction. These symptoms had to have occurred after the commencement of artificial nutrition and hydration for the diagnosis of refeeding syndrome to be made.
Setting	5	Ethical approval was 2006. Recruitment period 2007-2009, location was a large, single site university teaching hospital. Participants were recruited from all wards, intensive care and high dependency unit. Wards predominantly were surgical, medical, elderly, stroke and neurological. Data analysis was 2009-2011.
Participants	6	Eligibility criteria; adults >18 years of age commenced on artificial nutrition and hydration for the first time during that hospital admission. All participants were recruited within 48 hours of the commencement of artificial nutrition and hydration. Study participation was for the duration of artificial nutrition and hydration to a maximum of 15 consecutive days. Informed consent was obtained from participants or next of kin prior to recruitment. Participants were followed up from baseline, then every third day up to day 15 of study participation.
Variables	7	Diagnostic criteria to confirm refeeding syndrome taken from reference number three in the references section. . 1. Serum electrolyte concentrations falls as follows from the start of artificial nutrition and hydration; potassium < 2.5 mmol/L, phosphate < 0.32 mmol/L and magnesium < 0.5 mmol/L. 2. Peripheral oedema or acute circulatory fluid overload. 3. Disturbance to organ function including respiratory failure, cardiac failure, pulmonary oedema. Risk Factors. BMI < 16 (kg/m^2), Unintentional weight loss >15% in the preceding three – six months, very little or no nutritional intake for more than 10 days, low levels of serum potassium, phosphate or magnesium prior to feed. Also these, BMI < 18.5 (kg/m^2), unintentional weight loss >10% in the preceding three – six months, very little or no nutritional intake for more than 5 days, history of alcohol or drug abuse.
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group The diagnostic criteria was obtained from the reference; National Institute for Health and Clinical Excellence. Nutrition support in adults. CG32, London, England.
Bias	9	The authors were not involved in the nutritional treatment, electrolyte supplementation or the diagnosis of refeeding syndrome.
Study size	10	The study size was calculated using the estimated reported occurrence of refeeding syndrome to be between 1 - 10% within an adult hospital

		population. A cohort of 240 participants was anticipated to produce between 2 - 24 positive cases of refeeding syndrome for analysis.
Quantitative variables	11	All participants were classified as having risk of refeeding syndrome or not at risk. Predictor variables were transformed to binary categories representing whether or not refeeding syndrome occurred. Sensitivity and specificity values for refeeding syndrome were calculated for each predictor based on the cohort of 243 participants.
Statistical methods	12	We used Fisher's exact test to compare groups at the $p<0.05$ level. Sensitivity and specificity analysis was conducted. The sensitivity level was 70%. We could not use multiple regression analysis due to the low number of positive cases of refeeding syndrome.
		A subgroup of energy intakes were examined separately which were Group 1. <800 kcal day versus Group 2. >800 kcal day. This analysis allowed energy intake and risk factors to be analysed separately.
		Missing data was not included in the analysis. Loss to follow up was not used.
Results		
Participants	13*	Total eligible participants 484, total recruited 243, total not recruited 241, total positive refeeding cases 3, total borderline cases with electrolyte depletion 2, total recruited with risk factors for refeeding syndrome 133.
		Reasons for non participation were; declined participation, unable to obtain consent/assent, tube feed stopped before recruitment, mortality, transfer from hospital and feeding tube removed.
		A flow diagram is included to provide clarity of the research process, diagnosis process and totals used in the analysis.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders 243 participants were recruited median age 57.0 years (interquartile range 44.0 – 69.0), sex 130 men. 133 participants had risk factors for refeeding syndrome of which 68 were men. 212 participants received enteral nutrition, 23 participants parenteral and 8 received enteral/parenteral tube feeding. Mortality during feeding was 13/243 and during admission 68/243 the cause of death was due to underlying disease. Mortality by location was ward 45/153, high dependency unit 14/46 and intensive care 9/44. The major confounder was the organizational policy of early electrolyte supplementation which is addressed in the strengths and weaknesses section.
		(b) Indicate number of participants with missing data for each variable of interest
		There was no missing data for diagnosis of refeeding syndrome. All participants were assigned a risk factor for refeeding syndrome. All participants were assigned a diagnostic criteria. The data was complete for all 243 participants who received electrolyte supplementation and B vitamin supplementation.
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time 243 participants recruited, 133 participants had risk factors for refeeding syndrome, 3 cases of refeeding syndrome were confirmed, 2 cases of borderline electrolyte depletion were recorded, 13 participants died during their participation in the study, 68 died during the hospital admission.
Main results	16	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included

		We did not adjust for any confounders. Precision was 70% for the sensitivity analysis and the 95% confidence interval levels have been included. .
Other analyses	17	We have performed a subgroup analysis of energy intake. This analysis enabled us to confirm that the risk factors were uniformly distributed between the two groups.
Discussion		
Key results	18	243 participants were recruited and 133 participants had risk factors for refeeding syndrome. Three participants developed refeeding syndrome despite receiving hypocaloric nutrition and preventative treatment to reduce the risk of the syndrome occurring. Occurrence of refeeding syndrome was difficult to predict which suggests that the risk factors used to predict the syndrome are weak predictors. Refeeding syndrome was a survivable phenomena with two participants admitted to the ICU and one treated on the ward. The study objectives were achieved. The primary outcome of occurrence of the refeeding syndrome was determined. The secondary outcome of sensitivity and specificity of the risk factors for predicting refeeding syndrome were determined. The tertiary outcome of mortality due to refeeding syndrome was found to be weak.
Limitations	19	The main limitation of this study was that only threee cases of refeeding syndrome were diagnosed. This small number of cases severely limited the statistical analyses that we could perform. We could not separate the effect of the medical teams prescribing early electrolytes which may have reduced the occurrence of refeeding syndrome. The electrolyte threshold values could be viewed as being too low to capture all cases. However, we determined that the chosen serum electrolyte thresholds would allow the researchers to confirm positive cases with complete confidence. The 157 participants that were not recruited represented a loss of data that might have influenced the results of this study. However, this aspect of none recruitment is a feature of all cohort studies. A limitation of this study, and the literature base, is that we do not have a similar design study methodology to compare our results to. Our results indicate that the risk factors for predicting refeeding syndrome were weak and therefore the practice of slow, hypocaloric nutrition may increase the risk of malnutrition. However, we accept that our results are only relevant to the cohort studied within one institution and influenced by the decisions of the medical teams in that institution. Our study raises the question for clinicians, should they take a preventative approach to feeding patients and continue to provide slow hypocaloric feeding? Or should they feed as normal and treat when symptoms of refeeding syndrome occur? A key finding of this research was that mortality due to refeeding syndrome can be prevented by early serum electrolyte replacement.
Interpretation	20	Occurrence of serum phosphate <0.5 mmol/L in this study was 3% at day one and 6% at day three which was higher than that reported in a general adult hospital population of 0.2% to 2%.This may have been due to the cohort containing a sample of participants from HDU and ICU. Very few participants developed severe electrolyte shifts although moderate serum concentrations of potassium, phosphate and magnesium occurred. The interpretation of the

		moderate electrolyte shifts, without symptoms of the syndrome, was cellular uptake of electrolytes in response to nutritional input. The subgroup analysis identified many participants with malnutrition profiles for the syndrome. Hypocaloric nutritional treatment may have prevented refeeding syndrome in some of these participants. However, the subgroup analysis revealed one group received more energy sooner and for longer but did not develop symptoms. This finding supports our interpretation that the risk factors for predicting the syndrome are weak and the practice of hypocaloric feeding may contribute to malnutrition. The impact of intravenous dextrose infusion as a precipitating factor for refeeding syndrome in the three cases cannot be under estimated. In starved individuals gluconeogenesis is the predominant metabolic pathway for energy production. Infusion of intravenous dextrose in the three participants caused suppression of gluconeogenesis and a switch to glycolysis. This switch caused insulin to be released causing rapid cellular uptake of serum phosphate, potassium and magnesium electrolytes. We propose that the initial infusion of dextrose in the three starved participants was the causal agent that triggered the refeeding syndrome. Hypocaloric feeding failed to prevent refeeding syndrome in these three cases for one important reason, it continued the input of simple carbohydrates causing more insulin to be released. This explanation is supported by other studies where intravenous dextrose infusion was attributed to hypophosphataemia of <0.7 mmol/L which progressed to respiratory failure at serum phosphate concentration 0.2 mmol/L - 0.36 mmol/L.The results of the present study indicate that dextrose infusion should be avoided in starved individuals who require fluid replacement and nutritional treatment. The finding that intravenous dextrose infusion act as a precipitator for the refeeding syndrome requires further research. However, in cases were there is a clear history of chronic starvation repeat serum electrolyte replacement may be required during the first seven to ten days of treatment. The small number of positive cases severely limited the statistical analyses that we could perform. This small number may have been due to the medical teams taking preventative actions to avoid refeeding syndrome. However we suspect that the most compelling reason for the low occurrence of refeeding syndrome was that genuine chronic starvation was absent from the majority of the cases that were recruited for this study.
Generalisability	21	The results are applicable to adults commenced on artificial nutrition and hydration for the first time. From a clinical importance the results are applicable to dietitian, nutrition teams and pharmacists who prescribe nutrition via a tube feed. From a clinical perspective we advise that individuals with a history of chronic starvation receive repeat serum electrolyte infusion until serum levels are stable. In subjects with a history of fasting we suggest routine electrolyte replacement as in the normal current practice.
Other information		
Funding	22	Funding; none declared for this study.

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5. Manuscript Title: PREVALENCE OF REFEEDING SYNDROME IN ADULTS COMMENCED ON ARTIFICIAL NUTRITION AND HYDRATION: PROSPECTIVE COHORT STUDY
6. Manuscript Identifying Number (if you know it):

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Occurrence of refeeding syndrome in adults commenced on artificial nutrition support: prospective cohort study.

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Title. Occurrence of refeeding syndrome in adults commenced on **artificial nutrition support**: prospective cohort study.

Alan Rio, Kevin Whelan, Louise Goff, Dianne Reidlinger, Nigel Smeeton.

Alan Rio, Nutrition and Dietetic Department, King's College Hospital, Denmark Hill, London, SE5 9RS, UK. Kevin Whelan, King's College London, School of Medicine, Diabetes and Nutritional Sciences Division, London, SE1 9NH, UK. Louise Goff, King's College London, School of Medicine, Diabetes and Nutritional Sciences Division, London, SE1 9NH, UK. Dianne Reidlinger, King's College London, School of Medicine, Diabetes and Nutritional Sciences Division, London, SE1 9NH, UK, Nigel Smeeton, King's College London, Division of Imaging Sciences & Biomedical Engineering, London, SE1 7EH, UK.

Correspondence to: A Rio, Alan.Rio.1@city.ac.uk

Article Summary

Article focus

Hypothesis: The risk factors for the refeeding syndrome are weak and cause unnecessary delay of nutrition.

Research question: Which risk factors reliably predict development of the refeeding syndrome?

Key messages

- Refeeding syndrome is a complex constellation of major characteristics which requires a multi-facet diagnostic criteria.
- Refeeding syndrome is a rare, survivable phenomena that can occur despite identification of risk and hypocaloric nutritional treatment.
- Intravenous glucose infusion prior to artificial nutrition support can precipitate the refeeding syndrome.
- Starvation is the most reliable predictor for onset of the syndrome.

Strengths and limitations of this study

The authors were not involved in the nutritional treatment, electrolyte supplementation or diagnosis of the refeeding syndrome. The diagnostic criteria provided unequivocal confirmation of the refeeding syndrome and omitted borderline results. The main source of data loss was the excluded group which may potentially have contained participants who went on to develop the refeeding syndrome.

Abstract

Background Refeeding syndrome is a potentially life threatening condition characterised by severe intracellular electrolyte shifts, acute circulatory fluid overload and organ failure. The initial symptoms are non specific but early clinical features are severely low serum electrolyte concentrations of potassium, phosphate or magnesium. Risk factors for the syndrome include starvation, chronic alcoholism, anorexia nervosa and surgical interventions that require lengthy periods of fasting. The causes of the refeeding syndrome are excess or unbalanced enteral, parenteral or oral nutritional intake. Prevention of the syndrome includes identification of individuals at risk, controlled hypocaloric nutritional intake and supplementary electrolyte replacement.

Objective To determine the occurrence of refeeding syndrome in adults commenced on artificial nutrition support.

Design Prospective cohort study.

Setting Large, single site university teaching hospital. Recruitment period 2007-2009.

Participants 243 adults commenced on artificial nutrition support for the first time during that admission recruited from wards and intensive care.

Main outcome measures Primary outcome: Occurrence of the refeeding syndrome. Secondary outcome: Analysis of the risk factors which predict the refeeding syndrome. Tertiary outcome: Mortality due to refeeding syndrome and all cause mortality.

Results 133 participants had one or more of the following risk factors: BMI < 16 - 18.5 $\geq$ (kg/m^2), unintentional weight loss >15% in the preceding three – six months, very little or no nutritional intake >10 days, history of alcohol or drug abuse and low baseline levels of serum potassium, phosphate or magnesium prior to recruitment. Poor nutritional intake for more than 10 days, weight loss >15% prior to recruitment and low serum magnesium level at baseline predicted the refeeding syndrome with a sensitivity of 66.7%: specificity was >80% apart from weight loss of >15% which was 59.1%. Baseline low serum magnesium was an independent predictor of the refeeding syndrome (p=0.021). Three participants (2% 3/243) developed severe electrolyte shifts, acute circulatory fluid overload and

disturbance to organ function following artificial nutrition support and were diagnosed with refeeding syndrome. There were no deaths attributable to the refeeding syndrome but (5.3% 13/243) participants died during the feeding period and (28% 68/243) died during the hospital admission. Death of these participants was due to cerebrovascular accident, traumatic injury, respiratory failure, organ failure or end of life causes.

Conclusion Refeeding syndrome was a rare, survivable phenomenon that occurred during hypocaloric nutrition support in participants identified at risk. Independent predictors for refeeding syndrome were starvation and baseline low serum magnesium concentration. Intravenous carbohydrate infusion prior to artificial nutrition support may have precipitated the onset of the syndrome.

Introduction

Refeeding syndrome has been defined as severe fluid and electrolyte shifts in malnourished patients during oral, enteral or parenteral refeeding.[1] A key risk factor for the syndrome is starvation with early published reports being prisoners of war.[2] In recent times refeeding syndrome has been confirmed in hunger strikers, individuals with anorexic nervosa and chronic alcoholics. The modern definition of refeeding syndrome is life threatening severely low serum electrolyte concentrations, fluid and electrolyte imbalance and disturbance of organ function resulting from over rapid or unbalanced nutrition support.[3] However, this definition is imprecise and lacks definitive electrolyte threshold values to confidently diagnose the refeeding syndrome.

The metabolic shift from starvation to feeding increases cellular uptake of glucose, potassium, phosphate and magnesium which lowers the serum concentration of these electrolytes.[4] The early signs of the refeeding syndrome are non specific but include severely low serum electrolyte concentrations of serum phosphate, potassium and magnesium which if untreated can progress to acute circulatory fluid overload, respiratory compromise and cardiac failure.[5] Severe hypophosphataemia has been described as the hallmark of refeeding syndrome.

Guidelines for the prevention and treatment of refeeding syndrome advise identification of individuals at risk, controlled hypocaloric nutritional treatment and supplementary electrolytes.[3] However, not all individuals with risk factors for refeeding syndrome develop symptoms during nutritional repletion.[6] A potential consequence of adherence to these untested guidelines is the delay of adequate nutrition to undernourished individuals. We conducted a prospective cohort study to determine the occurrence of refeeding syndrome in adults commenced on artificial nutrition support. Refeeding syndrome was confirmed using a three facet diagnostic criteria of defined severely low serum electrolyte concentrations, acute circulatory fluid overload and organ dysfunction.

Methods

Study design

This was a prospective cohort study conducted at a large, single site university teaching hospital. Criteria to determine risk of refeeding syndrome is displayed in Box 1. The risk factors were Body Mass Index (BMI) < 16 (kg/m^2), unintentional weight loss >15% in the preceding three – six months, very little or no nutritional intake for more than 10 days and low levels of serum potassium, phosphate or magnesium prior to artificial nutrition support. The three facet diagnostic criteria used by the research team to confirm refeeding syndrome is displayed in Box 2. Each participant's medical team diagnosed refeeding syndrome using serum electrolyte shifts and observed clinical complications of acute circulatory fluid overload and organ dysfunction. The medical teams documented this information in the participant's medical record as daily clinical observations and treatment. The research team used the participant's medical record to confirm that symptoms occurred from the onset of artificial nutrition support recording observations daily and serum electrolyte concentrations every third day from baseline. For each participant diagnosed with refeeding syndrome the research team compared the serum electrolyte concentrations, the acute circulatory fluid overload and organ dysfunction against the three facet diagnostic criteria. All three facets of the diagnostic criteria were required by the research team to unequivocally confirm the diagnosis of refeeding syndrome**.** To avoid any potential bias the authors were not involved in nutritional treatment,

electrolyte supplementation or the initial diagnosis of refeeding syndrome during the study period. The schematic for participant exclusion, recruitment and analysis is displayed in Flow chart 1.

Sample size

The sample size was estimated from the reported prevalence of refeeding syndrome, defined as hypophosphataemia <0.4 mmol/L, to be 1 - 10%. [7-8] A cohort of 240 would produce between 2 - 24 potential participants meeting the diagnostic criteria.

Participants

Participants commenced on enteral or parenteral artificial nutrition support were eligible to be recruited if they met the inclusion criteria. The inclusion criteria was: adults >18 years of age commenced on artificial nutrition support for the first time during that hospital admission. Exclusion criteria were: previous artificial nutrition support during the hospital admission, artificial nutrition support commenced at the previous institution, participants <18 years of age or failure to obtain consent/assent due to serious illness or lack of next of kin. Informed consent was obtained from participants or next of kin prior to enrolment. Study participation was for the duration of artificial nutrition support to a maximum of 15 consecutive days. All participants were recruited within 48 hours of the commencement of artificial nutrition support with enteral or parenteral feeding. Energy prescriptions for each participant were estimated by the dietetic speciality who used basal metabolic rate and stress related factors.[9] The hospital nutrition policy for adults with risk factors for refeeding syndrome was 800 kcal day or 50% of estimated adult energy requirements.

Outcome measures

The primary outcome of interest in this study was the occurrence of refeeding syndrome. The secondary outcome was analysis of the risk factor at predicting refeeding syndrome. The tertiary outcome measure was mortality due to refeeding syndrome and all cause mortality.

Data Collection

Baseline serum electrolyte concentrations were recorded within 24 hours of study enrolment then every third day for a maximum of 15 days during the period of artificial nutrition support. Serum electrolytes

were not recorded when artificial nutrition support was stopped. Serum electrolyte concentrations were obtained from the hospital electronic in-patient system (iSoft, v1.0 Oxon, England). The normal hospital adult serum reference ranges were potassium 3.5 – 5.0 mmol/L, phosphate 0.8 – 1.4 mmol/L and magnesium 0.7 – 1.00 mmol/L. Body weight (kg) was measured using balance and digital scales accurate to within 0.1kg (Seca, 22089 Hamburg, Germany) wearing light indoor clothing. Body weight was not recorded in participants who were sedated or unconscious. Height (m) was recorded using measured or recalled data as appropriate. Body mass index (kg/m^2) and percentage weight loss (normal body weight - current body weight/normal body weight x 100) were calculated. To determine which participants had poor nutritional intake prior to artificial nutrition support, dietary caloric intake was calculated by a research assistant**.** Each participant was asked to recall their dietary food and fluid intake in the 10 days preceding recruitment into the study. Food portion sizes were estimated from a reference guide[10] and total daily energy intake was calculated using a nutritional analysis software package, (Compeat, Oxon, England)[11] Participants unable to provide a diet history the next of kin was interviewed, failing this retrospective food intake records were used.

Data Analysis

Descriptive statistics were performed on the entire cohort of 243 participants to obtain diagnostic data, electrolyte supplementation and caloric intake. Each participant was classified at risk or not at risk of refeeding syndrome as per the diagnostic criteria displayed in Box 2. Sensitivity and specificity values for refeeding syndrome were calculated for the entire cohort of 243 participants. The precision of the sensitivity and specificity analysis was set at 70%. Predictor variables were transformed to binary categories representing whether or not refeeding syndrome had been diagnosed**.** The refeeding syndrome outcomes were analysed using Fisher's exact test at the $p<0.05$ level. A subgroup analysis of the 133 participants with risk factors for refeeding syndrome was performed to provide data on the secondary outcome measure of the study. This subgroup analysis stratified these 133 participants according to their baseline energy intake as: Group 1 <800 kcal day versus Group 2 >800 kcal day, Flow chart 1. This stratification of baseline energy intake allowed hypocaloric versus normal caloric intake to be analysed.

There was no further analysis of the 110 participants without risk factors who did not develop symptoms of the syndrome. All data analysis was performed using SPSS version 17 (Chicago, Il, US).

Results

Four hundred and eighty four participants were eligible to be recruited, displayed in Flow chart 1. A total of 243 participants were recruited median age 57.0 years (interquartile range 44.0 – 69.0), sex 130 (53.5%) men. There were 133 participants with risk factors for refeeding syndrome of which 68 were men. Recruitment locations were wards 153 (63.0%), high dependency unit 46 (18.9%) and intensive care 44 (18.1%), see Table 1. In total 212 (87.2%) participants received enteral, 23 (9.5%) participants parenteral and 8 (3.3%) received enteral/parenteral tube feeding. There were 2615 total feed days, median duration 13 days (interquartile range 6-15). A total of 2765 serum electrolyte results were recorded, 1014 for potassium, 1006 for phosphate and 745 for magnesium. The total number of participants who received electrolyte supplementation were potassium 71, magnesium 52 and phosphate. Occurrence of moderate and severely low serum electrolyte concentration with mortality is displayed in Table 2. Mortality was not attributed to refeeding syndrome either during feeding (5.3%, 13/243) or hospital admission (28% 68/243). Cause of death in these participants was due to underlying disease with mortality by location: ward 45/153, high dependency unit 14/46 and intensive care 9/44.

Using the criteria in Box 2 the research team confirmed the diagnosis of refeeding syndrome in three participants, asymptomatic electrolyte depletion in two participants and the remaining 238 participants did not develop symptoms. Poor nutritional intake for more than 10 days, weight loss >15% prior to recruitment and a low serum magnesium level at baseline had sensitivity values of 66.7%. By contrast, all specificity values were high (>80%) apart from weight loss >15%, which had a specificity of 59.1%. Low baseline serum magnesium (p=0.021) independently predicted refeeding syndrome: other independent variables were not significantly associated. The pre-existing risk factors for refeeding syndrome within groups one and two are displayed in Table 3. Characteristics of the three participants diagnosed with

refeeding syndrome are displayed in Table 4. Number of participants in the two risk groups that received electrolyte supplementation is displayed in Table 5.

Participant diagnosed with refeeding syndrome

Participant X, a 48 year female who presented with confusion, bilateral leg weakness, alcohol withdrawal, poor nutritional intake with repeat vomiting for seven days, C2 fracture, translocation at C2/3 and high urinary ketones. The participant received two intravenous doses of a standard vitamins B and C **formulation** in 0.9% sodium chloride followed by 100 mg oral thiamine. Day two the patient received one litre of intravenous potassium chloride and two litres of 5% glucose followed by enteral tube feeding. Day three serum phosphate was recorded at 0.33 mol/L and 50 mmol/L intravenous phosphate in 500ml was infused over 12 hours. At day four the participant developed peripheral oedema with tachycardia and was transferred to the intensive care unit due to respiratory failure and acute circulatory fluid overload.

Participant Y, a 23 year old female, with Crohn's disease and subtotal bowel colectomy presented with frontal occipital headaches radiating to neck with history of nausea, vomiting and weight loss of 26kg. At day 117 of admission a nasogastric tube was inserted due to poor nutritional intake. Nutrition was stopped within two hours due to vomiting and abdominal pain. The participant collapsed 24 hours later due to hypotension, hypothermia, dehydration and pseudo-bowel obstruction. The participant was transferred to the high dependency unit for fluid resuscitation. Intravenous 10% glucose was commenced and a 16Fr wide bore nasogastric tube was inserted for gastric drainage. Day two serum electrolytes levels were potassium 3.2 mmol/L, phosphate 0.26 mmol/L, magnesium 0.55 mmol/L. Intravenous phosphate replacement was commenced with 50 mmol/L phosphate in 500ml. The participant was transferred to the intensive care unit, intubated and commenced on haemofiltration due to multi-organ failure.

Participant Z, a 31 year old female, with decompensated liver cirrhosis secondary to alcohol, with existing chronic pancreatitis and opiate dependency with a weekly alcohol intake of 56 units was admitted to the

hepatology unit with abdominal pain, vomiting and dehydration. Usual body weight was 48kg, admission dry weight was 40kg. The participant received a standard formulation of vitamins B and C followed by one litre of 5% glucose containing 20mmol/L potassium chloride. Oral thiamine 100 mg and oral vitamin B compound were prescribed. The participant had a nasogastric tube inserted for artificial nutrition support. At day three serum electrolytes were potassium 2.5 mmol/L, phosphate 0.37 mmol/L, magnesium 0.56 mmol/L. The participant developed acute circulatory fluid overload, symptoms of tachycardia and pneumonia. The participant was given 50 mmol/L intravenous phosphate in 500ml infused over 12 hours in one litre of 5% glucose, 25mmol magnesium and a repeat intravenous dose of a standard vitamin B and C formulation.

Discussion

This study applied a three facet diagnostic criteria to confirm the occurrence of refeeding syndrome in adults commenced on artificial nutrition support. This unequivocal clinical diagnostic criteria comprised: defined severe serum electrolyte concentrations, acute circulatory fluid overload and organ dysfunction. These symptoms occurred within 72 hours of hypocaloric artificial nutrition support in three participants identified at risk. Two participants developed respiratory failure and multi-organ failure and required admission to the intensive care unit whilst the third participant, who developed acute circulatory fluid overload and tachycardia, was treated on the ward. The survival of these three participants represents advances in the medical management of severely malnourished individuals compared to the fatal outcomes of early reports.[2,5] This study does not support previous reports that refeeding syndrome can be prevented by identification of risk and treatment with hypocaloric feeding. In this study refeeding syndrome occurred in three participants who had been identified at risk and treated with hypocaloric feeding. Risk factors distinct to the three refeeding syndrome participants were a history of starvation and baseline low serum magnesium concentration. Two of the three participants received an intravenous dose of standard vitamins B and C formulation prior to artificial nutrition support which may have prevented Wernicke's encephalopathy. The small number of participants diagnosed with refeeding syndrome in this study may have been due to the medical teams having a policy of early electrolyte replacement. However,

we suspect that the most compelling reason for the low occurrence of refeeding syndrome in this study was that starvation was a characteristic of only three participants. The analysis of the two subgroups showed strikingly similar malnutrition profiles but substantially different energy intakes. We interpret this to suggest that for refeeding syndrome to occur a risk factor was required. The compelling risk factor of the three diagnosed participants was starvation. This interpretation is supported by the analysis of those participants who reported a short period of fasting prior to artificial nutrition support and experienced moderate falls in their serum electrolyte concentrations.

Strengths and weaknesses of the study

The results of this study should be interpreted with caution. The study was not designed to assess the mechanism of refeeding syndrome. The strengths of the study were the standardised diagnostic criteria, the risk factor analysis and comparison of the hypocaloric and normal caloric nutrition groups. The results have a limited external validity due to the inherent bias of the narrow selection criteria. This selection bias effect and exclusion of participants who were able to take oral nutritional intake may explain the low occurrence of refeeding syndrome recorded in the study population. A large number of potentially eligible participants could not be recruited due to difficulty obtaining consent. A further reduction in potential participants was death within 24 hours of commencing artificial nutrition support. The cause of death in these participants was due to their underlying medical condition of cerebrovascular accident, traumatic injury, respiratory failure due to degenerative neurological disease, organ failure or end of life causes. Since death occurred within 24 hours of starting artificial nutrition support we cannot exclude complications of refeeding syndrome as a contributing factor. Confusion, communication impairment and cognitive problems due to refeeding syndrome may also explain why a large number of severely ill individuals refused participation in this cohort study. Equally valid is the possibility that these severely ill individuals refused participation due to the limited benefit inclusion in this study would provide.

The diagnosis of only three participants limited the statistical analyses that we could perform which excluded regression analyses. The low occurrence of refeeding syndrome may have been due to the

medical teams taking preventative actions such as early electrolyte replacement. The severely low electrolyte concentrations may be interpreted as too low to confirm the syndrome. However, the serum electrolyte concentrations were obtained from a review of the evidence to enable an unequivocal diagnosis of refeeding syndrome. This discreet approach was taken to avoid falsely diagnosing participants with single, abnormal electrolyte concentrations. Whilst the review of evidence was consistent for severely low serum electrolyte concentrations the authors identified a lack of consensus on the electrolyte concentration values to diagnose the syndrome. To avoid bias the authors were not involved in nutritional treatment, electrolyte supplementation or the initial diagnosis of the syndrome.

Interpretation

Occurrence of serum phosphate <0.5 mmol/L in this study was 3% at day one and 6% at day three which was higher than that reported in the adult hospital population of 0.2% to 2%.[7,8, 12, 13] The higher occurrence of hypophosphataemia in this study may have been due to the cohort containing participants recruited from the high dependency and intensive care units. Very few participants developed severe electrolyte shifts although moderate serum concentrations of potassium, phosphate and magnesium occurred. The interpretation of the moderate electrolyte shifts, without symptoms of the syndrome, was cellular uptake of electrolytes in response to nutritional input. The subgroup analysis identified many participants with risk factors for the syndrome. Hypocaloric nutritional treatment may have prevented refeeding syndrome in some of these participants. However, the subgroup analysis revealed that one group received more energy sooner and for longer but did not develop symptoms. Applying the diagnostic criteria in Box 2 revealed the risk factors[3] to be weak predictors of the syndrome.

The impact of intravenous glucose infusion, without adequate and repeated electrolyte replacement in the three diagnosed participants, cannot be under estimated. In starved individuals gluconeogenesis is the predominant metabolic pathway for energy production**.** Infusion of intravenous glucose potentially suppressed gluconeogenesis which caused a switch to glycolysis in these three participants. This switch caused insulin to be released causing rapid cellular uptake of serum phosphate, potassium and magnesium

electrolytes. We propose that the initial infusion of glucose in the three starved participants potentially triggered the metabolic sequence that resulted in the development of the syndrome. Hypocaloric feeding failed to prevent refeeding syndrome in these three participants for one important reason, it continued the input of simple carbohydrates causing more insulin to be released. This explanation is supported by other studies where intravenous glucose infusion was attributed to hypophosphataemia of <0.7 mmol/L[14] which progressed to respiratory failure at serum phosphate concentration 0.2 mmol/L - 0.36 mmol/L.[15-17] The results of the present study indicate that glucose infusion should be avoided in starved individuals who require fluid and nutritional treatment. The finding that intravenous glucose infusion in starved individuals may initiate the refeeding syndrome requires further research. A potential hypothesis to be tested is that electrolyte replacement strategies are more effective at preventing the syndrome than caloric restriction.

Comparison with other studies

The era of hypercaloric feeding in cachectic individuals was associated with cardiac abnormalities,[18] respiratory failure and death.[5] Two decades later controlled hypocaloric nutritional treatment and electrolyte supplementation prevented refeeding syndrome in eight prisoners who had been on hunger strike for 43 days.[19] Under controlled conditions hypocaloric nutritional treatment and intravenous phosphate containing 25 mmol/L over 12 hours with effervescent oral phosphate (16mmol) twice daily prevented serious complications associated with refeeding syndrome in a 30 year old male who endured 44 days of self imposed starvation.[20] Refeeding syndrome was prevented in 29 anorexic nervosa participants given 500 to 2,000 mg phosphate daily.[21] The energy prescription was 1,900 kcal at day one and 2,200 kcal at day three yet moderate hypophosphataemia (0.31 - 0.8 mmol/L) did not occur. These varied studies reflect the increased awareness of the syndrome where serious complications and mortality can be avoided.[22-23] In the present study refeeding syndrome was a rare, survivable phenomenon that occurred in starved individuals who crucially were identified at risk and treated with hypocaloric nutrition.[24] However, intravenous glucose infusion prior to artificial nutrition support may have triggered the onset of the refeeding syndrome.

Other information

Funding: none declared.

Contributors: AR was responsible for the conception, design, initiation and overall co-ordination of the study: AR drafted the paper, is responsible for its intellectual content, interpretation and analysis of the results. KW was involved in the design of the study, interpretation of results and writing the manuscript. NS conducted statistical analysis, interpretation of results and editing of the manuscript. DR and LG assisted with data collection and interpretation of the results: AR is the guarantor.

Competing interests: All authors declare that the answer to the questions on your competing interests form are all no and therefore have nothing to declare. All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) they have no relationships with any companies that might have an interest in the submitted work in the previous 3 years: (2) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work: and (3) have no specified or non-financial interests that may be relevant to the submitted work.

Ethical approval. King's College Hospital Research Ethics Committee (06/Q0703/131).

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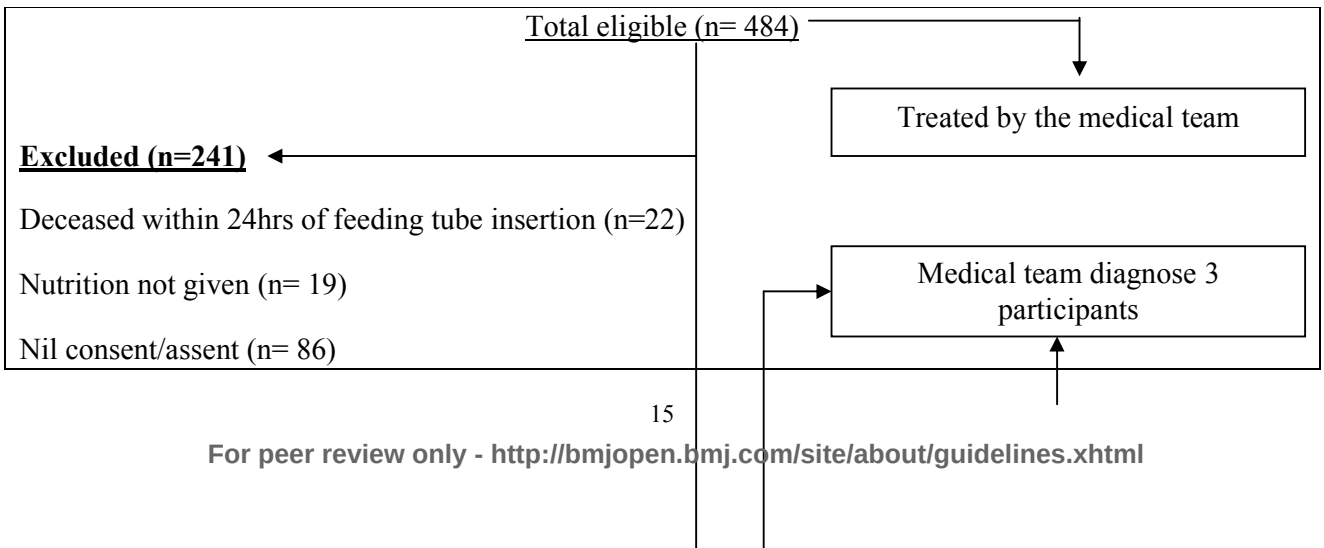
Flow chart 1. Flow chart showing number of participants at each stage of the study and stratification.



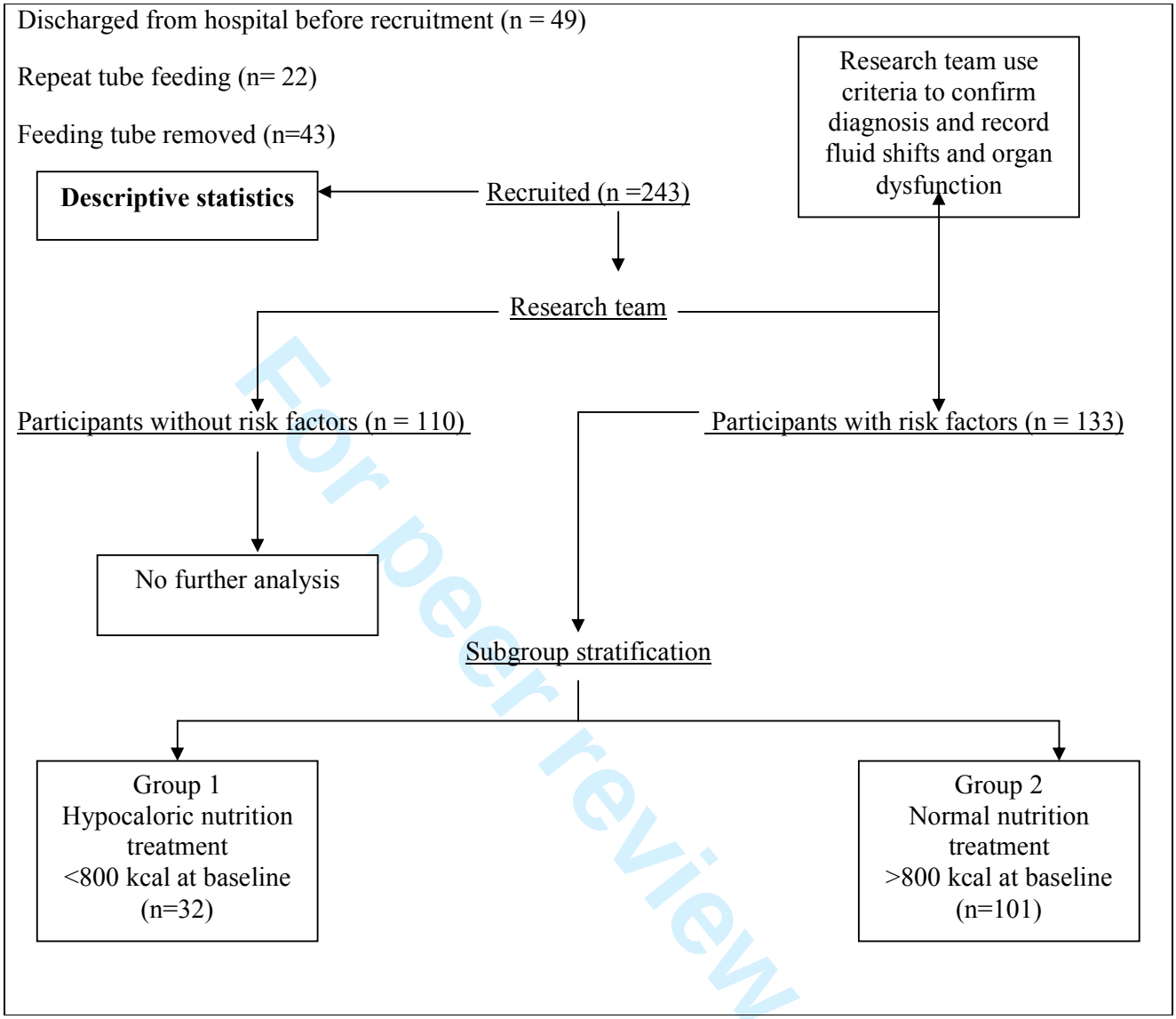


Table 1. Cohort information, diagnostic data, supplementation totals and energy intake. (n= 243)

Factor	**Location**		
	Ward (n= 153)	**HDU (n= 46)**	**ICU (n= 44)**
Male	78	25	27
Female	75	21	17
Age			
Median	62.0	53.0	52.5
IQR	47.0 – 73.0	39.0 – 67.5	41.0 – 61.7
Diagnostic categories			
Neurological	39	20	16
Respiratory	6	5	2
Trauma	6	0	0
Medicine	9	0	0
Hepatology	25	2	10

Renal	8	1	0
Pancrease	9	0	1
Gastroenterology	6	3	4
Cancer	13	2	0
Cardiovascular	22	9	4
Surgical	7	1	5
Sepsis	3	3	2
Length of stay (days)			
Median	28.5	38.0	29.5
IQR	17.0 – 47.5	17.0 – 67.5	20.5 – 42.7
Electrolyte supplementation totals			
Potassium	72	29	37
Phosphate	48	24	21
Magnesium	46	28	35
B vitamin supplementation totals	43	10	8
Duration of artificial nutrition (days)			
Median	10.5	15.0	15.0
IQR	5.0 – 15.0	9.5 – 15.0	12.3 – 15.0
Energy intake kcal/day			
Baseline			
Median (IQR)	**675 (390 – 1300)**	**690 (480 – 1000)**	**760 (420 - 1124)**
Day 3			
Median (IQR)	**1113 (848 – 1600)**	**1440 (1120 – 1606)**	**1470 (10005 – 1809)**
Day 6			
Median (IQR)	**1547 (1094 – 1850)**	**1500 (1292 – 1826)**	**1370 (965 – 1750)**
Day 9			
Median (IQR)	**1500 (900 – 1877)**	**1449 (960 – 1700)**	**1590 (1200 – 1907)**

IQR = inter quartile range at 25th and 75th centiles.

Table 2. Moderately and severely low serum electrolyte values with mortality (total participants = 243).

Number of electrolyte values recorded	**Number of moderately low values**	**Mortality**	**Number of severely low values**	**Mortality**
Potassium	<3.4 mmol/L		<2.5 mmol/L	
Baseline (n 243)	20	0	1	0
Day 3 (n 226)	22	0	3	0
Day 6 (n 180)	11	0	0	0
Day 9 (n 152)	7	1	1	0
Phosphate	<0.5 mmol/L		<0.32 mmol/L	
Baseline (n 243)	7	1	3	0
Day 3 (n 222)	15	3	1	0
Day 6 (n 177)	4	0	0	0

Day 9 (n 151)	2	0	0	0
Magnesium	<0.6 mmol/L		<0.5 mmol/L	
Baseline (n 243)	14	0	5	0
Day 3 (n 164)	5	0	2	0
Day 6 (n 132)	4	0	2	0
Day 9 (n 112)	5	0	3	0

Normal hospital reference ranges potassium 3.5 – 5.0 mmol/L, phosphate 0.8 – 1.4 mmol/L and magnesium 0.7 – 1.00 mmol/L.

Table 3. Malnutrition profiles of the two groups. Figures are totals within each group.

Risk factors	**Group 1** Hypocaloric nutrition **<800** kcal/day at baseline (n= 32)	**Group 2** Normal nutrition **>800** kcal at baseline (n= 101)	**Totals**
BMI < (16kg/m^2)	6	4	10
BMI < (14kg/m^2)	1	1	2
Wt loss > 15% within the previous 3-6 months	16	9	25
Poor nutritional intake > 10 days	20	15	35
Low baseline serum electrolyte concentrations			
Potassium <3.5 mmol/L	14	6	20
Phosphate <0.8 mmol/L	20	14	34
Magnesium <0.7 mmol/L	11	10	21

Table 4. Characteristics of the three participants confirmed with refeeding syndrome.

	Participant x	Participant y	Participant z
Age years	48	23	31
Diagnostic group	trauma	gastroenterology	hepatology

Chronic condition	alcoholism	malnutrition	alcoholism
Route of artificial nutrition support	enteral	enteral	enteral
Baseline received energy kcal/day	800	294	325
Baseline energy kcal/kg	12.7	6.3	8.1
Potassium replacement	**Yes**	**Yes**	**Yes**
Phosphate replacement	**Yes**	**Yes**	**Yes**
Magnesium replacement	**No**	**No**	**Yes**
Body weight/kg	63	47	40
BMI (kg/m^{-2})	20	16	16
Intravenous carbohydrate	yes	yes	yes
Survival outcome	survived	survived	survived

Table 5. Number of participants in the two risk groups that received electrolyte supplementation.

	Group 1 Hypocaloric nutrition **<800** kcal/day at baseline (n=32)	**Group 2** Normal nutrition **>800** kcal at baseline (n=101)
Baseline		
Potassium	28	22
Phosphate	21	19
Magnesium	20	20
Day 3		
Potassium	8	34
Phosphate	6	30
Magnesium	5	32
Day 6		
Potassium	8	34
Phosphate	5	30
Magnesium	7	32
Day 9		
Potassium	4	27
Phosphate	5	22
Magnesium	3	21

Box 1. Criteria for the determination of refeeding syndrome risk.[3]

One of the following:	**Two of the following:**
• BMI < 16 (kg/m^2) • Unintentional weight loss >15% in the preceding	• BMI < 18.5 (kg/m^2) • Unintentional weight loss >10% in

three – six months • Very little or no nutritional intake for more than 10 days • Low levels of serum potassium, phosphate or magnesium prior to feed	the preceding three – six months • Very little or no nutritional intake for more than 5 days • History of alcohol or drug abuse

Box 2. Criteria for confirmation of refeeding syndrome from the commencement of artificial nutrition support.

1. Electrolytes. • Potassium • Phosphate • Magnesium 2. Peripheral oedema or acute circulatory fluid overload. 3. Disturbance to organ function including respiratory failure, cardiac failure, pulmonary oedema.	Severely low electrolyte concentrations[4] < 2.5 mmol/L* < 0.32 mmol/L < 0.5 mmol/L

*King's College Hospital severely low serum potassium concentration value requiring replacement.

Data sharing statement No additional data is available.

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Title. Occurrence of refeeding syndrome in adults commenced on **artificial nutrition support**: prospective cohort study.

Alan Rio, Kevin Whelan, Louise Goff, Dianne Reidlinger, Nigel Smeeton.

Alan Rio, Nutrition and Dietetic Department, King's College Hospital, Denmark Hill, London, SE5 9RS, UK. Kevin Whelan, King's College London, School of Medicine, Diabetes and Nutritional Sciences Division, London, SE1 9NH, UK. Louise Goff, King's College London, School of Medicine, Diabetes and Nutritional Sciences Division, London, SE1 9NH, UK. Dianne Reidlinger, King's College London, School of Medicine, Diabetes and Nutritional Sciences Division, London, SE1 9NH, UK, Nigel Smeeton, King's College London, Division of Imaging Sciences & Biomedical Engineering, London, SE1 7EH, UK.

Correspondence to: A Rio, Alan.Rio.1@city.ac.uk

Article Summary

Article focus

Hypothesis: The risk factors for the refeeding syndrome are weak and cause unnecessary delay of nutrition.

Research question: Which risk factors reliably predict development of the refeeding syndrome?

Key messages

- Refeeding syndrome is a complex constellation of major characteristics which requires a multi-facet diagnostic criteria.
- Refeeding syndrome is a rare, survivable phenomena that can occur despite identification of risk and hypocaloric nutritional treatment.
- Intravenous glucose infusion prior to **artificial nutrition support** can precipitate the refeeding syndrome.
- Starvation is the most reliable predictor for onset of the syndrome.

Strengths and limitations of this study

The authors were not involved in the nutritional treatment, electrolyte supplementation or diagnosis of the refeeding syndrome. The diagnostic criteria provided unequivocal confirmation of the refeeding syndrome and omitted borderline results. The main source of data loss was the excluded group which may potentially have contained participants who went on to develop the refeeding syndrome.

Abstract

Background Refeeding syndrome is a potentially life threatening condition characterised by severe intracellular electrolyte shifts, acute circulatory fluid overload and organ failure. The initial symptoms are non specific but early clinical features are severely low serum electrolyte concentrations of potassium, phosphate or magnesium. Risk factors for the syndrome include starvation, chronic alcoholism, anorexia nervosa and surgical interventions that require lengthy periods of fasting. The causes of the refeeding syndrome are excess or unbalanced enteral, parenteral or oral nutritional intake. Prevention of the syndrome includes identification of individuals at risk, controlled hypocaloric nutritional intake and supplementary electrolyte replacement.

Objective To determine the occurrence of refeeding syndrome in adults commenced on **artificial nutrition support.**

Design Prospective cohort study.

Setting Large, single site university teaching hospital. Recruitment period 2007-2009.

Participants 243 adults commenced on **artificial nutrition support** for the first time during that admission recruited from wards and intensive care.

Main outcome measures Primary outcome: Occurrence of the refeeding syndrome. Secondary outcome: Analysis of the risk factors which predict the refeeding syndrome. Tertiary outcome: Mortality due to refeeding syndrome and all cause mortality.

Results 133 participants had one or more of the following risk factors: BMI < 16 - 18.5 ≥ (kg/m^2), unintentional weight loss >15% in the preceding three – six months, very little or no nutritional intake >10 days, history of alcohol or drug abuse and low baseline levels of serum potassium, phosphate or magnesium prior to recruitment. Poor nutritional intake for more than 10 days, weight loss >15% prior to recruitment and low serum magnesium level at baseline predicted the refeeding syndrome with a sensitivity of 66.7%: specificity was >80% apart from weight loss of >15% which was 59.1%. Baseline low serum magnesium was an independent predictor of the

refeeding syndrome (p=0.021). Three participants (2% 3/243) developed severe electrolyte shifts, acute circulatory fluid overload and disturbance to organ function following artificial nutrition support and were diagnosed with refeeding syndrome. There were no deaths attributable to the refeeding syndrome but (5.3% 13/243) participants died during the feeding period and (28% 68/243) died during the hospital admission. Death of these participants was due to cerebrovascular accident, traumatic injury, respiratory failure, organ failure or end of life causes.

Conclusion Refeeding syndrome was a rare, survivable phenomenon that occurred during hypocaloric nutrition support in participants identified at risk. Independent predictors for refeeding syndrome were starvation and baseline low serum magnesium concentration. Intravenous carbohydrate infusion prior to artificial nutrition support may have precipitated the onset of the syndrome.

Introduction

Refeeding syndrome has been defined as severe fluid and electrolyte shifts in malnourished patients during oral, enteral or parenteral refeeding.[1] A **key risk factor** for the syndrome is starvation with **early** published reports being prisoners of war.[2] In recent times refeeding syndrome has been confirmed in hunger strikers, individuals with anorexic nervosa and chronic alcoholics. **The modern definition of refeeding syndrome is life threatening severely low serum electrolyte concentrations, fluid and electrolyte imbalance and disturbance of organ function resulting from over rapid or unbalanced nutrition support.[3]** However, this definition is imprecise and lacks definitive electrolyte threshold values to confidently diagnose the refeeding syndrome.

The metabolic shift from starvation to feeding increases cellular uptake of glucose, potassium, phosphate and magnesium which lowers the serum concentration of these electrolytes.[4] The early signs of the refeeding syndrome are non specific but include severely low serum electrolyte concentrations of serum phosphate, potassium and magnesium which if untreated can progress to acute circulatory fluid overload,

respiratory compromise and cardiac failure.[5] Severe hypophosphataemia has been described as the hallmark of refeeding syndrome.

Guidelines for the prevention and treatment of refeeding syndrome advise identification of individuals at risk, controlled hypocaloric nutritional treatment and supplementary electrolytes.[3] However, not all individuals with risk factors for refeeding syndrome develop symptoms during nutritional repletion.[6] A potential consequence of adherence to these untested guidelines is the delay of adequate nutrition to undernourished individuals. We conducted a prospective cohort study to determine the occurrence of refeeding syndrome in adults commenced on **artificial nutrition support**. Refeeding syndrome was confirmed using a three facet diagnostic criteria of defined severely low serum electrolyte concentrations, acute circulatory fluid overload and organ dysfunction.

Methods

Study design

This was a prospective cohort study conducted at a large, single site university teaching hospital. Criteria to determine risk of refeeding syndrome is displayed in Box 1. The risk factors were Body Mass Index (BMI) < 16 (kg/m^2), unintentional weight loss >15% in the preceding three – six months, very little or no nutritional intake for more than 10 days and low levels of serum potassium, phosphate or magnesium prior to **artificial nutrition support**. The three facet diagnostic criteria used by the research team to confirm refeeding syndrome is displayed in Box 2. **Each participant's medical team diagnosed refeeding syndrome using serum electrolyte shifts and observed clinical complications of acute circulatory fluid overload and organ dysfunction. The medical teams documented this information in the participant's medical record as daily clinical observations and treatment. The research team used the participant's medical record to confirm that symptoms occurred from the onset of artificial nutrition support recording observations daily and serum electrolyte concentrations every third day from baseline. For each participant diagnosed with refeeding syndrome the research team compared the serum electrolyte concentrations, the acute circulatory fluid overload and organ**

dysfunction against the three facet diagnostic criteria. All three facets of the diagnostic criteria were required by the research team to unequivocally confirm the diagnosis of refeeding syndrome. To avoid any potential bias the authors were not involved in nutritional treatment, electrolyte supplementation or the initial diagnosis of refeeding syndrome during the study period. The schematic for participant exclusion, recruitment and analysis is displayed in Flow chart 1.

Sample size

The sample size was estimated from the reported prevalence of refeeding syndrome, defined as hypophosphataemia <0.4 mmol/L, to be 1 - 10%. [7-8] A cohort of 240 would produce between 2 - 24 potential participants meeting the diagnostic criteria.

Participants

Participants commenced on enteral or parenteral artificial nutrition support were eligible to be recruited if they met the inclusion criteria. The inclusion criteria was: adults >18 years of age commenced on artificial nutrition support for the first time during that hospital admission. Exclusion criteria were: previous artificial nutrition support during the hospital admission, artificial nutrition support commenced at the previous institution, participants <18 years of age or failure to obtain consent/assent due to serious illness or lack of next of kin. Informed consent was obtained from participants or next of kin prior to enrolment. Study participation was for the duration of artificial nutrition support to a maximum of 15 consecutive days. All participants were recruited within 48 hours of the commencement of artificial nutrition support with enteral or parenteral feeding. **Energy prescriptions for each participant were estimated by the dietetic speciality who used basal metabolic rate and stress related factors.[9]** The hospital nutrition policy for adults with risk factors for refeeding syndrome was 800 kcal day or 50% of estimated adult energy requirements.

Outcome measures

The primary outcome of interest in this study was the occurrence of refeeding syndrome. The secondary outcome was analysis of the risk factor at predicting refeeding syndrome. The tertiary outcome measure was mortality due to refeeding syndrome and all cause mortality.

Data Collection

Baseline serum electrolyte concentrations were recorded within 24 hours of study enrolment then every third day for a maximum of 15 days during the period of artificial nutrition support. Serum electrolytes were not recorded when artificial nutrition support was stopped. Serum electrolyte concentrations were obtained from the hospital electronic in-patient system (iSoft, v1.0 Oxon, England). The normal hospital adult serum reference ranges were potassium 3.5 – 5.0 mmol/L, phosphate 0.8 – 1.4 mmol/L and magnesium 0.7 – 1.00 mmol/L. Body weight (kg) was measured using balance and digital scales accurate to within 0.1kg (Seca, 22089 Hamburg, Germany) wearing light indoor clothing. Body weight was not recorded in participants who were sedated or unconscious. Height (m) was recorded using measured or recalled data as appropriate. Body mass index (kg/m^2) and percentage weight loss (normal body weight - current body weight/normal body weight x 100) were calculated. To determine which participants had poor nutritional intake prior to artificial nutrition support, dietary caloric intake was calculated by a research assistant. **Each participant was asked to recall their dietary food and fluid intake in the 10 days preceding recruitment into the study. Food portion sizes were estimated from a reference guide[10] and total daily energy intake was calculated using a nutritional analysis software package, (Compeat, Oxon, England)[11]** Participants unable to provide a diet history the next of kin was interviewed, failing this retrospective food intake records were used.

Data Analysis

Descriptive statistics were performed on the entire cohort of 243 participants to obtain diagnostic data, electrolyte supplementation and caloric intake. Each participant was classified at risk or not at risk of refeeding syndrome as per the diagnostic criteria displayed in Box 2. Sensitivity and specificity values for refeeding syndrome were calculated for the entire cohort of 243 participants. The precision of the sensitivity and specificity analysis was set at 70%. Predictor variables were transformed to binary categories representing whether or not refeeding syndrome had been **diagnosed.** The refeeding syndrome outcomes were analysed using Fisher's exact test at the $p<0.05$ level. **A subgroup analysis of the 133 participants with risk factors for refeeding syndrome was performed**

to provide data on the secondary outcome measure of the study. This subgroup analysis stratified these 133 participants according to their baseline energy intake as: Group 1 <800 kcal day versus Group 2 >800 kcal day, Flow chart 1. This stratification of baseline energy intake allowed hypocaloric versus normal caloric intake to be analysed. There was no further analysis of the 110 participants without risk factors who did not develop symptoms of the syndrome. All data analysis was performed using SPSS version 17 (Chicago, Il, US).

Results

Four hundred and eighty four participants were eligible to be recruited, displayed in Flow chart 1. A total of 243 participants were recruited median age 57.0 years (interquartile range 44.0 – 69.0), sex 130 (53.5%) men. There were 133 participants with risk factors for refeeding syndrome of which 68 were men. Recruitment locations were wards 153 (63.0%), high dependency unit 46 (18.9%) and intensive care 44 (18.1%), see Table 1. In total 212 (87.2%) participants received enteral, 23 (9.5%) participants parenteral and 8 (3.3%) received enteral/parenteral tube feeding. There were 2615 total feed days, median duration 13 days (interquartile range 6-15). A total of 2765 serum electrolyte results were recorded, 1014 for potassium, 1006 for phosphate and 745 for magnesium. The total number of participants who received electrolyte supplementation were potassium 71, magnesium 52 and phosphate. Occurrence of moderate and severely low serum electrolyte concentration with mortality is displayed in Table 2. Mortality was not attributed to refeeding syndrome either during feeding (5.3%, 13/243) or hospital admission (28% 68/243). Cause of death in these participants was due to underlying disease with mortality by location: ward 45/153, high dependency unit 14/46 and intensive care 9/44.

Using the criteria in Box 2 the research team confirmed the diagnosis of refeeding syndrome in three participants, asymptomatic electrolyte depletion in two participants and the remaining 238 participants did not develop symptoms. Poor nutritional intake for more than 10 days, weight loss >15% prior to recruitment and a low serum magnesium level at baseline had sensitivity values of 66.7%. By contrast, all specificity values were high (>80%) apart from weight loss >15%, which had a specificity of 59.1%. Low

baseline serum magnesium (p=0.021) independently predicted refeeding syndrome: other independent variables were not significantly associated. The pre-existing risk factors for refeeding syndrome within groups one and two are displayed in Table 3. Characteristics of the three participants diagnosed with refeeding syndrome are displayed in Table 4. **Number of participants in the two risk groups that received electrolyte supplementation is displayed in Table 5.**

Participant diagnosed with refeeding syndrome

Participant X, a 48 year female who presented with confusion, bilateral leg weakness, alcohol withdrawal, poor nutritional intake with repeat vomiting for seven days, C2 fracture, translocation at C2/3 and high urinary ketones. The participant received two **intravenous doses of a standard vitamins B and C formulation** in 0.9% sodium chloride followed by 100 mg oral thiamine. Day two the patient received one litre of intravenous potassium chloride and two litres of 5% glucose followed by enteral tube feeding. Day three serum phosphate was recorded at 0.33 mol/L and **50 mmol/L intravenous phosphate in 500ml was infused over 12 hours**. At day four the participant developed peripheral oedema with tachycardia and was transferred to the intensive care unit due to respiratory failure and acute circulatory fluid overload.

Participant Y, a 23 year old female, with Crohn's disease and subtotal bowel colectomy presented with frontal occipital headaches radiating to neck with history of nausea, vomiting and weight loss of 26kg. At day 117 of admission a nasogastric tube was inserted due to poor nutritional intake. Nutrition was stopped within two hours due to vomiting and abdominal pain. The participant collapsed 24 hours later due to hypotension, hypothermia, dehydration and pseudo-bowel obstruction. The participant was transferred to the high dependency unit for fluid resuscitation. Intravenous 10% glucose was commenced and a 16Fr wide bore nasogastric tube was inserted for gastric drainage. Day two serum electrolytes levels were potassium 3.2 mmol/L, phosphate 0.26 mmol/L, magnesium 0.55 mmol/L. **Intravenous phosphate**

replacement was commenced with 50 mmol/L phosphate in 500ml. The participant was transferred to the intensive care unit, intubated and commenced on haemofiltration due to multi-organ failure.

Participant Z, a 31 year old female, with decompensated liver cirrhosis secondary to alcohol, with existing chronic pancreatitis and opiate dependency with a weekly alcohol intake of 56 units was admitted to the hepatology unit with abdominal pain, vomiting and dehydration. Usual body weight was 48kg, admission dry weight was 40kg. **The participant received a standard formulation of vitamins B and C** followed by one litre of 5% glucose containing 20mmol/L potassium chloride. Oral thiamine 100 mg and oral vitamin B compound were prescribed. The participant had a nasogastric tube inserted for **artificial nutrition support.** At day three serum electrolytes were potassium 2.5 mmol/L, phosphate 0.37 mmol/L, magnesium 0.56 mmol/L. The participant developed acute circulatory fluid overload, symptoms of tachycardia and pneumonia. The participant was **given 50 mmol/L intravenous phosphate in 500ml infused over 12 hours in one litre of 5% glucose, 25mmol magnesium and a repeat intravenous dose of a standard vitamin B and C formulation.**

Discussion

This study applied a three facet diagnostic criteria to confirm the occurrence of refeeding syndrome in adults commenced on artificial nutrition support. This unequivocal clinical diagnostic criteria comprised: defined severe serum electrolyte concentrations, acute circulatory fluid overload and organ dysfunction. These symptoms occurred within 72 hours of hypocaloric artificial nutrition support in three participants identified at risk. Two participants developed respiratory failure and multi-organ failure and required admission to the intensive care unit whilst the third participant, who developed acute circulatory fluid overload and tachycardia, was treated on the ward. The survival of these three participants represents advances in the medical management of severely malnourished individuals compared to the fatal outcomes of early reports.[2,5] This study does not support previous reports that refeeding syndrome can be prevented by identification of risk and treatment with hypocaloric feeding. In this study refeeding syndrome occurred in three participants who had been identified at risk and treated

with hypocaloric feeding. Risk factors distinct to the three refeeding syndrome participants were a history of starvation and baseline low serum magnesium concentration. Two of the three participants received an **intravenous dose of standard vitamins B and C formulation prior to artificial nutrition support** which may have prevented Wernicke's encephalopathy. The small number of participants diagnosed with refeeding syndrome in this study may have been due to the medical teams having a policy of early electrolyte replacement. However, we suspect that the most compelling reason for the low occurrence of refeeding syndrome in this study was that starvation was a characteristic of only three participants. The analysis of the two subgroups showed strikingly similar malnutrition profiles but substantially different energy intakes. We interpret this to suggest that for refeeding syndrome to occur a risk factor was required. The compelling risk factor of the three diagnosed participants was starvation. This interpretation is supported by the analysis of those participants who reported a short period of fasting prior to artificial nutrition support and experienced moderate falls in their serum electrolyte concentrations.

Strengths and weaknesses of the study

The results of this study should be interpreted with caution. The study was not designed to assess the mechanism of refeeding syndrome. **The strengths of the study were the standardised diagnostic criteria, the risk factor analysis and comparison of the hypocaloric and normal caloric nutrition groups. The results have a limited external validity due to the inherent bias of the narrow selection criteria. This selection bias effect and exclusion of participants who were able to take oral nutritional intake may explain the low occurrence of refeeding syndrome recorded in the study population. A large number of potentially eligible participants could not be recruited due to difficulty obtaining consent. A further reduction in potential participants was death within 24 hours of commencing artificial nutrition support. The cause of death in these participants was due to their underlying medical condition of cerebrovascular accident, traumatic injury, respiratory failure due to degenerative neurological disease, organ failure or end of life causes. Since death occurred within 24 hours of starting artificial nutrition support we cannot exclude complications of refeeding**

syndrome as a contributing factor. Confusion, communication impairment and cognitive problems due to refeeding syndrome may also explain why a large number of severely ill individuals refused participation in this cohort study. Equally valid is the possibility that these severely ill individuals refused participation due to the limited benefit inclusion in this study would provide.

The diagnosis of only three participants limited the statistical analyses that we could perform which excluded regression analyses. The low occurrence of refeeding syndrome may have been due to the medical teams taking preventative actions such as early electrolyte replacement. The severely low electrolyte concentrations may be interpreted as too low to confirm the syndrome. However, the serum electrolyte concentrations were obtained from a review of the evidence to enable an unequivocal diagnosis of refeeding syndrome. This discreet approach was taken to avoid falsely diagnosing participants with single, abnormal electrolyte concentrations. Whilst the review of evidence was consistent for severely low serum electrolyte concentrations the authors identified a lack of consensus on the electrolyte concentration values to diagnose the syndrome. To avoid bias the authors were not involved in nutritional treatment, electrolyte supplementation or the initial diagnosis of the syndrome.

Interpretation

Occurrence of serum phosphate <0.5 mmol/L in this study was 3% at day one and 6% at day three which was higher than that reported in the adult hospital population of 0.2% to 2%.[7,8, 12, 13] The higher occurrence of hypophosphataemia in this study may have been due to the cohort containing participants recruited from the high dependency and intensive care units. Very few participants developed severe electrolyte shifts although moderate serum concentrations of potassium, phosphate and magnesium occurred. The interpretation of the moderate electrolyte shifts, without symptoms of the syndrome, was cellular uptake of electrolytes in response to nutritional input. The subgroup analysis identified many participants with risk factors for the syndrome. Hypocaloric nutritional treatment may have prevented refeeding syndrome in some of these participants. However, the subgroup analysis revealed **that** one group received more

energy sooner and for longer but did not develop symptoms. **Applying the diagnostic criteria in Box 2 revealed the risk factors[3] to be weak predictors of the syndrome.**

The impact of intravenous glucose infusion, without adequate and repeated electrolyte replacement in the three diagnosed participants, cannot be under estimated. In starved individuals gluconeogenesis is the predominant metabolic pathway for energy production**. Infusion of intravenous glucose potentially suppressed gluconeogenesis which caused a switch to glycolysis in these three participants. This switch caused insulin to be released causing rapid cellular uptake of serum phosphate, potassium and magnesium electrolytes. We propose that the initial infusion of glucose in the three starved participants potentially triggered the metabolic sequence that resulted in the development of the syndrome.** Hypocaloric feeding failed to prevent refeeding syndrome in these three participants for one important reason, it continued the input of simple carbohydrates causing more insulin to be released. This explanation is supported by other studies where intravenous glucose infusion was attributed to hypophosphataemia of <0.7 mmol/L[14] which progressed to respiratory failure at serum phosphate concentration 0.2 mmol/L - 0.36 mmol/L.[15-17] **The results of the present study indicate that glucose infusion should be avoided in starved individuals who require fluid and nutritional treatment. The finding that intravenous glucose infusion in starved individuals may initiate the refeeding syndrome requires further research. A potential hypothesis to be tested is that electrolyte replacement strategies are more effective at preventing the syndrome than caloric restriction.**

Comparison with other studies

The era of hypercaloric feeding in cachectic individuals was associated with cardiac abnormalities,[18] respiratory failure and death.[5] Two decades later controlled hypocaloric nutritional treatment and electrolyte supplementation prevented refeeding syndrome in eight prisoners who had been on hunger strike for 43 days.[19] Under controlled conditions hypocaloric nutritional treatment and intravenous phosphate containing 25 mmol/L over 12 hours with effervescent oral phosphate (16mmol) twice daily prevented serious complications associated with refeeding syndrome in a 30 year old male who endured 44 days of self imposed starvation.[20] Refeeding syndrome was prevented in 29 anorexic nervosa

participants given 500 to 2,000 mg phosphate daily.[21] The energy prescription was 1,900 kcal at day one and 2,200 kcal at day three yet moderate hypophosphataemia (0.31 - 0.8 mmol/L) did not occur. These varied studies reflect the increased awareness of the syndrome where serious complications and mortality can be avoided.[22-23] In the present study refeeding syndrome was a rare, survivable phenomenon that occurred in starved individuals who crucially were identified at risk and treated with hypocaloric nutrition.[24] **However, intravenous glucose infusion prior to artificial nutrition support may have triggered the onset of the refeeding syndrome.**

Other information

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Contributors: AR was responsible for the conception, design, initiation and overall co-ordination of the study: AR drafted the paper, is responsible for its intellectual content, interpretation and analysis of the results. KW was involved in the design of the study, interpretation of results and writing the manuscript. NS conducted statistical analysis, interpretation of results and editing of the manuscript. DR and LG assisted with data collection and interpretation of the results: AR is the guarantor.

Competing interests: All authors declare that the answer to the questions on your competing interests form are all no and therefore have nothing to declare. All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that (1) they have no relationships with any companies that might have an interest in the submitted work in the previous 3 years: (2) their spouses, partners, or children have no financial relationships that may be relevant to the submitted work: and (3) have no specified or non-financial interests that may be relevant to the submitted work.

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Flow chart 1. Flow chart showing number of participants at each stage of the study and stratification.

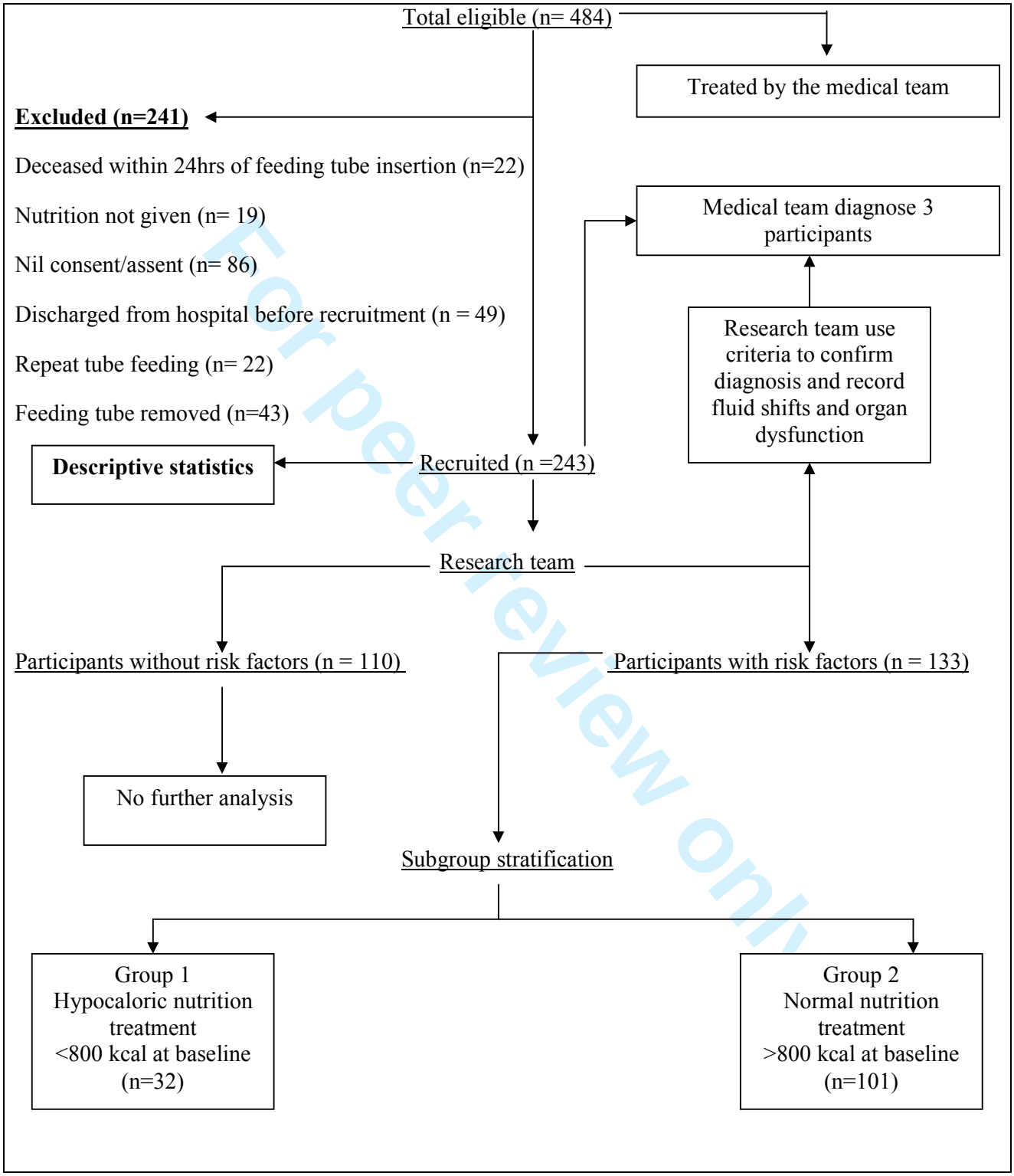

Table 1. Cohort information, diagnostic data, supplementation totals and energy intake. (n= 243)

Factor	**Location**		
	Ward (n= 153)	**HDU (n= 46)**	**ICU (n= 44)**
Male	78	25	27
Female	75	21	17
Age			
Median	62.0	53.0	52.5
IQR	47.0 – 73.0	39.0 – 67.5	41.0 – 61.7
Diagnostic categories			
Neurological	39	20	16
Respiratory	6	5	2
Trauma	6	0	0
Medicine	9	0	0
Hepatology	25	2	10
Renal	8	1	0
Pancrease	9	0	1
Gastroenterology	6	3	4
Cancer	13	2	0
Cardiovascular	22	9	4
Surgical	7	1	5
Sepsis	3	3	2
Length of stay (days)			
Median	28.5	38.0	29.5
IQR	17.0 – 47.5	17.0 – 67.5	20.5 – 42.7
Electrolyte supplementation totals			
Potassium	72	29	37
Phosphate	48	24	21
Magnesium	46	28	35
B vitamin supplementation totals	43	10	8
Duration of artificial nutrition (days)			
Median	10.5	15.0	15.0
IQR	5.0 – 15.0	9.5 – 15.0	12.3 – 15.0
Energy intake kcal/day			
Baseline			
Median (IQR)	**675 (390 – 1300)**	**690 (480 – 1000)**	**760 (420 - 1124)**
Day 3			
Median (IQR)	**1113 (848 – 1600)**	**1440 (1120 – 1606)**	**1470 (10005 – 1809)**
Day 6			
Median (IQR)	**1547 (1094 – 1850)**	**1500 (1292 – 1826)**	**1370 (965 – 1750)**
Day 9			
Median (IQR)	**1500 (900 – 1877)**	**1449 (960 – 1700)**	**1590 (1200 – 1907)**

IQR = inter quartile range at 25th and 75th centiles.

Table 2. Moderately and severely low serum electrolyte values with mortality (total participants = 243).

Number of electrolyte values recorded	Number of moderately low values	Mortality	Number of severely low values	Mortality
Potassium	<3.4 mmol/L		<2.5 mmol/L	
Baseline (n 243)	20	0	1	0
Day 3 (n 226)	22	0	3	0
Day 6 (n 180)	11	0	0	0
Day 9 (n 152)	7	1	1	0
Phosphate	<0.5 mmol/L		<0.32 mmol/L	
Baseline (n 243)	7	1	3	0
Day 3 (n 222)	15	3	1	0
Day 6 (n 177)	4	0	0	0
Day 9 (n 151)	2	0	0	0
Magnesium	<0.6 mmol/L		<0.5 mmol/L	
Baseline (n 243)	14	0	5	0
Day 3 (n 164)	5	0	2	0
Day 6 (n 132)	4	0	2	0
Day 9 (n 112)	5	0	3	0

Normal hospital reference ranges potassium 3.5 – 5.0 mmol/L, phosphate 0.8 – 1.4 mmol/L and magnesium 0.7 – 1.00 mmol/L.

Table 3. Malnutrition profiles of the two groups. Figures are totals within each group.

Risk factors	Group 1 Hypocaloric nutrition **<800** kcal/day at baseline (n= 32)	Group 2 Normal nutrition **>800** kcal at baseline (n= 101)	Totals
BMI < (16kg/m^2)	6	4	10
BMI < (14kg/m^2)	1	1	2
Wt loss > 15% within the previous 3-6 months	16	9	25
Poor nutritional intake > 10 days	20	15	35
Low baseline serum electrolyte concentrations			
Potassium <3.5 mmol/L	14	6	20
Phosphate <0.8 mmol/L	20	14	34
Magnesium <0.7 mmol/L	11	10	21

Table 4. Characteristics of the three participants confirmed with refeeding syndrome.

	Participant x	Participant y	Participant z
Age years	48	23	31
Diagnostic group	trauma	gastroenterology	hepatology
Chronic condition	alcoholism	malnutrition	alcoholism
Route of artificial nutrition support	enteral	enteral	enteral
Baseline received energy kcal/day	800	294	325
Baseline energy kcal/kg	12.7	6.3	8.1
Potassium replacement	**Yes**	**Yes**	**Yes**
Phosphate replacement	**Yes**	**Yes**	**Yes**
Magnesium replacement	**No**	**No**	**Yes**
Body weight/kg	63	47	40
BMI (kg/m^{-2})	20	16	16
Intravenous carbohydrate	yes	yes	yes
Survival outcome	survived	survived	survived

Table 5. Number of participants in the two risk groups that received electrolyte supplementation.

	Group 1 Hypocaloric nutrition **<800** kcal/day at baseline (n=32)	**Group 2** Normal nutrition **>800** kcal at baseline (n=101)
Baseline		
Potassium	28	22
Phosphate	21	19
Magnesium	20	20
Day 3		
Potassium	8	34
Phosphate	6	30
Magnesium	5	32
Day 6		
Potassium	8	34
Phosphate	5	30
Magnesium	7	32
Day 9		
Potassium	4	27
Phosphate	5	22
Magnesium	3	21

Box 1. Criteria for the determination of refeeding syndrome risk.[3]

One of the following:	**Two of the following:**
• BMI < 16 (kg/m^2) • Unintentional weight loss >15% in the preceding three – six months • Very little or no nutritional intake for more than 10 days • Low levels of serum potassium, phosphate or magnesium prior to feed	• BMI < 18.5 (kg/m^2) • Unintentional weight loss >10% in the preceding three – six months • Very little or no nutritional intake for more than 5 days • History of alcohol or drug abuse

Box 2. Criteria for confirmation of refeeding syndrome from the commencement of artificial nutrition support.

1. Electrolytes. • Potassium • Phosphate • Magnesium 2. Peripheral oedema or acute circulatory fluid overload. 3. Disturbance to organ function including respiratory failure, cardiac failure, pulmonary oedema.	Severely low electrolyte concentrations[4] < 2.5 mmol/L* < 0.32 mmol/L < 0.5 mmol/L

*King's College Hospital severely low serum potassium concentration value requiring replacement.

Data sharing statement No additional data is available.

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STROBE checklist.

	Item No	Recommendation
Title and abstract	1	Occurrence of the refeeding syndrome in adults commenced on artificial nutrition support: prospective cohort study.
		Background Refeeding syndrome is the metabolic response to excess nutrition in starved individuals characterised by severe intracellular electrolyte shifts, acute circulatory fluid overload and organ failure. It can occur during enteral, parenteral or oral feeding. **Objective** To determine the occurrence of refeeding syndrome in adults commenced on artificial nutrition support. **Design** Prospective cohort study. **Setting** Large, single site university teaching hospital. Recruitment period 2007-2009. **Participants** 243 adults commenced on artificial nutrition supportfor the first time during that admission recruited from wards and intensive care. **Main outcome measures** Primary outcome: Occurrence of the refeeding syndrome. Secondary outcome: Sensitivity and specificity of the risk factors for predicting refeeding syndrome. Tertiary outcome: Mortality due to refeeding syndrome and all cause mortality. **Results** 133 participants had one or more of the following risk factors; BMI < 16 - 18.5 ≥ (kg/m^2), unintentional weight loss >15% in the preceding three – six months, very little or no nutritional intake >10 days, history of alcohol or drug abuse and low baseline levels of serum potassium, phosphate or magnesium prior to recruitment. Poor nutritional intake for more than 10 days, weight loss >15% prior to recruitment and low serum magnesium level at baseline predicted the refeeding syndrome with a sensitivity of 66.7%; specificity was >80% apart from weight loss of >15% which was 59.1%. Baseline low serum magnesium was the only independent predictor of the refeeding syndrome (p=0.021). Three participants (2% 3/243) developed severe electrolyte shifts, acute circulatory fluid overload and disturbance to organ function following tube feeding and were diagnosed with refeeding syndrome. There were no deaths attributable to the refeeding syndrome but (5.3% 13/243) participants died during the feeding period and (28% 68/243) died during the hospital admission. Death of these participants was due to cerebrovascular accident, traumatic injury, respiratory failure or terminal end of life conditions. **Conclusion** Refeeding syndrome was a rare, survivable phenomenon that occurred during hypocaloric nutrition support in participants identified at risk. Predictors for refeeding syndrome were starvation and baseline low serum magnesium concentration. Intravenous carbohydrate infusion prior to artificial nutrition support may have precipitated the onset of the syndrome.
Introduction		
Background/rationale	2	Refeeding syndrome is the metabolic response to excess carbohydrate or nutrition in starved individuals characterised by severe intracellular electrolyte shifts, acute circulatory fluid overload and organ failure. It

		can occur during enteral, parenteral or oral feeding. However, a precise diagnostic criteria is lacking. The accuracy of risk factors for predicting refeeding syndrome are unknown.
Objectives	3	Primary outcome: Occurrence of the refeeding syndrome. Secondary outcome: Sensitivity and specificity of the risk factors for predicting refeeding syndrome. Tertiary outcome: Mortality due to refeeding syndrome.
Methods		
Study design	4	Prospective cohort study which recruited adults referred for artificial nutrition support. Recruitment was within 48 hours of commencing artificial nutrition support. Serum electrolyte concentration levels were recorded at baseline then every third day for the duration of study participation at day 15. A three facet diagnostic criteria was used to confirm positive cases of refeeding syndrome. Symptoms of the refeeding syndrome were severely low electrolyte concentrations, acute circulatory fluid overload and organ dysfunction. These symptoms had to have occurred after the commencement of artificial nutrition supportfor the diagnosis of refeeding syndrome to be made.
Setting	5	Ethical approval was 2006. Recruitment period 2007-2009, location was a large, single site university teaching hospital. Participants were recruited from all wards, intensive care and high dependency unit. Wards predominantly were surgical, medical, elderly, stroke and neurological. Data analysis was 2009-2011.
Participants	6	Eligibility criteria; adults >18 years of age commenced on artificial nutrition supportfor the first time during that hospital admission. All participants were recruited within 48 hours of the commencement of artificial nutrition support. Study participation was for the duration of artificial nutrition supportto a maximum of 15 consecutive days. Informed consent was obtained from participants or next of kin prior to recruitment. Participants were followed up from baseline, then every third day up to day 15 of study participation.
Variables	7	Diagnostic criteria to confirm refeeding syndrome taken from reference number three in the references section. . 1. Serum electrolyte concentrations falls as follows from the start of artificial nutrition support; potassium < 2.5 mmol/L, phosphate < 0.32 mmol/L and magnesium < 0.5 mmol/L. 2. Peripheral oedema or acute circulatory fluid overload. 3. Disturbance to organ function including respiratory failure, cardiac failure, pulmonary oedema. Risk Factors. BMI < 16 (kg/m^2), Unintentional weight loss >15% in the preceding three – six months, very little or no nutritional intake for more than 10 days, low levels of serum potassium, phosphate or magnesium prior to feed. Also these, BMI < 18.5 (kg/m^2), unintentional weight loss >10% in the preceding three – six months, very little or no nutritional intake for more than 5 days, history of alcohol or drug abuse.
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group The diagnostic criteria was obtained from the reference; National Institute for Health and Clinical Excellence. Nutrition support in adults. CG32, London, England.

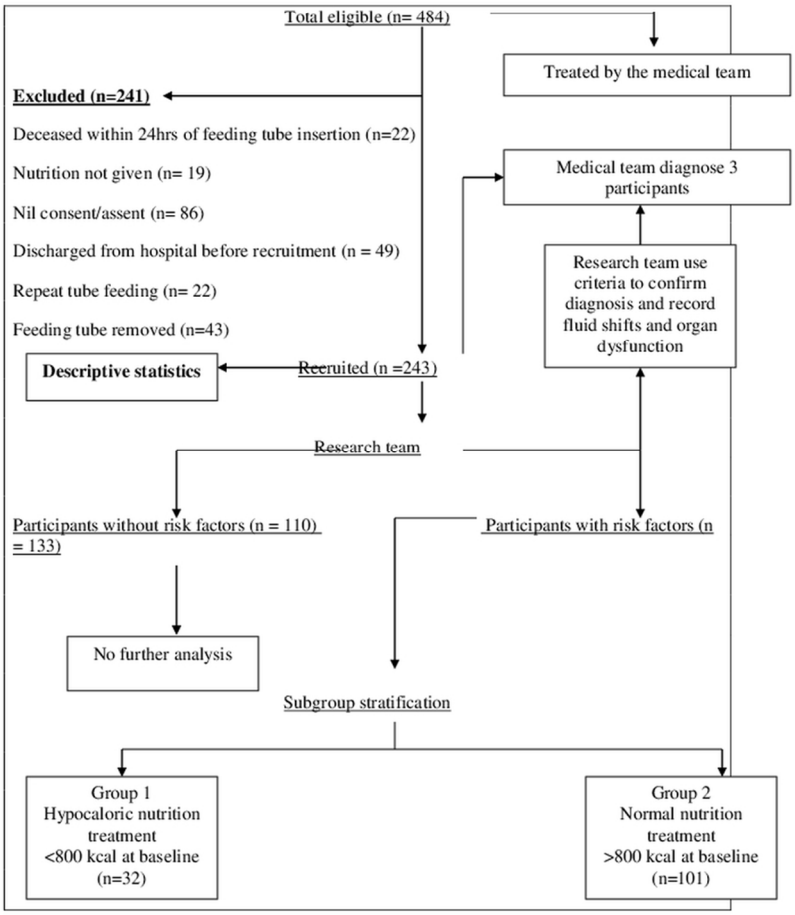
Bias	9	**The authors accept that the results have a limited external validity due to the inherent bias of the narrow selection criteria. However, this is offset by the focus of the study which aimed to recruit participants commenced on artificial nutrition support.** **The results are limited by the diagnostic criteria used which has not previously been reported.** **The selection bias effect and exclusion of participants who were able to eat offers a viable explanation for the low occurrence of refeeding syndrome reported. A large number of potentially eligible participants could not be recruited due to difficulty obtaining consent. Some patients, particularly those on intensive care and high dependency were seriously ill including some were close to death. Therefore obtaining consent or assent from these individuals was problematic. Some of these potential participants died within 24 hours of commencing artificial nutrition support.** **The causes of death have been documented however since death occurred within 24 hours of starting artificial nutrition support we cannot exclude complications associated with refeeding syndrome in these individuals. Some of these complications may have resulted in confusion, communication impairment and cognitive problems. Whilst the authors are unable to provide evidence in these un-recruited individuals there is the possibility that these severely ill individuals refused consent as they perceived participation in this study to be of limited benefit to their treatment or palliative care needs.** **The diagnosis of only three participants limited the statistical analyses that we could perform and therefore regression analyses could not be performed.** **The authors acknowledge that the low occurrence of refeeding syndrome may have been due to the medical teams taking preventative actions such as early electrolyte replacement. The authors did not influence electrolyte replacement and the benefit of this is that we were able to contrast current medical treatment of malnourished individuals to past reports of fatal outcomes.**
Study size	10	The study size was calculated using the estimated reported occurrence of refeeding syndrome to be between 1 - 10% within an adult hospital population. A cohort of 240 participants was anticipated to produce between 2 - 24 positive cases of refeeding syndrome for analysis.
Quantitative variables	11	All participants were classified as having risk of refeeding syndrome or not at risk. Predictor variables were transformed to binary categories representing whether or not refeeding syndrome occurred. Sensitivity and specificity values for refeeding syndrome were calculated for each predictor based on the cohort of 243 participants.

Statistical methods	12	We used Fisher's exact test to compare groups at the $p<0.05$ level. Sensitivity and specificity analysis was conducted. The sensitivity level was 70%. We could not use multiple regression analysis due to the low number of positive cases of refeeding syndrome.
		A subgroup of energy intakes were examined separately which were Group 1. <800 kcal day versus Group 2. >800 kcal day. This analysis allowed energy intake and risk factors to be analysed separately.
		Missing data was not included in the analysis. Loss to follow up was not used.
Results		
Participants	13*	**Total eligible participants 484, total recruited 243, total not recruited 241, total positive refeeding cases 3, total borderline cases with electrolyte depletion 2, total recruited with risk factors for refeeding syndrome 133.**
		Reasons for non recruitment were; previous treatment with artificial nutrition support, declined participation, unable to obtain consent/assent, tube feed stopped before recruitment, mortality, transfer from hospital and feeding tube removed, serum electrolyte concentrations not recorded,
		A flow diagram is included to provide clarity of the research process, diagnosis process and totals used in the analysis.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders 243 participants were recruited median age 57.0 years (interquartile range 44.0 – 69.0), sex 130 men. 133 participants had risk factors for refeeding syndrome of which 68 were men. 212 participants received enteral nutrition, 23 participants parenteral and 8 received enteral/parenteral tube feeding. Mortality during feeding was 13/243 and during admission 68/243 the cause of death was due to underlying disease. Mortality by location was ward 45/153, high dependency unit 14/46 and intensive care 9/44. The major confounder was the organizational policy of early electrolyte supplementation which is addressed in the strengths and weaknesses section.
		(b) Indicate number of participants with missing data for each variable of interest
		There was no missing data for diagnosis of refeeding syndrome. All participants were assigned a risk factor for refeeding syndrome. All participants were assigned a diagnostic criteria. The data was complete for all 243 participants who received electrolyte supplementation and B vitamin supplementation.
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time 243 participants recruited, 133 participants had risk factors for refeeding syndrome, 3 cases of refeeding syndrome were confirmed, 2 cases of borderline electrolyte depletion were recorded, 13 participants died during their participation in the study, 68 died during the hospital admission.
Main results	16	Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included We did not adjust for any confounders. Precision was 70% for the sensitivity analysis and the 95% confidence interval levels have been included. .
Other analyses	17	We have performed a subgroup analysis of energy intake. This analysis enabled us to confirm that the risk factors were uniformly distributed between the two groups.

Discussion		
Key results	18	243 participants were recruited and 133 participants had risk factors for refeeding syndrome. Three participants developed refeeding syndrome despite receiving hypocaloric nutrition and preventative treatment to reduce the risk of the syndrome occurring. Occurrence of refeeding syndrome was difficult to predict which suggests that the risk factors used to predict the syndrome are weak predictors. Refeeding syndrome was a survivable phenomena with two participants admitted to the ICU and one treated on the ward. The study objectives were achieved. The primary outcome of occurrence of the refeeding syndrome was determined. The secondary outcome of sensitivity and specificity of the risk factors for predicting refeeding syndrome were determined. The tertiary outcome of mortality due to refeeding syndrome was found to be weak.
Limitations	19	The main limitation of this study was that only threee cases of refeeding syndrome were diagnosed. This small number of cases severely limited the statistical analyses that we could perform. We could not separate the effect of the medical teams prescribing early electrolytes which may have reduced the occurrence of refeeding syndrome. The electrolyte threshold values could be viewed as being too low to capture all cases. However, we determined that the chosen serum electrolyte thresholds would allow the researchers to confirm positive cases with complete confidence. The 157 participants that were not recruited represented a loss of data that might have influenced the results of this study. However, this aspect of none recruitment is a feature of all cohort studies. A limitation of this study, and the literature base, is that we do not have a similar design study methodology to compare our results to. Our results indicate that the risk factors for predicting refeeding syndrome were weak and therefore the practice of slow, hypocaloric nutrition may increase the risk of malnutrition. However, we accept that our results are only relevant to the cohort studied within one institution and influenced by the decisions of the medical teams in that institution. Our study raises the question for clinicians, should they take a preventative approach to feeding patients and continue to provide slow hypocaloric feeding? Or should they feed as normal and treat when symptoms of refeeding syndrome occur? A key finding of this research was that mortality due to refeeding syndrome can be prevented by early serum electrolyte replacement.
Interpretation	20	Occurrence of serum phosphate <0.5 mmol/L in this study was 3% at day one and 6% at day three which was higher than that reported in a general adult hospital population of 0.2% to 2%.This may have been due to the cohort containing a sample of participants from HDU and ICU. Very few participants developed severe electrolyte shifts although moderate serum concentrations of potassium, phosphate and magnesium occurred. The interpretation of the moderate electrolyte shifts, without symptoms of the syndrome, was cellular uptake of electrolytes in response to nutritional input. The subgroup analysis identified many participants with malnutrition profiles for the syndrome. Hypocaloric nutritional treatment may have prevented refeeding syndrome in some of these participants. However, the subgroup analysis revealed one group received more energy sooner and for longer but did not develop

		symptoms. This finding supports our interpretation that the risk factors for predicting the syndrome are weak and the practice of hypocaloric feeding may contribute to malnutrition. The impact of intravenous dextrose infusion as a precipitating factor for refeeding syndrome in the three cases cannot be under estimated. In starved individuals gluconeogenesis is the predominant metabolic pathway for energy production. Infusion of intravenous dextrose in the three participants caused suppression of gluconeogenesis and a switch to glycolysis. This switch caused insulin to be released causing rapid cellular uptake of serum phosphate, potassium and magnesium electrolytes. We propose that the initial infusion of dextrose in the three starved participants was the causal agent that triggered the refeeding syndrome. Hypocaloric feeding failed to prevent refeeding syndrome in these three cases for one important reason, it continued the input of simple carbohydrates causing more insulin to be released. This explanation is supported by other studies where intravenous dextrose infusion was attributed to hypophosphataemia of <0.7 mmol/L which progressed to respiratory failure at serum phosphate concentration 0.2 mmol/L - 0.36 mmol/L.The results of the present study indicate that dextrose infusion should be avoided in starved individuals who require fluid replacement and nutritional treatment. The finding that intravenous dextrose infusion act as a precipitator for the refeeding syndrome requires further research. However, in cases were there is a clear history of chronic starvation repeat serum electrolyte replacement may be required during the first seven to ten days of treatment. The small number of positive cases severely limited the statistical analyses that we could perform. This small number may have been due to the medical teams taking preventative actions to avoid refeeding syndrome. However we suspect that the most compelling reason for the low occurrence of refeeding syndrome was that genuine chronic starvation was absent from the majority of the cases that were recruited for this study.
Generalisability	21	The results are applicable to adults commenced on artificial nutrition support for the first time. From a clinical importance the results are applicable to dietitian, nutrition teams and pharmacists who prescribe nutrition via a tube feed. From a clinical perspective we advise that individuals with a history of chronic starvation receive repeat serum electrolyte infusion until serum levels are stable. In subjects with a history of fasting we suggest routine electrolyte replacement as in the normal current practice.
Other information		
Funding	22	Funding; none declared for this study.

Flow chart 1. Flow chart showing number of participants at each stage of the study and stratification.



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