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The incidence of the Refeeding Syndrome. A systematic review and meta-analyses of literature

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Abstract

Background & Aims: The refeeding syndrome (RFS) has been recognized as a potentially life-threatening metabolic complication of re-nutrition, but the definition widely varies and, its incidence is unknown. The aim of this systematic review and meta-analyses was to estimate the incidence of RFS in adults by considering the definition used by the authors as well as the recent criteria proposed by the American Society of Parenteral and Enteral Nutrition (ASPEN) consensus. Furthermore, the incidence of refeeding hypophosphatemia (RH) was also assessed.

Methods: Four databases were systematically searched until September 2020 for retrieving trials and observational studies. The incidences of RFS and RH were expressed as percentage and reported with 95% confidence intervals (CI).

Results: Thirty-five observational studies were included in the analysis. The risk of bias was serious in 16 studies and moderate in the remaining 19. The incidence of RFS varied from 0% to 62% across the studies. No substantial change in the originally reported incidence of RFS was found by applying the ASPEN criteria. Similarly, the incidence of RH ranged between 7% and 62%. In the subgroup analyses, inpatients from Intensive Care Units (ICUs) and those initially fed with > 20 kcal/kg/day seemed to have a higher incidence of both RFS (pooled incidence=44%; 95% CI 36% to 52%) and RH (pooled incidence=27%; 95% CI 21% to 34%). However, due to the high heterogeneity of data, summary incidence measures are meaningless.

Conclusion: The incidence rate of both RFS and RH greatly varied according to the definition used and the population analyzed, being higher in ICU inpatients and in those with increased initial caloric supply. Therefore, a universally accepted definition for RFS, taking different clinical contexts and groups of patients into account, is still needed to better characterize the syndrome and its approach.

Keywords: artificial nutritional support, critically ill, eating disorders, inpatients, cohort studies.

Introduction

The refeeding syndrome (RFS) is described as a set of metabolic and electrolyte alterations occurring as the result of the reintroduction of calories through oral, enteral, parenteral nutrition after a period of consistent reduction of energy intake or starvation in individuals with pre-existent malnutrition and/or in a catabolic state [1–3]. The subjects at risk of developing RFS are characterized by reduced insulin secretion and increased glucagon release, with a metabolic shift towards the utilization as energy sources of proteins and fats instead of glucose with resulting muscle mass loss, and a decrease in intracellular vitamins and minerals, particularly phosphate, potassium, and magnesium, due to undernutrition [4]. During replenishment, the supply of nutrients, above all carbohydrates, results in enhanced insulin secretion, stimulating both glycolysis, the synthesis of glycogen, fats, proteins and increased sodium and water retention [5]. The anabolic processes require minerals and coenzymes such as thiamine [4,6]. These changes determine a further depletion of the mineral and vitamin pool (with depletion of ATP), a decrease in urinary sodium and water excretion, and a rapid fluid overload that can lead to congestive cardiac failure, respiratory failure, and impairment in many physiological processes up to death [4,6].

The incidence of RFS is at present uncertain due to heterogeneity of subjects involved and the lack of a universally accepted definition [3,4,7]. Previous systematic reviews [2,8] showed that studies on RFS were highly heterogenous since most definitions were based on blood electrolyte disturbances, mainly refeeding hypophosphatemia (RH), while others considered the presence of overt signs and symptoms as well (i.e., edema, respiratory or heart failure). Consequently, the reported incidence rates varied between 0% and 80% depending on the definition and the population studied [2,8].

In 2006, the National Institute for Health and Clinical Excellence (NICE) published a risk-assessment tool for the definition of the RFS risk [9]. Later, diagnostic criteria and algorithms for the RFS diagnosis based on both electrolyte abnormalities and clinical manifestations have been proposed [5,10,11]. In April 2020, the American Society for Parenteral and Enteral Nutrition (ASPEN) published a consensus recommendation for screening, diagnosis, and treatment of the RFS [1]. Two main criteria for RFS diagnosis were proposed: 1) a decreasing from 10% upwards of serum phosphorus, potassium, and/or magnesium concentrations and/or the presence of organ dysfunction resulting from a reduction in any of these and/or due to thiamin deficiency; and 2) the occurrence of these impairments within 5 days of reinitiating or substantially increasing energy supplies [1,12]. The entity of electrolyte depletion and the presence of organ dysfunction allow to define the severity of the syndrome [1].

The lack of a universally accepted definition, the non-specificity of the clinical manifestations of the RFS, the physician unawareness of the existence of the syndrome, make this potentially serious condition still frequently overlooked [13,14]. Estimating its occurrence is certainly the starting point to sensitize health professionals to suspect and promptly recognize the RFS.

Therefore, the present systematic review and meta-analyses aimed to estimate the incidence of RFS in adults by considering the definition used by the authors as well as the recent criteria proposed by the ASPEN consensus (when applicable). In addition, the incidence of RH was also assessed since it is considered the hallmark of the syndrome. Finally, factors associated with the incidence of RFS, such as its definition, study design, type of population, age, initial caloric intake, and type of feeding were assessed by subgroup analysis.

Materials and Methods

A systematic review of the published literature was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15].

Search strategy

The following electronic databases were queried using a combination of search terms until the 3rd of September 2020: PubMed (National Library of Medicine), EMBASE, Cochrane library and Cumulative Index to Nursing and Allied Health Literature (CINAHL). The construction of the search strategy was performed using database specific subject headings and keywords. Both medical subject headings (MeSH) and free text search terms were employed. The search strategy was performed using the combination of the following terms “refeeding” or “refeeding syndrome” and incidence, anorexia nervosa, critically ill patients, cancer patients, elderly or aged people, inpatients or hospitalized patients, artificial nutrition, mortality, malnutrition, phosphorus, potassium, magnesium, alcoholism, surgery and fasting. The full search strategy is presented in the supplementary material (Table S1). The protocol was registered in the PROSPERO (CRD42020220272).

The limits for search included data from adult subjects, whereas no filters were applied for study design, language, and publication date. The search strategy was implemented by hand searching the references of all the included studies and systematic reviews or meta-analyses on the field.

Eligibility criteria and study selection

The records identified were evaluated independently by two researchers (I.C., M.P.) initially using titles and abstracts. Studies were identified as ‘excluded’ (with reason) or ‘assessed for eligibility’. Any disagreement about inclusion was resolved by discussing with a third review author (V.P.). We selected the studies according to the following characteristics: 1) including adult subjects aged ≥ 18 years who were starting re-nutrition; 2) reporting the definition of RFS adopted; 3) assessing the decline or any changes in serum levels of electrolytes such as potassium, magnesium, and phosphate after the start of refeeding and 4) reporting the incidence rate of RFS or data for its calculation.

Articles were excluded if: i) participants were aged ≤18 years or the study reported a mean age ≤18 years old, ii) their data were based on case reports, audits, or surveys; iii) their results were exclusively focused on refeeding procedure, without giving information on the RFS incidence; iv) data for calculating RFS incidence could not be extrapolated and v) published before 1990.

Outcome

The outcome of this systematic review was to evaluate the incidence of RFS by considering the following definitions: those adopted by the authors, the incidence of RH, and the last one proposed by the ASPEN consensus. Sub-group analyses were performed by evaluating the incidence rate of both RFS and RH according to the following factors: RFS definition, study design, risk of bias, age, diseases or conditions of the participants, the amount of calories initially provided during refeeding (kcal per kilogram of body weight per day) and the type of re-feeding.

Data collection and extraction

Two authors (I.C., V.P.) independently examined participant characteristics and reported data from papers which met the inclusion criteria using specific data extraction templates. From each included study, the following information were extracted: 1) first author name and year of publication; 2) study design and aims; 3) inclusion and exclusion criteria of participants; 4) number of subjects; 5) age, gender and body mass index (BMI) of participants; 6) definition used for the RFS; 7) incidence of the RFS; 8) time of RFS occurrence; 9) serum levels of potassium, phosphorous and magnesium or their changes; 10) the type of the adopted feeding support; 11) the amount of calories supplied; and 12) any clinical signs, symptoms or outcomes pertaining to the RFS.

Risk of bias assessment

The risk of bias assessment for each included study was independently conducted by two authors (F.B., S.B.) using the seven domains of ROBINS-I (Risk Of Bias In Non-randomized Studies of Intervention scale) tool [16]. A judgement for each bias domain, and for overall risk of bias, can be 'Low', 'Moderate', 'Serious' or 'Critical' risk of bias. A judgment of 'Low' indicated that the study is comparable to a well-performed randomized trial; 'Moderate' indicated that the study seems to provide sound evidence for a non-randomized study but cannot be considered comparable to a well-performed randomized trial; 'Serious' indicated that the study has one or more important problems; and 'Critical' indicated that the study is too problematic to provide any useful evidence and should not be included in any synthesis.

Statistical analyses

The pooled incidence of the RFS and of the RH were expressed as percentage with 95% confidence interval (CI). Since some studies reported zero events, the pooled estimates were calculated by using the Freeman-Tukey Double Arcsine Transformation.

Random-effect models were applied to provide a summary estimate. Inter-study heterogeneity was assessed using Cochrane Q statistic and quantified by I^2 test [17].

The source of incidence heterogeneity was explored by performing subgroup analyses according to the study design, risk of bias, participant diseases or conditions, age, calories initially provided and type of re-feeding.

Statistical analyses were performed by using STATA (Stata Statistical Software, Release 14; StataCorp LP, College Station, TX) and "metaprop_one" command to obtain pooled estimates.

Results

A total of 4679 records were identified in the initial literature search. After removing duplicates, 975 records were screened for titles and abstracts, and then, after excluding articles not meeting the inclusion criteria, 107 full papers were assessed for eligibility and 35 articles met the criteria for the inclusion in the analysis. The flowchart relative to the selection process is reported in **Figure 1**. All selected studies had an observational design, 23 were retrospective cohort studies [18–40] and 12 were prospective cohort studies [3,11,41–50]. All details are presented in **Table 1**.

Characteristics of the studies

The number of analyzed participants ranged from 11 [32] to 967 [3] patients; 2 studies [21,25] reported data relative to the group of subjects developing the RFS only. Most studies included inpatients, except for one who enrolled outpatients [50] and another one who included people living in a nursing home [21]. Fifteen studies showed a balanced proportion of males and females [11,21,23–25,27,32,33,35,42–45,47,48]; 9 studies enrolled a greater number of males [3,26,30,34,37,38,41,49,50]; 7 studies on patients with eating disorders (EDs) enrolled mainly [18,28,29,36,39] or exclusively females [20,31]. Four studies did not give information about gender [19,22,40,46].

Seven studies were performed in patients with EDs, mainly anorexia nervosa [18,20,28,29,31,36,39], 6 involved inpatients from Intensive Care Unit (ICU) [22,26,34,38,46,49], 7 examined adults or older adults affected by malnutrition [3,21,32,40,44,45,48], 9 assessed different type of patients from high dependency unit, ICU and wards [11,19,24,27,33,35,37,43,47] and 6 evaluated patients with malnutrition due to different diseases: (chronic obstructive pulmonary disease (COPD) [30], tuberculosis [41], frailty [42], gastrointestinal fistula [25], cancer [50], other unspecified chronic diseases [23].

Age of participants ranged from 18 years old (patients with EDs) [18,31] to over 80 years old [42,45]. Body weight and BMI of participants varied from severe underweight [18,20,21,28,29,31,32,36,39,41] to normal weight/overweight [3,19,23,24,26,30,33,34,36,37,42,44,45,48–50]; and 3 studies [19,24,35] included individuals with obesity. In 9 studies [11,22,25,27,38,40,43,46,47] no information about the weight status of participants was given.

Studies were performed in the following countries: 7 in USA [19,20,26,28,29,35,46], 7 in UK [11,24,27,40,43,47,48], 3 in China [21,25,38], 2 in Australia [18,23], 2 in Israel [42,45], 2 in the Netherlands [34,44], 1 in India [41], 1 in Turkey [22], 1 in Switzerland [3], 1 in Taiwan [30], 1 in

Germany [31], 1 in Spain [32], 1 in Malaysia [49], 1 in Denmark [50], 1 in France [36], 1 in Japan [39], 1 in Singapore [37] and 1 in Brazil [33].

Initial estimates of calorie rates

The initial daily calories provided during refeeding was reported in 24 studies, ranging from 10 kcal/kg [24,38,42] to 34 kcal/kg [21]; in one study [41] 61 kcal/kg were initially provided. Patients were fed by artificial nutrition more frequently. In 7 studies, oral nutrition was administered alone [28,29,31,50] or in combination with oral nutritional supplements [3,50] or with artificial nutrition [23,30,50]. Among studies using artificial nutrition support, parental nutrition (PN) was used in 11 studies [19,24,27,32,33,35,37,43,46–48], enteral nutrition (EN) in 8 studies [18,21,26,38,41,42,45,49], and the combination of PN and EN in 5 studies [11,22,25,34,40]. Four studies did not give any information [20,35,38,44].

Risk of bias assessment

Based on the ROBINS-I assessment of the risk of bias, 16 studies showed a serious risk of bias [18,23–25,27,32,33,37,40–43,45,47,48,50] and the remaining 19 studies had a moderate risk [3,11,19–22,26,28–31,34–36,38,39,44,46,49], as reported in **Table 2**. The observed serious risk of bias was mainly related to the first two domains, bias due to confounding factors and bias due to the selection of participants.

Definition of the refeeding syndrome

The risk of developing the RFS was assessed in 19 studies, as shown in **Table 3**. Specifically, the NICE tool was applied in 17 studies [11,21,23,24,27–29,34,36–38,40,41,43,44,48,50], and the algorithm proposed by Friedli et al. [5] in 2 studies [3,39].

Different definitions were used for identifying the syndrome (**Table 3**). The RFS was defined as a decline in serum level of electrolytes, mainly in phosphate, after the start of refeeding in 26 studies. In 9 studies, the diagnosis was performed in the presence of electrolytes reduction and clinical manifestations, such as peripheral edema, respiratory insufficiency, or heart failure

[3,11,23,25,27,31,39,41,50]. The time required for the RFS occurrence after re-feeding ranged from 1 day [25] to 18 days [39] (in most cases, 5 days) depending on the timing of serum electrolytes assessment. This information was not available in 4 papers [29,35,36,50].

Incidence of the refeeding syndrome

The incidence of RFS varied markedly across the studies, ranging from 0% [23,24,27,31,32,41] up to 62% [43]. As presented in **Figure 2**, pooled data from 35 studies showed a large heterogeneity (I^2> 90%), therefore summary incidence measures are meaningless. Great variations in RFS incidence were evident among studies due to differences in the employed RFS definitions and characteristics of participants. We observed that incidence rates were highly dependent on the definition used. Several studies reported incidence rates lower than 1% when the diagnosis for RFS required the presence of both clinical signs and electrolyte abnormalities [11,23,27,31]. On the other hand, the highest incidence rates (> 50%) were observed in studies recruiting malnourished elderly patients, ICU inpatients [22,43], or using less stringent electrolyte threshold values for the RFS diagnosis [19,20,28,29].

The incidence of RFS has been explored in different subgroups, but the heterogeneity remained large within all subgroups (I2> 80%). In the subgroup analyses, a higher incidence of the syndrome was found in studies employing less stringent criteria, i.e., the use of electrolyte declines only, with respect to those adopting clinical signs as additional criteria [3,11,23,25,27,31,39,41,50] (Figure S1). The highest RFS incidence was found in ICU inpatients, ranging from 17% [38] to 52% [22] (**Figure 3**). Among malnourished individuals, including mostly geriatric patients as well as patients with underlying diseases, the incidence varied from 0% [23,32,41] to 38% [30]. Among patients with EDs (above all, anorexia nervosa) the incidence rate ranged from 0% [31] to 45% [28], with the lowest rate in the study [31] requiring the presence of clinical manifestations for the RFS diagnosis. A similar heterogeneity in RFS incidence rate was found in subgroup analyses based on age range, study design and risk of bias, as reported in the supplementary material (Figure S2, Figure S3 and Figure S4, respectively).

The stratification by initial calories provided during refeeding (>20 kcal/kg/day *vs* ≤20 kcal/kg/day) showed a higher RFS incidence with higher caloric intakes [21,22,26,28,32,36,41,43,46] when compared to lower amounts [3,11,19,23–25,30,35,37,38,42,45,48–50] (**Figure 4**). Apart from 2 studies [32,41] reporting an incidence of 0 (probably because of the different RFS definition) other studies with increased initial caloric provision described the RFS in more than one third of the participants [22,26,28,43,46]. Finally, the use of EN [18,26,30,34,37,42,45,49] seemed to be associated with higher incidence rates (> 15%), except for one study [41] (Figure S5).

ASPEN criteria

The criteria proposed by the ASPEN consensus [1] were applied to estimate the incidence rate of RFS in the selected studies. Fourteen were ineligible due to the lack of the necessary information [28,35,36,50] or because the diagnosis of RFS was performed after 5 days from the start of refeeding [21,23,26,31,32,39,42,45,47,49]. Among the 21 studies eligible for applying the ASPEN criteria, the RFS incidence rates changed in 6 studies only, resulting higher than that reported by the Authors in 5 of them [11,24,27,37,41] and lower in 1 study only [18], as shown in the supplementary material (Table S2 and Figure S6).

Definition and incidence of refeeding hypophosphatemia

Since the presence of RH is considered the main criterion of the syndrome, its incidence has been assessed as well. The diagnosis of RH was based on different cutoff points, which ranged from 0.49 mmol/L [32] to 0.87 mmol/L [20,28,29,39,42], according to the reference values adopted by each laboratory. In addition, 4 studies defined RH as a decrease in serum phosphate by 15% [30] or by 30% [24,39,43] with respect to the baseline values, without providing any cutoff.

Pooled data from 29 studies showed inconsistent results on the incidence of RH, due to a high heterogeneity (I^2> 90%), which varied from 7% [11] up to 62% [43], as shown in **Figure 5**.

Heterogeneity in the RH incidence rates were also found in most subgroup analyses. The RH incidence was high, especially in ICU patients (from 17% up to 52%) and in those malnourished with underlying diseases (24% to 56%), as reported in **Figure 6**. Overall, the subgroup analyses based on age groups (Figure S7), study design (Figure S8) and the risk of bias (Figure S9) showed a similar heterogeneity to that observed in the RFS subgroup analyses. Pooled data according to caloric intake showed an increased RH incidence in studies including patients who starting re-feeding with >20 kcal/kg/day [22,26,28,32,41,43,46] (pooled incidence=44%; 95% CI 36% to 52%) with respect to those providing ≤20 kcal/kg/day [11,19,23,24,30,35,37,38,42,45,48–50] (pooled incidence=27%; 95% CI 21% to 34%; p=0.01; I2=62.1%), as presented in **Figure 7**. The RH incidence rates were similar among individuals fed with EN, mixed, and oral nutrition, while the studies with PN showed a greater heterogeneity, ranging between 7% [11] and 62% [43] (Figure S10).

Discussion

The present study showed that the incidence of RFS is highly dependent on the definition used and the population analyzed, ranging from 0% up to 62%. Similar results were observed for the incidence of RH, which consistently varied across the studies. Patients from ICU and those who were initially fed with more than 20 kcal/kg/day showed a higher incidence of RH and RFS. Unfortunately, owing to the high heterogeneity of data, summary incidence measures are meaningless.

Although the RFS has been firstly described many years ago [51,52], its incidence is still difficult to determine, because there is no universally accepted definition [2,6,13]. Many authors have recognized the presence of RH or even a significant decline in electrolytes after the re-introduction of calories as the hallmark of the syndrome [2,5]. To date, the diagnosis of RFS overlaps with that of RH very commonly [5]. Other authors indeed have argued that relying exclusively on electrolytes disturbances (e.g., on low phosphorus levels) can be misleading [11,23,31,41].

A previous systematic review [2] reported a RFS incidence rate ranging from 0% to 80%, with lower rates in the studies using both clinical and electrolyte abnormalities for RFS diagnosis when compared to those basing exclusively on the electrolyte decline. Accordingly, we found a high heterogeneity in the incidence rate, that resulted to be very low (0-1%) in studies requiring clinical signs as diagnostic criteria [11,23,24,27,31,35,41], and much higher (52-62%) in the presence of definitions based on electrolyte abnormalities only [19,22,43]. It is likely that the definition using clinical signs as additional criteria, being more specific, includes most severe patients, i.e., those who displayed the overt syndrome [11,23,24,27,31,35,41]. As a further complication, the reference values for diagnosing RH greatly differed among studies [2,28,29,32], ranging from 0.49 mmol/L [32] to 0.87 mmol/L [20,28,29,39,42], thus representing an additional cause of heterogeneity of the estimated incidence rates among studies.

Recently, to overcome these discrepancies, the ASPEN Committee has published a consensus recommendation for diagnosing patients with RFS [1], based on decline in electrolytes and/or the related organ dysfunction and/or thiamin deficiencies occurring within 5 days, but without including any signs and/or clinical manifestations associated with RFS. Some doubts about the applicability of these criteria have been recently raised [31] because of their lack of suitability for detecting the syndrome in severely malnourished patients with anorexia nervosa. Applying these criteria to all the evaluated studies was not possible; anyway, with the limit of available data, we observed no substantial change in the originally reported incidence of the syndrome among the studies in which the ASPEN criteria were applied.

Subgroup analyses

Specific groups of patients appear to be at higher risk for developing RFS [12–14] due to their demographic and clinical characteristics. As expected, illness severity and aging were associated with a higher RFS incidence [12,53]. In particular, incidence in ICU inpatients was high, ranging from 17% [38] up to 52% [22], probably because all patients were severely malnourished, and RFS was diagnosed more frequently in the presence of RH, i.e., less stringent criteria. Indeed, the presence of electrolytes abnormalities, especially of low phosphate levels, has been frequently observed in ICU inpatients due to insulin therapy, respiratory alkalosis, increased losses caused by diuretics, continuous renal replacement therapy, mechanical ventilation, sepsis, and other complications [12,54], not necessarily related to the refeeding process. Although these confounding factors have been accounted for by the exclusion criteria [22,34], it seemed inadequate to use the presence of RH alone for detecting RFS in the ICU inpatients [55].

In patients with EDs, the heterogeneity observed was relative to the definition and the cutoff used for the RFS definition [28,29,31]. Moreover, half of the studies have been conducted in specialized center for highly compromised patients with EDs [20,28,29], which were focused on the identification of medical complications related to the refeeding process and were treating more severe cases, potentially contributing to the early diagnosis and higher incidence of the syndrome. A previous systematic review [2] did not find any differences in the RFS incidence between subgroups of anorectic and non-anorectic patients. However, differently from us, the Authors did not consider the syndrome incidence in specific subsets of patients, such as ICU inpatients or malnourished individuals, and included studies performed in adolescents as well.

We failed to find difference in the incidence of RFS by type of study design (retrospective *vs* prospective), overall risk of bias (moderate *vs* serious) or age subgroups (≤60 years *vs* >60 years), suggesting that the severity of the underlying disease or condition might be a more important factor associated with the syndrome.

A higher incidence of both RH and RFS was evident with increased initial caloric provision (> 20kcal/kg/day), pointing up that an initial low-calorie intake can be protective, especially in specific subset of patients. A recent systematic review [8] evaluating the effect of the initial amount of supplied calorie on the incidence of RFS in adult patients in acute settings, showed no difference between ≤20 kcal/kg/day and >20 kcal/kg/day, as well as among the types of feeding (EN, PN, or oral nutrition). However, it is worth noting that the studies included in our systematic review were not the same of the previous review [8] due to different primary endpoints and inclusion criteria. Indeed, in our review, several studies reporting <20 kcal/kg/day initial supply and published very recently have been included [3,18,23,35,37,38,48].

Another recent systematic review on RH incidence in critically ill adults and children showed that calorie restriction during refeeding could attenuate the severity of RH and improve survival, even if these results are affected by the paucity of data [55]. A previous randomized controlled trial performed in 339 ICU inpatients showed that initial caloric restriction (< 20 kcal/kg/day) improved in-hospital, 60 and 90-days survival compared to standard care treatment in the subgroup of patients with RH [56]. Similarly, Olthof et al. [34] observed that, within the RFS group, a lower caloric intake during the first 3 days of refeeding was associated with a reduced 6-month mortality risk. Accordingly, the beneficial effect of starting refeeding with hypocaloric nutrition during the first 72 h, followed by a slow progression to calorie target, is recommended by the ESPEN guidelines in ICU patients, in order to facilitate the control of electrolyte disturbances [57] and improve survival [34,56].

Clinical implications

At present, the RFS is still unrecognized by many physicians, even though it may have fatal complications [13]. To prevent RFS, it is useful to screen patients at risk for RFS before the start of nutritional replacement. Only in half of evaluated studies, an analysis of the risk for RFS was performed; therefore, at present, the lack of suspicion of the syndrome, determined by the fact that the risk of inpatient malnutrition is not evaluated, remains still the first issue.

The lack of a universally accepted definition is a further problem. A reduction in plasma electrolytes during illness per se might be not specific enough for diagnosing the RFS and should be interpreted in the context of the overall individual nutritional and clinical status [2].

The main guidelines [1,9] recommend to start refeeding with a low caloric intake (10-20 kcal/kg/day) in individuals at high risk for RFS, and slowly increase the amounts over 7–10 days. However, the impact of the type and amount of refeeding on the development of RFS is particularly debated in literature, still showing inconclusive results [5,8,55]. Therefore, further randomized controlled studies should be planned to assess the effect of different nutritional strategies, tailored for specific subsets of patients, to identify the optimal approach for preventing the RFS occurrence.

Strength and limitations

The strength of the present systematic review was to provide an update on the RFS and RH incidence rates, by analyzing the most recent papers and performing several subgroup analyses. Furthermore, the recent ASPEN criteria were considered too.

Several limitations, however, should be recognized. First, the high heterogeneity among studies, due to the lack of a universally accepted RFS definition, made it meaningless to estimate a summary mean incidence. The observational nature of the evaluated research, the retrospective design of many of the included studies, the small sample size, as well as their serious risk of bias did not allow to obtain reliable estimates too.

Conclusions

To date, there is still no consensus regarding the RFS definition, and its incidence is therefore difficult to obtain. The findings of this systematic review suggested that specific subgroups of population, such as inpatients from ICU and those initially supplied with higher caloric intakes, might have an increased risk for RFS/RH, but robust evidence is still lacking. Therefore, a universally accepted definition for the RFS is needed for evaluating its incidence and management in different clinical contexts and groups of patients.

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Credit author statement

Iolanda Cioffi: Conceptualization, Data curation, Methodology, Writing- Original draft preparation, Writing - Review & Editing. Valentina Ponzo: Data curation, Writing - Review & Editing. Marianna Pellegrini: Data curation, Writing - Review & Editing. Andrea Evangelista: Formal analysis; Software. Fabio Bioletto: Data curation, Writing - Review & Editing. Giovannino Ciccone: Visualization, Writing - Review & Editing, Supervision. Fabrizio Pasanisi: Visualization, Writing - Review & Editing. Ezio Ghigo: Visualization, Writing - Review & Editing. Simona Bo: Conceptualization, Methodology, Writing- Original draft preparation, Writing - Review & Editing, Supervision.

Conflict of interest

Authors declare no conflict of interest.

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Figure captions

Figure 1. Flow diagram of the literature search process

Figure 2. Incidence of the Refeeding Syndrome (RFS)

The plotted points are the percentage of RFS incidence and the horizontal error bars represent the 95% confidence intervals. The vertical dashed line indicates the pooled estimate of the incidence.

Figure 3. Incidence of the Refeeding Syndrome (RFS) according to the characteristics of patients

The plotted points are the percentage of RFS incidence and the horizontal error bars represent the 95% confidence intervals. The vertical dashed line indicates the pooled estimate of the incidence.

Figure 4. Incidence of the Refeeding Syndrome (RFS) by the amount of the initially provided calories

The plotted points are the percentage of RFS incidence and the horizontal error bars represent the 95% confidence intervals. The vertical dashed line indicates the pooled estimate of the incidence.

Figure 5. Incidence of the Refeeding Hypophosphatemia (RH)

The plotted points are the percentage of RFS incidence and the horizontal error bars represent the 95% confidence intervals. The vertical dashed line indicates the pooled estimate of the incidence.

Figure 6. Incidence of the Refeeding Hypophosphatemia (RH) according to the characteristics of patients

The plotted points are the percentage of RFS incidence and the horizontal error bars represent the 95% confidence intervals. The vertical dashed line indicates the pooled estimate of the incidence.

Figure 7. Incidence of the Refeeding Hypophosphatemia (RH) by the amount of the initially provided calories

The plotted points are the percentage of RFS incidence and the horizontal error bars represent the 95% confidence intervals. The vertical dashed line indicates the pooled estimate of the incidence.

Table 1. Characteristics of the selected studies

Reference	Study design	Population study	N	Study groups	Age (years)	Gender (M/F)	BMI (kg/m²)
Braude et al [18]	Retrospective study	Hospitalized patients with severe AN	95		21.0 ^ (IQR 18.0–29.0)	10/85	17.1±3.8
Braun et al [19]	Retrospective study	Hospitalized adults receiving PN,77% of whom were on surgical units	733	Electrolyte abnormal (EA) (n=431) Normal electrolyte (NE) (n=302)	66.3±0.54° 63.9±0.07°	NR NR	26.5±3.5 30.7±4.1
Brown et al [20]	Retrospective study	Patients with severe AN admitted to the medical stabilization unit for Eds	123	RH (n=41) No-RH (n=82)	28.0 (IQR 23-39)	0/41 0/82	12.3±1.5 13.3±1.5
Chebrolu et al [41]	Prospective study	Adult inpatients with tuberculosis	27		35.0 ^ (IQR 24.5-55.0)	19/8	15.2 ^ (IQR 14.3-17.1)
Chen et al [21]	Retrospective study	Patients within a high-risk group for developing RFS or with prolonged starvation	56	RFS (n=11) No-RFS (n=45)	67.9 ± 19.3 NR	7/4 NR	16.7 ± 3.8 NR
Coskun et al [22]	Retrospective study	Adult patients treated in the ICU for longer than 48 h, and received either EN or PN	117	RH (n=61) No-RH (n=56)	64.8 ± 17.9 66.8 ± 15.3	NR NR	NR NR
Dror et al [42]	Prospective study	Hospitalized geriatric patients	53	Cases (n=27): refeeding by EN after prolonged starvation Controls (n=26): fed by EN for more than 3 months	84.5 ± 5.0 82.5 ± 6.0	11/16 10/16	23.0 ± 4.4 24.6 ± 4.9
Drysdale et al [23]	Retrospective study	Adult inpatients at risk for RFS	70		61.0 ± 20.0	39/31	22.0 ± 6.7
Elnenaei et al [24]	Prospective study	Consecutive inpatients referred for starting PN	35		53.0 ± 3.3°	19/16	22.5±4.0
Fan et al [25]	Retrospective study	Inpatients with gastrointestinal fistula	158	RFS (n=15) No-RFS (n=143)	46.3 ± 11.5 NR	9/6 NR	NR NR
Friedli et al [3]	Prospective analysis of RCT	Inpatients at nutritional risk with an expected length of hospital stay ≥5 days	967	RFS (n=141) No-RFS (n=826)	73.0 ^ (IQR 63.0- 80.0) 74.0 ^ (IQR 64.0-82.0)	84/57 440/386	24.6 ± 4.9 25.3 ± 5.5

Reference	Study design	Population study	N	Study groups	Age (years)	Gender (M/F)	BMI (kg/m^2)
Fuentes et al [26]	Retrospective study	Adult patients admitted to the surgical ICUs who received EN for at least 72 hours	213	RFS (n=83) No-RFS (n=130)	62.0 ^ (IQR 51-73) 64.0 ^ (IQR 51-77)	54/29 98/32	25.4 ^ (IQR 22.5-28.4) 27.0 ^ (IQR 23.0-31.0)
Fung et al [27]	Retrospective study	Hospitalized adult patients receiving PN	57		59.1± 16.9	35/22	NR
Gaudiani et al [28]	Retrospective study	Patients with severe AN admitted to the medical stabilization unit for EDs	25		26.0±7.0	3/22	13.1^ (IQR 11.0-14.4)
Gaudiani et al [29]	Retrospective study	Patients with severe AN admitted to the medical stabilization unit for EDs	142	Group 1: > 30y (n=78) Group 2 30-40y (n=32) Group 3 >40y (n=32)	23.0 ^ (IQR 20.0–26.0) 33.0 ^ (IQR 32.0–36.0) 48.0 ^ (IQR 47.0–56.0)	12/66 2/30 1/31	12.7±1.7 13.2±1.5 13.2±1.9
Goyale et al [43]	Prospective study	Patients referred for PN admitted to different units	52		55.0 ^ (IQR 44.0-59.0)	28/24	NR
Jih et al [30]	Retrospective study	Inpatients with acute exacerbation of COPD	61	RFS (n=23) No-RFS (n=38)	75.3 ± 10.8 67.2 ± 14.8	22/1 37/1	20.7 ± 2.2 24.3 ± 2.3
Koerner et al [31]	Retrospective study	Adult female patients with AN	103		23.8±5.3	0/103	<13
Kraaijenbrink et al [44]	Prospective study	Patients acutely admitted to the Department of Internal Medicine	178		66.8 ±17.4	94/84	24.4 ±6.4
Lubart et al [45]	Prospective study	Geriatric inpatients with prolonged (> 3 days) and progressive feeding difficulties after starting EN via NGT	40		81.0±5.0	16/24	23.0±7.0
Luque et al [32]	Retrospective study	Patients with moderate to severe malnutrition who received ≥ 5 days of TPN and who were at risk for the RFS	11		64.0 (95% CI: 53.5-74.5)	7/4	15.4 (95% CI: 14.8-16.0)
Marik et al [46]	Prospective study	Critically ill inpatients from ICU	62	RH (n=21) No-RH (n=41)	65.0±17.0 66.0 ±15.0	NR NR	NR NR

Reference	Study design	Population study	N	Study groups	Age (years)	Gender (M/F)	BMI (kg/m²)
Marvin et al [47]	Prospective study	Adult inpatients started PN	250		63.0 (Range: 18.0-92.0)	136/114	NR
Md Ralib et al [49]	Prospective study	Adult patients admitted to ICU for at least 48 hours	109	RH (n=44) No-RH (n=65)	52.0±18.0 50.0±17.0	28/16 40/25	27.8±8.6 26.8±5.6
Meira et al [33]	Retrospective study	Inpatients receiving PN	197	RFS (n=50) No RFS (n=147)	59.3±11.5 56.1±16.7	110/87	24.8±5.9 23.2±5.5
Olthof et al [34]	Retrospective study	Adult critically ill patients mechanically ventilated for > 7 days in a mixed medical-surgical ICU and fed by EN or PN	337	RFS (n=124) No-RFS (n=213)	66.4±13.2 66.6±13.6	74/50 137/76	26.6±5.7 27.2±5.5
Pantoja et al [48]	Prospective study	Adult inpatients requiring TPN	80		55.8 ± 17.3	39/41	22.2 ± 4.6
Rasmussen et al [50]	Prospective study	Adult patients (both in- and outpatients) with HNC	54		59.7±11.8	37/17	25.4±5.0
Rio et al [11]	Prospective study	Patients from different units started on enteral or parenteral nutritional support	243		57.0 ^ (IQR 44.0–69.0)	130/113	NR
Solomon et al [35]	Retrospective study	Inpatients receiving ≥2 consecutive days of PN	595	Old group (≥65 y) (n=245) Young group (<65 y) =350	76.0 ^ (IQR 70.0–81.0) 53.0 ^ (IQR 42.0–58.0)	122/123 170/180	26.0 ^ (IQR 23.1–30.8) 26.3 ^ (IQR 21.7–32.9)
Vignaud et al [36]	Retrospective study	AN patients admitted to ICUs	68		31.0±12.0	6/62	12.0±3.0
Wong et al [37]	Retrospective study	ICU inpatients treated with PN for at least 48 hours	149		Range 62.0–66.0	101/48	Range 21.8-22.7
Xiong et al [38]	Retrospective study	Neurocritical patients at nutritional risk receiving full EN	328		56.5 ± 16.5	229/99	NR
Yamakazi et al [39]	Retrospective study	Inpatients with EDs	142		29.8 ± 11.9	5/137	14.3 ± 2.9
Zeki et al [40]	Retrospective study	Adult patients fed by PN or NGT	321		62.0 ± 18.3	NR	NR

Data are expressed as mean ± SD, unless otherwise specified (° SE; ^ median value). AN (anorexia nervosa); CI (confidence interval); COPD (Chronic obstructive pulmonary disease); EN (enteral nutrition); ED (eating disorder); HNC (head neck cancer); ICU (intensive care unit); IQR (interquartile range); NGT (nasogastric tube); NR (not reported); PN (Parenteral Nutrition); RH (refeeding hypophosphatemia); RFS (refeeding syndrome); SD (standard deviation); SE (Standard error).

Table 2. Risk of bias assessment

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in measurement classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall*
Braude et al [18]	Serious	Moderate	Low	Low	Low	Low	Low	Serious
Braun et al [19]	Moderate	Low	Moderate	Low	Low	Moderate	Low	Moderate
Brown et al [20]	Moderate	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
Chebrolu et al [41]	Serious	Low	Moderate	Serious	Serious	Serious	Moderate	Serious
Chen et al [21]	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Coskun et al [22]	Moderate	Moderate	Low	Low	Moderate	Low	Low	Moderate
Dror et al [42]	Serious	Moderate	Moderate	Low	Low	Low	Low	Serious
Drysdale et al [23]	Serious	Moderate	Moderate	Low	Moderate	Low	Low	Serious
Elnenaei et al [24]	Low	Serious	Low	Low	Moderate	Low	Low	Serious
Fan et al [25]	Moderate	Serious	Low	Low	Unknown	Low	Low	Serious
Friedli et al [3]	Low	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
Fuentes et al [26]	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Fung et al [27]	Moderate	Serious	Moderato	Low	Low	Moderate	Low	Serious
Gaudiani et al [28]	Low	Moderate	Low	Low	Low	Low	Low	Moderate
Gaudiani et al [29]	Moderate	Moderate	Moderate	Low	Moderate	Low	Low	Moderate
Goyale et al [43]	Moderate	Serious	Low	Low	Moderate	Low	Low	Serious
Jih et al [30]	Moderate	Low	Moderate	Low	Low	Moderate	Low	Moderate
Koerner et al [31]	Moderate	Moderate	Moderate	Low	Low	Low	Low	Moderate
Kraaijenbrink et al [44]	Low	Moderate	Low	Low	Low	Moderate	Low	Moderate
Lubart et al [45]	Moderate	Serious	Serious	Low	Low	Serious	Low	Serious

Luque et al [32]	Serious	Serious	Serious	Low	Low	Low	Low	Serious
Marik et al [46]	Moderate	Low	Unknown	Low	Low	Low	Low	Moderate
Marvin et al [47]	Serious	Serious	Low	Low	Moderate	Low	Low	Serious
Md Ralib et al [49]	Moderate	Moderate	Moderate	Low	Low	Low	Low	Moderate
Meira et al [33]	Serious	Serious	Low	Low	Serious	Low	Low	Serious
Olthof et al [34]	Moderate	Moderate	Moderate	Low	Low	Moderate	Low	Moderate
Pantoja et al [48]	Moderate	Serious	Moderate	Low	Serious	Serious	Low	Serious
Rasmussen et al [50]	Moderate	Serious	Moderate	Low	Low	Low	Low	Serious
Rio et al [11]	Moderate	Moderate	Low	Low	Moderate	Moderate	Low	Moderate
Solomon et al [35]	Moderate	Moderate	Low	Low	Low	Moderate	Low	Moderate
Vignaud et al [36]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Wong et al [37]	Moderate	Serious	Moderate	Low	Moderate	Low	Low	Serious
Xiong et al [38]	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
Yamakazi et al [39]	Moderate	Moderate	Low	Low	Low	Unknown	Low	Moderate
Zeki et al [40]	Serious	Moderate	Low	Low	Unknown	Low	Low	Serious

*Overall assessment derived from the seven domains of ROBINS-I (Risk Of Bias In Non-randomized Studies -of Intervention scale) tools

Table 3. Definition used for the refeeding syndrome

Study	Screening for RFS	Definition adopted for identifying the RFS	Main outcome	Occurrence (days)
Braude et al [18]	-	Decline in phosphate levels after refeeding.	Electrolytes	4
Braun et al [19]	-	Decline in serum levels of electrolytes.	Electrolytes	3
Brown et al [20]	-	Decline in serum phosphorus levels from baseline.	Electrolytes	4
Chebrolu et al [41]	NICE	Decline in phosphate levels along with a change in physical exam, electrolytes, or electrocardiogram.	Electrolytes + clinical signs	3
Chen et al [21]	NICE	Decline in phosphate levels after refeeding.	Electrolytes	5-8
Coskun et al [22]	-	Decline in serum levels of electrolytes.	Electrolytes	7
Dror et al [42]	-	Decline in serum phosphorus levels from baseline.	Electrolytes	7
Drysdale et al [23]	NICE	Based on the Rio diagnostic criteria: severely low-serum electrolyte concentrations, acute circulatory fluid overload, and organ dysfunction.	Electrolytes + clinical signs	7
Elnenaei et al [24]	NICE	Decline in phosphate levels after refeeding.	Electrolytes	7
Fan et al [25]	-	Symptoms and signs of electrolyte disturbances after starting refeeding.	Electrolytes + clinical signs	1
Friedli et al [3]	Friedli, 2018	Based on electrolyte concentrations in conjunction with clinical symptoms (peripheral edema, respiratory insufficiency, or heart failure) after the start of nutrition	Electrolytes + clinical signs	3
Fuentes et al [26]	-	Decline in serum phosphorus levels from baseline.	Electrolytes	8
Fung et al [27]	NICE	Decline in electrolytes with fluid balance changes based on Crook [10]	Electrolytes + clinical signs	3
Gaudiani et al [28]	NICE	Decline in phosphate levels after refeeding.	Electrolytes	<5
Gaudiani et al [29]	NICE	Decline in phosphate levels after refeeding.	Electrolytes	NR
Goyale et al [43]	NICE	Decline in phosphate levels after refeeding.	Electrolytes	<2
Jih et al [30]	-	Decline in phosphate levels after refeeding.	Electrolytes	4
Koerner et al [31]	-	Decline in serum phosphate levels, including other metabolic markers, and critical deterioration of the general conditions (e.g., severe edema, pericardial effusion, and weakness).	Electrolytes + clinical signs	7

Kraaijenbrink et al [44]	NICE	Decline in phosphate levels after refeeding.	Electrolytes	< 5
Lubart et al [45]	-	Decline in serum electrolytes after starting refeeding.	Electrolytes	2-3
Luque et al [32]	-	Decline in serum electrolytes after starting refeeding.	Electrolytes	7
Marik et al [46]	-	Decline in phosphate levels after refeeding.	Electrolytes	2
Marvin et al [47]	-	Decline in phosphate levels after refeeding.	Electrolytes	7
Md Ralib et al [49]	-	Decline in phosphate levels after refeeding.	Electrolytes	7
Meira et al [33]	-	Decline in phosphate levels or two electrolytes after refeeding.	Electrolytes	3
Olthof et al [34]	NICE	Decline in phosphate levels after refeeding.	Electrolytes	3
Pantoja et al [48]	NICE	Decline in phosphate levels after refeeding.	Electrolytes	4
Rasmussen et al [50]	NICE	Defined as any decline in phosphate levels in conjunction with any of the following clinical symptoms: edema, confusion, dyspnea, hypotension, arrhythmia, and seizures.	Electrolytes + clinical signs	NR
Rio et al [11]	NICE	Based on the Rio diagnostic criteria: severely low-serum electrolyte concentrations, acute circulatory fluid overload, and organ dysfunction.	Electrolytes + clinical signs	3
Solomon et al [35]	-	Decline in phosphate levels after refeeding.	Electrolytes	NR
Vignaud et al [36]	NICE	All adverse events occurring during nutritional rehabilitation of patients with malnutrition or a prolonged fast.	Electrolytes	NR
Wong et al [37]	NICE	Decline in phosphate levels after refeeding.	Electrolytes	3 – 7
Xiong et al [38]	NICE	Decline in phosphate levels after refeeding.	Electrolytes	3
Yamakazi et al [39]	Friedli, 2018	Decline in phosphate levels after refeeding.	Electrolytes + clinical signs	18
Zeki et al [40]	NICE	Decline in phosphate levels after refeeding.	Electrolytes	< 4

NICE (National Institute for Health and Clinical Excellence); NR (not reported); RFS (refeeding syndrome).