Top Clin Nutr
Vol. 36, No. 1, pp. 36–51

NARRATIVE REVIEW

A Systematic Review of the Role of Thiamine Supplementation in Treatment of Refeeding Syndrome

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The purpose of this systematic review is to identify studies where measurable thiamine supplementation was provided to patients at risk for or with refeeding syndrome to improve treatment guidelines. A systematic review of PubMed and CINAHL Plus databases was conducted using the terms refeeding syndrome, hypophosphatemia, thiamine, and vitamin B_1. A total of 173 articles were retrieved and 11 case studies and 1 retrospective study met inclusion criteria. All studies identified symptoms of thiamine deficiency, and all studies indicated thiamine supplementation was associated with improved clinical symptoms and no harmful outcomes. Average dose provided was 173-mg thiamine/day. **Key words:** *B_1*, *hypophosphatemia*, *refeeding*, *refeeding syndrome*, *thiamine*

REFEEDING syndrome is defined as the metabolic process in response to the reintroduction of calories after starvation.[1-3] It is often diagnosed by electrolyte abnormalities and poor management can be fatal.[1,2,4]

Refeeding syndrome was first recognized in prisoners of war following the Second World War but continues to lack definitive criteria and remains poorly recognized in the hospital setting despite significant incidence.[2,3] For example, some sources indicate that refeeding syndrome affects up to 25% of cancer patients and 14% of the geriatric population.[4,5] The majority of evidence on refeeding syndrome is limited to case studies in eating disorders or prolonged voluntary fasts[6] where refeeding syndrome is self-induced because ethical barriers inhibit controlled trials. Related to the paucity of studies and lack of comparability within the research available, evidence-based treatment is not clearly defined.[5] However, slow reintroduction of calories, electrolyte repletion, and vitamin supplementation including thiamine is often recommended to manage refeeding sydrome.[4,7,8]

PATHOPHYSIOLOGY OF REFEEDING SYNDROME

Refeeding syndrome represents the shift to anabolic metabolism as nutrition is reinitiated.[5] This metabolism shift contributes to corresponding electrolyte abnormalities especially abnormal potassium, magnesium, and phosphorus.[5] During starvation, fat and protein become the main source of energy because glycogen stores are exhausted and insulin is suppressed.[7,9,10] Once eating is

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The authors have disclosed that they have no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

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DOI: 10.1097/TIN.0000000000000235

reinitiated, blood glucose increases promoting insulin secretion and contributes to a shift in electrolytes, as energy synthesis pathways are upregulated.[4,5,10] Hypophosphatemia is not exclusive in recognition of refeeding syndrome but is often the hallmark feature.[3,5,10] Hypophosphatemia is precipitated from the insulin surge as eating restarts because serum phosphorus is depleted quickly.[4,11] Phosphorus is depleted related to increased demand in phosphorylated intermediates such as creation of adenosine triphosphate for glucose phosphorylation.[4,11] Hypokalemia is likely caused by cellular uptake of potassium, as pathways like glycogen synthesis are upregulated.[4] It is also possible that the sodium/potassium adenosine triphosphatase pump, which generally maintains blood potassium, is overwhelmed with refeeding contributing to increased urinary excretion and hypokalemia.[12] Potassium abnormalities are often what can make refeeding syndrome fatal, but any of the electrolyte abnormalities can contribute to symptoms.[4,10] The clinical features of refeeding syndrome including delirium, seizures, edema and heart failure, metabolic alkalosis, and rhabdomyolysis can be attributed to these electrolyte abnormalities.[4,10,12] However, these symptoms could have causes besides electrolyte abnormalities in refeeding syndrome such as thiamine deficiency.[5,13]

THIAMINE IN REFEEDING SYNDROME

Wernicke-Korsakoff syndrome or symptoms associated with wet or dry beriberi such as ophthalmoplegia, ataxia, paralysis, confusion, congestive heart failure (CHF), and edema are often identified in refeeding syndrome and could be explained by thiamine deficiency.[5,14] Thiamine deficiency is likely in refeeding syndrome because of increased metabolic needs. Thiamine is required as a cofactor in many of the metabolic pathways that are upregulated once feeding is reinitiated.[4,5] This could contribute to thiamine deficiency if there is a deficiency at baseline or available thiamine stores are depleted.[4,5] For example, thiamine pyrophosphate is needed in synthesis of branched chain amino acids and fatty acids, anabolic pathways that are upregulated once subjects begin eating again after starvation.[5,14] Thiamine pyrophosphate is also a cofactor in carbohydrate metabolism associated with pyruvate dehydrogenase.[12-16] In this pathway, thiamine deficiency could be rate limiting causing pyruvate to be used in anaerobic metabolism instead of aerobic resulting in lactic acidosis.[12-16] Lactic acidosis is frequently one of the clinical symptoms of refeeding syndrome, which could be explained by thiamine deficiency.[12-16] In protein and lipid metabolism, thiamine is needed for adenosine triphosphate production and here thiamine deficiency limits the ability of pyruvate to convert to acetyl CoA.[12-16] In amino and fatty acid synthesis, thiamine is required in the pentose-phosphate shunt for nicotinamide adenine dinucleotide phosphate and thiamine deficiency limiting the pentose-phosphate shunt could inhibit myelin sheath repair and impair nucleic acid synthesis.[12-17] In refeeding syndrome, these metabolic pathways are upregulated increasing thiamine needs and depleting thiamine if intake or stores are inadequate.

Inadequate thiamine is likely in refeeding syndrome for reasons in addition to increased needs. Thiamine cannot be synthesized endogenously and storage is limited; therefore, inadequate exogenous intake can rapidly precipitate deficiency.[4,5] Inadequate thiamine intake independent of refeeding syndrome can contribute to deficiency in as little as 2 weeks.[13] Prolonged starvation is one of the key risk factors in refeeding syndrome, predisposing patients for thiamine deficiency in addition to refeeding induced increased metabolic demand for thiamine and increased cellular thiamine use.[4,5] Malnutrition and alcohol intake are additional risk factors for refeeding syndrome that predispose patients for poor thiamine intake or deficiency at baseline.[4,5] For example, thiamine supplementation is frequently recommended as part of treatment in alcohol withdrawal

often to avoid Wernicke's encephalopathy but also because thiamine use is impaired in alcoholic patients because of changes in gluconeogenesis or decreased intestinal absorption making deficiency likely.[18]

It is not conclusive whether thiamine deficiency is present at baseline in refeeding syndrome or caused by refeeding syndrome.[14,15] Lack of evidence differentiating this can be attributed to limited thiamine measurement in the research because some measures are not accurate and others are difficult to measure. Serum thiamine is not an accurate measurement because it only identifies a portion of total body thiamine and concentrations are not indicative of thiamine stores.[5,18] Thiamine is a cofactor for transketolase, an enzyme involved in many metabolism pathways and its activity increased in response to increased thiamine.[5] Erythrocyte transketolase activity and a thiamine loading test are the best measure to identify thiamine deficiency because enzyme activity increases after thiamine pyrophosphate loading.[5] However, erythrocyte transketolase activity requires high-performance liquid chromatography for measurement, which requires a specialized laboratory for evaluation that may not be readily available in a hospital laboratory.[5] In addition, it lacks specificity and sensitivity, is expensive, and is time consuming to measure, so deficiency is often assumed.[5,13] Thiamine supplementation is commonly initiated without measuring erythrocyte transketolase because it is low risk and refeeding syndrome requires immediate treatment.[5,13] Lack of clinical measurement also makes it difficult to differentiate acute thiamine deficiency from refeeding syndrome-associated deficiency because clinical symptoms are identical.[19]

Whether present at baseline or induced metabolically in refeeding syndrome, thiamine deficiency can be attributed to many of the clinical symptoms, so supplementation is often recommended in management of refeeding syndrome. Case reports indicate resolution of clinical symptoms of refeeding syndrome such as edema or cardiac abnormalities with thiamine supplementation.[13] Cases also identify the concept that supplementation prior to initiating feeding may be beneficial in avoiding clinical symptoms from precipitating because thiamine availability would be adequate for the increased metabolic needs.[14] This theory explains why National Institute for Health and Care Excellence (NICE) criteria recommend starting thiamine supplementation prior to reintroducing calories. NICE guidelines recommend thiamine supplementation 200 to 300 mg/day orally or 200 to 300 mg/day intravenously (IV) as part of an undefined B vitamin preparation if needed, initiated before refeeding and for the first 10 days of calorie reintroduction.[8] The NICE guidelines do not define when to use IV supplementation instead of oral.[8] NICE guidelines were selected for comparison in this review because multiple treatment guidelines for refeeding syndrome base thiamine recommendations on them or have the same recommendations as these guidelines for thiamine supplementation in refeeding syndrome including Friedli et al,[4] the Irish Society for Clinical Nutrition and Metabolism, and CNSG East Cheshire guidelines.[20,21] One source states that the NICE guidelines are the most widely used guidelines for treatment of refeeding syndrome.[4] However, utilization remains poor.[8,22,23] A retrospective audit on physicians and dietitians has already identified limited compliance in following NICE guidelines, and per the American Society of Parenteral and Enteral Nutrition (ASPEN), the guidelines had poor validity as a screening tool for identifying risk of refeeding syndrome.[8,22,23] It is also noted that differentiated from NICE guidelines, in one source, ASPEN states current guidelines recommend 300-mg thiamine provided as IV prior to feeding and an additional 200 to 300 mg/day IV or orally for 3 days and possibly continuing 100 mg/day after this in treatment of refeeding; however, there is no source included for these guidelines.[18] Additionally, different from these previous ASPEN recommendations, in the 2020 ASPEN consensus recommendations

for refeeding syndrome, 100 mg of thiamine is recommended before initiating feeding or IV fluids and 100 mg/day for 5 to 7 days or longer in patients with severe starvation, chronic alcoholism, or signs of deficiency or high risk for deficiency, which is slightly lower than NICE supplementation guidelines.[23] No reviews identify whether thiamine supplementation recommendation per NICE or other guidelines is followed in the literature.

Additional higher quality studies are needed to define evidence-based guidelines for refeeding syndrome treatment including thiamine supplementation and to increase awareness and recognition of refeeding syndrome in the hospital setting. Evidence identifies a correlation between refeeding syndrome and thiamine deficiency and suggests thiamine supplementation may be beneficial in treatment.[8,13,14] To date the authors of this article found no systematic review addressing thiamine supplementation and dosage in cases of refeeding syndrome. The purpose of this review was to systematically evaluate and identify the studies available that identified refeeding syndrome or refeeding risk with a measurable dose of thiamine supplementation included in treatment intervention. The authors also identified how the doses provided compared to NICE guidelines for thiamine supplementation. Table 1 identifies some key questions this systematic review aims to address.

METHODS

Given the paucity of data on thiamine supplementation and refeeding syndrome, a systematic review was conducted to identify studies of hospitalized individuals with refeeding syndrome or risk for refeeding syndrome that included treatment with measurable doses of thiamine. Supplementation dosage provided was compared to NICE guidelines. Additionally, symptoms indicative of thiamine deficiency and documentation of improvement in these symptoms were including to further understand the role of thiamine supplementation in refeeding syndrome and dosage needed for clinical improvement. Data were extracted individually from the literature by researchers.

A comprehensive database search for publications was conducted in PubMed and CINAHL Plus with full text on September 7, 2019. MeSH terms searched included refeeding syndrome, refeeding, hypophosphatemia, thiamine, and B_1. There were no exclusion terms and no exclusions based on publication date. References were exported to Mendeley Desktop and duplicates were removed using authors, title, and year. No authors were contacted for additional information and no studies were excluded based on funding source.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

Table 1. Aims of Systematic Review: Key Questions

What is already known about this subject?
- Refeeding syndrome has a high incidence in many populations in the hospital setting but definition and management continue to lack consensus and the majority of evidence available is limited to case reports. Thiamine supplementation is often recommended in management.

What does this study add?
- This is a systematic review of case studies describing signs, symptoms, diagnosis, and management of refeeding syndrome with thiamine supplementation doses and outcomes. This is the only systematic review identified to date by the authors on thiamine supplementation dosage in refeeding syndrome.

How might this impact clinical practice?
- Causation cannot be concluded but these case studies identify that thiamine likely has a role in refeeding syndrome and supplementation is not likely harmful in nature and could be beneficial in improving clinical outcomes.

statement[24] for systematic reviews and the PRISMA checklist[24] were used in conducting this study. A total of 173 abstracts identified in the initial search were screened individually and excluded if they did not meet inclusion criteria. If the abstract did not have enough detail for inclusion, the full-text article was screened for inclusion criteria. Studies were included if they were written in English, refeeding syndrome was identified, or at least 1 risk factor for refeeding syndrome was present in human subjects. Additionally, thiamine dose provided needed to be measurable and articles could not be reviews. NICE criteria for patients at risk for refeeding syndrome (Table 2) were included in identifying studies because cases where refeeding syndrome was not identified could help to determine if thiamine could decrease symptoms and severity of refeeding syndrome or if thiamine supplementation prior to feeding could prevent refeeding syndrome from occurring in at-risk patients.[4,25] NICE criteria were used to identify risk for refeeding syndrome in this review; however, other sources like the ASPEN consensus statement have different criteria used to identify risk for refeeding syndrome.[23]

Table 2. NICE Criteria for Identifying Patients at Risk for Refeeding Syndrome[a]

Patient has a minimum of 1 of the following criteria:
- Body mass index <16 kg/m^2
- Unintentional weight loss $>15\%$ in the past 3–6 mo
- Minimal or no nutritional intake for the past ≥ 10 d
- Hypomagnesemia, hypokalemia, or hypophosphatemia before feeding

Or patient has at least 2 of the following criteria:
- Body mass index <18.5 kg/m^2
- Unintentional weight loss $>10\%$ in the past 3–6 mo
- Minimal or no nutritional intake for the past ≥ 5 d
- A history of alcohol abuse or drug use including diuretics, chemotherapy, insulin, or antacids

[a]Source: NICE.[8] Used with permission.

The majority of the literature available was case studies, which limited which quality evaluation tools could be used. The Downs and Black Checklist was used to assess quality at the study level because it has been validated to evaluate noncontrolled trials.[26]

Study selection

The Figure is a flowchart identifying the study selection process. Initially 173 references were identified through electronic database searches in PubMed and CINAHL Plus full text. Once duplicates were removed, 76 references remained for screening. Using the exclusion and inclusion criteria, 55 references were excluded initially. The majority of references were excluded because they were review articles, but references were also excluded because they were not available in English, used animal populations, or because they were not addressing refeeding syndrome or refeeding risk factors (eg, a case study on vitamin D and rickets or a case of vitamin C deficiency in Parkinsonism). After screening, 21 references were identified and read in full text and reevaluated using the exclusion and inclusion criteria. Of the remaining 21 references, 9 more were excluded primarily because thiamine supplementation was not addressed at all or the dosage of thiamine supplemented was not quantifiable. For example, a case of refeeding syndrome where a multivitamin supplement was prescribed, however, brand and dosing were not identified so amount of thiamine given could not be defined or another case where 2 different doses of thiamine were described were excluded.[27,28] Studies were also excluded after full-text review because refeeding syndrome was not identified or there was not sufficient data included to identify a risk factor for refeeding syndrome. Twelve studies met inclusion criteria.

Quality assessment

The literature review revealed no controlled trials and the majority of studies

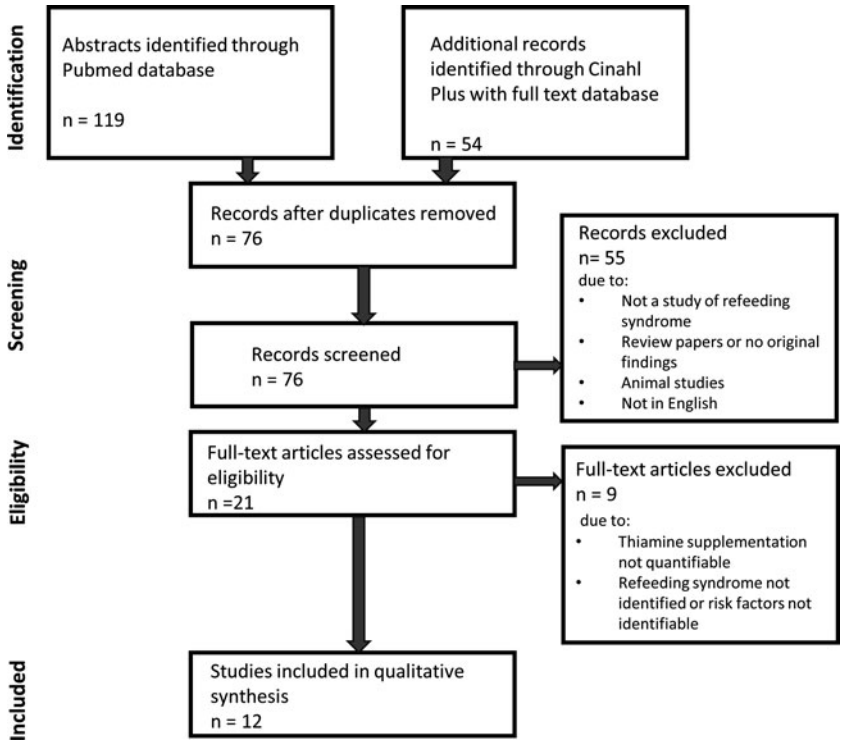

Figure. Flowchart of study selection based on PRISMA guidelines. Sources: PRISMA.[24]

included were case studies. However, it is important to assess the available research so that health care professionals can identify evidence-based guidelines for treatment within the limitations of the literature. Many limitations and barriers to higher quality studies of refeeding syndrome exist such as ethics. Case studies included were generally observational and retrospective. Quality assessment[26] revealed that all studies included were poor quality evidence and no studies that met inclusion criteria had a score higher than 14/31 per Downs and Black. The one retrospective study included[29] had a score of 11, the highest score but was still poor quality evidence per Downs and Black related to lack of control group and blinding. All studies based on Downs and Black scores indicated high chance of reporting bias because outcomes were poorly described, no statistical analysis was used, and confounders were not addressed. Outcomes used (eg, hospital stay) introduced bias because, regardless of refeeding or thiamine supplementation, more acutely ill patients had longer hospital stays. No studies had a control group for comparison. External validity was also poor because recruitment was not defined and studies with a population of 1 lacked generalizability to the population. Internal validity bias was high because no studies had a control group or were blinded, which limited validity and reliability. Population of 1 and lack of control group subjected each case study to a high probability for confounding and selection bias. For example, there are other causes for electrolyte abnormalities in the hospital setting.[5] It is difficult to compare the case studies related to performance bias because the treatment protocols in the case studies were not clearly defined and there was a high number of cointerventions such as differing feeding methods. None of the studies included can address causality.[30]

RESULTS

Cases included in the case review by Stanga et al[31] were addressed individually in tables because individual data from the cases could be extrapolated. The retrospective study by Chen et al[29] was counted as 1 study in text and tables except in the case of identifying symptoms (where proportions of 11 participants were used) because individual data could not be extrapolated.

Initial thiamine dose

Despite the fact that there are recognized guidelines for refeeding syndrome,[4,8,22] no case or retrospective study identified followed NICE guidelines for thiamine supplementation. In the cases identified, initial doses of thiamine supplementation ranged from 2.0 ± 0.5 mg/day[29] to 1500 mg in a day.[32] It is notable that in 1 case of low initial supplementation, the subject was only 6 years old[33] where subjects in the majority of other cases were adults. However, in other cases, age did not affect dosage.[34] For example, in a case of a 13-month-old, thiamine supplementation was provided at 200 mg/day comparable to adult doses provided.[34] The most common initial dose prescribed was 100 mg, which was used in 5 or 33% of the cases identified.[31,35-38] This corresponds with recommendations in the ASPEN consensus statement.[23] Four cases presented used an initial dose of 200 mg/day including a pediatric case.[31,34,39] Two cases started initial dose at 300 mg/day.[31,40] Low-dosage outliers started supplementation at 2.5 mg/day including a pediatric case[29,33] and high-dosage outliers started supplementation at 300 mg 3 times per day[41] or 500 mg 3 times per day in adult cases.[32] Excluding these 4 outliers average initial dose was 173 mg thiamine/day compared to NICE guidelines, which recommend 200 to 300 mg/day.[8] Six cases[31,34,39,40] or 40% of cases identified did provide initial doses within the NICE guideline range; however, length of supplementation and when supplementation was initiated excluded them from following NICE recommendations directly.

Change in thiamine dosage

In 10 or 67% of the cases,[31,34,36-40] dosage of thiamine remained the same during hospital stay or throughout duration of supplementation. In 2 cases, initial dose was started lower then dosage was increased.[29,33] In 2 cases, in which the highest doses were initiated, dosage was steadily decreased over time.[32,41] In 1 case, dose was decreased then increased again; however, this was attributed to medical error because 75% of the initial dose prescribed was missed related to transfer of medical care and administered once the error was identified.[35] Contrary to some of the cases, NICE guidelines[8] and ASPEN consensus[23] do not recommend changing thiamine dosage during 10-day supplementation.

Route of thiamine supplementation

The majority of thiamine supplementation provided was initiated as IV often with fluids or with parenteral nutrition. Eleven cases or 73% of cases presented started with initial thiamine supplementation provided as IV.[31-33,35-37,39-41] In 1 case, initial thiamine was provided orally and as IV.[39] In 2 cases, thiamine supplementation was started orally[31,38] and route of administration was unclear in 1 case.[34] Another retrospective study of cases started with oral supplements but then it was unclear whether patients remained on an oral supplementation once dose was increased.[29] In 3 cases, supplementation was initially started as IV and then transitioned to oral.[32,33,41] In 1 case, supplementation alternated between IV and oral but intended to deliver all as IV doses and then transition to oral.[35] However, IV doses were initially missed due to medical error.[35] In another case, administration of supplementation remained as IV but supplementation was stopped and restarted related to changes in feeding and intake during hospital stay.[31]

Length of supplementation

Length of supplementation was highly variable and difficult to compare ranging from a 1-time dose[31] to long-term supplementation of 18 months or more.[32] In 6 of the cases or studies, the researcher was unable to determine length of supplementation.[29,31,32,35,38,39] In general, these were the cases where supplementation was prescribed long-term after hospital discharge. Of the cases where length of supplementation was quantified, length included 1 day,[31] 5 days,[31] 7 days,[31] 11 days,[34] 2 weeks,[36,40] 3 weeks,[33] 28 days,[37] and 31 days.[41] In many of these cases, supplementation was prescribed the entire length of hospital stay and length of stay was variable related to comorbidities. An average length of supplementation was not found because of high variability in supplementation length and outliers. NICE guidelines recommend supplementation for the first 10 days of feeding,[8] and no studies identified had length of supplementation congruent with this. ASPEN consensus recommends a minimum of 5 days of supplementation.[23]

Supplementation in cases where refeeding is not directly identified

NICE guidelines and ASPEN consensus also recommend starting thiamine supplementation prior to starting oral intake in patients at risk for or with refeeding syndrome because it is possible that initiating supplementation prior to feeding could help to avoid refeeding syndrome or lessen symptoms. Therefore, cases where refeeding syndrome was not directly identified[32,36,38,41] and thiamine supplementation was provided were included due to the possibility of refeeding syndrome developing without supplementation. These cases were included if 1 or more risk factors were present per NICE criteria identified in Table 2. Risk criteria identified in each of the cases or studies can be identified in Table 3. In many cases some criteria were unable to be determined, but a sufficient number of other risk factors were present for inclusion. Of the cases where refeeding syndrome was not directly identified, 3/8[32] or 5/8[36,38,41] of the risk factors were most commonly present or an average of 56% of the risk factors. In comparison, in cases where refeeding syndrome was directly diagnosed, 1/8[29,33] to 7/8[35] risk factors were present with an average of 3.5/8 risk factors present. However, this average was skewed by outliers. In these cases,[28,32,34,37] supplementation improved clinical symptoms but it cannot be determined without a control group if symptoms would be worsened or unresolved without supplementation.

Timing of thiamine supplementation and feeding

NICE guidelines and ASPEN consensus recommend starting thiamine supplementation prior to reintroducing calories.[8,23] Thiamine supplementation and feeding timing were unable to be determined in 4 studies.[32,35,36,41] The majority of cases (7/15)[31,33,34,39] started thiamine supplementation after initiating feeding and symptoms still showed improvement. Four cases started supplementation at the same time as feeding.[29,37,38,40] Of the cases where refeeding syndrome was not directly diagnosed, feeding timed with supplementation was unable to be determined[32,36,41] and in 1 case,[38] supplementation started at the same time as feeding. It is notable that in all cases[32,36,38,41] where refeeding syndrome was not directly diagnosed, electrolyte abnormalities were present. In 1 case,[38] hypophosphatemia present before feeding became more severe within 24 hours of feeding and the initiation of the thiamine supplement. In this case it cannot be determined whether starting thiamine prior to feeding would have had a positive effect on phosphorus or refeeding symptoms.[38] It can also not be determined from the cases identified where refeeding syndrome was diagnosed if supplementation of thiamine prior to refeeding would have affected symptoms or electrolytes. Regardless of supplement timing, all cases showed some improvement with thiamine.

Table 3. Risk Factors for Refeeding Syndrome[a]

Reference	BMI <16 kg/m^2	Unintentional Weight Loss >15% in the Past 3–6 mo	Minimal or No Nutrition Intake ≥10 d	Hypomagnesemia, Hypokalemia, or Hypophosphatemia Prior to Feeding	BMI <18.5 kg/m^2	Unintentional Weight Loss >10% in the Past 3–6 mo	Minimal or No Nutrition Intake ≥5 d	History of Alcohol Use or Diuretics, Chemo, Insulin or Antacids
Peters et al[35]	Y	42% weight loss × 6 mo	Y (restricting intake to <1000 kcal/d majority fruit and vegetables)	Y, hypophosphatemia	Y	Y	Y	UTD
Mushtaq et al[36]	Y	UTD	Y (eating 1 cup yogurt, fruit, and cucumber only)	Y, hypomagnesemia, hypokalemia	Y	UTD, −12.5% × 2 y	Y	UTD
Al Sharkawy et al[34]	Y	UTD	Y, decreased oral intake × 14 d	N (hypophosphatemia within 24 h of hospital feeding)	Y	UTD (over 9 mo weight loss from 50th to 3rd percentile)	Y	UTD
Saad et al[41]	N	UTD	Y, history of restrictive dieting	Y, hypomagnesemia, hypophosphatemia (but hospital nutrition not addressed)	Y	UTD	Y	Y, alcohol
Stanga et al[31] (1)	Y	Y, −17% × 2 wk	Y (only coffee and tea with sugar × 4 mo)	N (hypomagnesemia, hypokalemia, hypophosphatemia after 3 d of feeding)	Y	Y	Y	UTD
Stanga et al[31] (2)	N	UTD	Y (only sips of liquids × 14 d)	N (hypokalemia, hypophosphatemia following feeding)	N	UTD (−35 kg × 4 mo but initial weight not addressed)	Y	UTD
Stanga et al[31] (3)	Y	UTD	Y (only eating apples × 3 y)	Y, hypophosphatemia (hypomagnesemia, hypokalemia, and further hypophosphatemia after feeding)	Y	UTD, −50% × 3 y	Y	UTD
Stanga et al[31] (4)	N	UTD	UTD	N (hypomagnesemia after feeding)	Y	UTD	UTD	Y, alcohol

(*continues*)

Table 3. Risk Factors for Refeeding Syndrome[a] (*Continued*)

Reference	BMI <16 kg/m^2	Unintentional Weight Loss >15% in the Past 3–6 mo	Minimal or No Nutrition Intake ≥10 d	Hypomagnesemia, Hypokalemia, or Hypophosphatemia Prior to Feeding	BMI <18.5 kg/m^2	Unintentional Weight Loss >10% in the Past 3–6 mo	Minimal or No Nutrition Intake ≥5 d	History of Alcohol Use or Diuretics, Chemo, Insulin or Antacids
Vicinanza et al[33]	UTD	UTD	UTD	N (hypomagnesemia, hypokalemia, and hypophosphatemia after feeding)	UTD	UTD	UTD	Y, furosemide
Chiappetta et al[40]	N	N	Y (malabsorption and diet lacking protein)	N (hypomagnesemia, hypokalemia, and hypophosphatemia after feeding)	N	N	Y	Y, diuretics
Yamashita et al[37]	N	UTD	UTD	Y, hypomagnesemia, hypokalemia (hypophosphatemia with initiation of feeding and further hypomagnesemia)	Y	UTD	UTD	Y, chemotherapy
Hershkowitz et al[39]	Y	UTD ("considerable weight loss prior to admit × 1 y")	Y (anorexia prior to admit)	Y, hypokalemia (hypophosphatemia and further hypokalemia after eating)	Y	UTD	Y	UTD
Korbonits et al[38]	N	Y (−25% × 44 d)	Y (44-d fast, water only intake)	Y, hypophosphatemia (more severe hypophosphatemia within 24 h of eating)	N	Y	Y	UTD
Chen et al[29] (Subjects enrolled in study based on NICE risk factors)	Some	Some	Some	Some	Some	Some	Some	Some
Karakonstantis et al[32]	N	UTD	Y (liquid only diet broth, tea, water × 2 mo prior to admit)	Y, hypokalemia	N	UTD (stated −30 kg × 3 mo)	Y	UTD

Abbreviations: BMI, body mass index; Chemo, chemotherapy; N, no; UTD, unable to determine; Y, yes.
[a]Sources: Details from each case presented in Stanga et al[31] are reported individually in the table in order of appearance in the article.

Symptoms of refeeding syndrome

Symptoms of refeeding syndrome that were identified in the cases are addressed in detail in Table 4. Symptoms of wet or dry beriberi indicative of thiamine deficiency were identified. The most common symptom present was edema noted in 68% of cases[29,31,33,34,38-40] (in calculating the percent 11 subjects were used from Chen et al[29] because symptoms were differentiated between participants). Other common symptoms included nausea or vomiting,[29,31,32,34,40] ataxia,[32,35,36,39-41] confusion,[32,33,35-37,39-41] hypotension,[31,35,38,39] Wernicke's encephalopathy,[32,35,36,39,41] weakness,[31,32,35,39,40] anxiety or breathing difficulty,[29,31,35,39,40] and opthalmoplegia.[31,32,35,39-41]

Although the majority of studies identified symptoms indicative of thiamine deficiency, thiamine deficiency was only confirmed biochemically with laboratory values in 5 studies.[31,37-40] In 2 cases,[37,40] deficiency was measured upon admission without follow-up to confirm repletion, and in 1 case,[31] deficiency was confirmed on the second day after feeding and thiamine supplementation started and repletion was not confirmed. In another case, thiamine deficiency was confirmed prior to supplementation but feeding had already been initiated and repletion was not confirmed.[39] Only 1 case confirmed repletion after thiamine deficiency was identified with elevated erythrocyte transketolase activity upon admission prior to feeding.[38] This case found that deficiency resolved and erythrocyte transketolase activity returned to baseline within 3 days of oral intake and 100-mg oral thiamine supplement.[38] Interestingly, despite confirmation that deficiency resolved, in this case, thiamine supplementation was continued long-term for more than 48 days.[38]

Although repletion of thiamine was not confirmed biochemically in most studies, improvement in symptoms was noted. Improvement in symptoms had variable timelines and in 5 cases[31,34,38,40] the researcher was unable to determine timeline for improvement. However, it was identified in 3 of these cases[31,34,40] that symptoms resolved. In 1 case,[31] some symptoms resolved but vertical nystagmus remained. In 4 cases,[31,35,41] thiamine supplementation was associated with almost immediate improvement of symptoms or improvement within 24 hours. Some patients continued to improve after discharge,[35] but in some cases neurological symptoms remained for longer than 30 days[31] and memory deficits were still present at 6-month follow-up.[41] Follow-up time for cases was not the same. In 2 cases,[32,39] symptoms showed improvement within 48 hours of thiamine supplementation, but in 1 case,[32] despite improvement in some symptoms, ataxia remained longer than 18 months. In another case, supplementation was started at a lower dose for 2 weeks without improvement and then showed improvement within 48 hours of starting higher dose supplementation.[33] One case identified some resolution in symptoms after 5 days of supplementation, but some neurological symptoms remained long-term.[37] It is important to note that medically this patient was unstable related to comorbidities including cancer.[37] One case[36] and 1 study[29] found improvement in symptoms after 2 weeks of supplementation, but it is noted that despite clinical improvement 33% of these patients had died at follow-up likely related to other comorbidities. In all cases, supplementation contributed to improvement in clinical symptoms; however, symptoms were not completely resolved in all cases.

DISCUSSION

Despite high prevalence in the hospitalized population, refeeding syndrome continues to lack recognition and defined guidelines for treatment. Based on its mechanism of action, thiamine undoubtedly plays a role although there is a lack of evidence from randomized controlled trials to support its efficacy in refeeding syndrome. The cases identified indicate that thiamine supplementation often contributes to improvement in clinical outcomes and improvement of symptoms. Many of the cases[20,29,35] identify almost immediate improvement in clinical

Table 4. Refeeding Syndrome Symptoms at Admit or During Hospital Stay[a]

Reference	Ataxia	Nystagmus	Confusion, Disorientation	Poor Attention or Memory Impairment	Tachycardia (Heart Rate >100)	Hypotension (<90 Systolic or <60 Diastolic)	Wernicke's Encephalopathy Diagnosed	Bradycardia	Weakness	Difficulty breathing	Ptosis Gaze palsy
Peters et al[35]	Y	Y	Y	Y, bradyphrenia	Y	Y	Y	Borderline prolonged QTc interval	Y	Y	
Mustaq et al[36]	Y	Y	y	Y			Y				Both
Al Sharkawy et al[34]											
Saad et al[41]	Y		Y				Y				
Stanga at al[31] (1)		Y							Y		
Stanga et al[31] (2)					Y	Y, orthopnea				Tachypnea	
Stanga et al[31] (3)					Y					Dyspnea	
Stanga et al[31] (4)						Y					Diplopia
Vicinanza et al[33]			Unconscious at admit					(bradycardia at admit) Prolonged QT interval			
Chiappetta et al[40]	Gait disorders		Y						Y	Respiratory failure	Diplopia
Yamashita et al[37]			Seizures, altered consciousness, unresponsiveness		Y				Y		Anisocoria
Hershkowitz et al[39]	Trembling, unsteady gait		Y	Y		Syncope	Y		Y	Y	
Korbonits et al[38]						Y					
Chen et al[29]										Poor ventilator weaning noted in some	
Karakonstantis et al[32]	Y	Y	Y, dysarthria				Y		Y, fatigue lethargy		Asymmetric lateral rectus palsy

Abbreviations: N, no; QT interval, Q wave and T wave on electrocardiogram; Y, yes.

[a]Sources: Details from each case presented in Stanga et al[31] are reported individually in the table in order of appearance in the article.

symptoms with thiamine supplementation and continued improvement throughout hospital stay with prolonged supplementation. Despite prolonged supplementation in some cases,[20,26,31,35] deficits like nystagmus, ataxia, and neurologic symptoms remained long-term. None of the cases presented indicated harmful or detrimental effects from thiamine supplementation, indicating that even though high-quality evidence is lacking, benefits of supplementation likely outweigh risks. All cases showed some clinical improvement with thiamine supplementation regardless or timing, dosage, and length although this could be related to confounding factors. Despite the paucity of evidence, thiamine supplementation in refeeding syndrome cannot be excluded as a contributing factor to clinical improvement. Some cases of refeeding syndrome excluded from this review demonstrate improvement without thiamine supplementation.[38,39]

The studies presented have strength in the amount of detail provided, which can help clinicians. However, they lack generalizability and comparability, have small sample sizes, and limited statistical power. These limitations in the research make developing guidelines for treatment of refeeding syndrome difficult. Randomized controlled trials are needed, although ethical barriers are a limitation and clinicians have to rely on the available evidence. For example, a randomized controlled trial could not ethically starve patients and withhold treatment like electrolyte correction. In order to improve evidence of refeeding syndrome, researchers would also need to control and standardize other variables that could be affecting the role of thiamine such as a protocol for reintroduction of calories. The NICE guidelines attempt to standardize guidelines but continue to be poorly followed and no cases identified followed NICE guidelines for thiamine supplementation. Consistent dosage, timing of supplementation with introduction of calories, length of supplement, and route of supplementation in studies would make comparative analysis of thiamine more feasible. Current evidence indicates that, regardless of dose and timing, thiamine contributed to improvement of symptoms. One case indicated higher doses are more beneficial because improvement was not shown until a higher dose was administrated.[27]

Few of the cases identified confirmed thiamine deficiency or repletion with laboratory values, which limits validation of supplementation guidelines. Thiamine is a difficult assay requiring a specialized laboratory to obtain,[13] and the timeliness with which refeeding syndrome needs to be managed to avoid death will likely continue to inhibit higher quality studies to address this. Several confounding variables limit studying thiamine. Similar symptoms and contributing factors make differentiating acute thiamine deficiency from deficiency induced by refeeding nearly impossible. However, because of these similarities it cannot be ignored that they are likely closely related and thiamine is beneficial in treatment of refeeding.[19] For example, malnutrition, prolonged inadequate intake, and alcoholism, which are risk factors for refeeding syndrome, are also risk factors for thiamine deficiency. Research is also confounded by overlapping symptoms, which make identifying refeeding syndrome and defining the role of thiamine compared with the contributions of other comorbidities difficult. For example, in patients with CHF on furosemide (a potential risk factor), the CHF, a symptom of both thiamine deficiency and refeeding syndrome, was likely independent of the 2 even though thiamine supplementation improved ejection fraction.[15] Thiamine needs and usage in the individual with refeeding syndrome could also be individualized.[14] For example, on the genetic level human thiamine transporter-2 has genetic differences and can affect intestinal carrier-mediated thiamine uptake and promote deficiency.[14]

Limitation in recognition, diagnosis, and standardization of treatment of refeeding syndrome continues to inhibit research and is also complicated by confounding variables. For example, there are many causes of the electrolyte abnormalities and clinical outcomes found in refeeding syndrome.[5] Low phosphorus, which is often the defining symptom of

refeeding syndrome, can be caused by renal tubular phosphate loss, phosphate binder use, malabsorption, liver disease, alcoholism affecting intake, or IV glucose causing cellular phosphate redistribution.[5]

Ethics is likely the biggest barrier in the advancement of higher quality research on refeeding syndrome because lack of prompt interventions could be fatal. Currently, clinicians need to rely on the evidence available for management. Despite limitations, the case studies included support that thiamine supplementation improves clinical symptoms. The evidence does not suggest a standardized amount to begin supplementation, but the majority of cases initiate supplementation at approximately 200-mg IV and increase dosage if symptoms do not almost immediately start to show some improvement. Timing and length of supplementation also lacks definitive guidelines in the literature, but because supplementation is not harmful, it is likely beneficial to begin supplementation in patients with refeeding syndrome or at risk for refeeding syndrome, as clinical improvement is identified in all cases. Supplementation is often continued throughout hospital stay. The available evidence has not determined if supplementation prior to feeding or prior to refeeding syndrome diagnosis is beneficial in decreasing symptoms or avoiding refeeding syndrome.

CONCLUSION

Refeeding syndrome is often a complication of malnutrition that can be fatal if poorly managed. Thiamine deficiency has a role in clinical symptoms of refeeding syndrome. Refeeding syndrome continues to lack recognition and clear management in the hospital setting, which limits standardized evidence-based treatment. High-quality and conclusive evidence is lacking, but thiamine deficiency could be closely related to refeeding syndrome. No case identified used NICE guidelines for thiamine supplementation, but all found clinical improvement regardless of the amount, timing, or length of thiamine supplementation. Ideally, randomized controlled trials would help to standardize treatment guidelines for refeeding syndrome and thiamine supplementation dosing. Currently, health care professionals must rely on the paucity of evidence available for clinical guidance. Thiamine supplementation is not harmful and clinicians should consider supplementation in patients at risk for or with refeeding syndrome to improve clinical outcomes.

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