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# Hypophosphataemia and parenteral nutrition; biochemical monitoring, incidence and outcomes

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Introducing artificial nutrition support is important for patients who are malnourished or cannot meet their nutritional demands independently during their hospital stay.[1] Parenteral nutrition (PN), intravenous feeding of the patient, should be considered when enteral intake is inadequate or unsafe, or when the gastrointestinal tract is inaccessible or non-functional. A multidisciplinary approach and close patient monitoring is important for patients on PN. A 2006 publication by the National Institute for Health and Clinical Excellence (NICE) in the UK provides guidelines for early detection of patients at risk of malnutrition.[1]

The refeeding syndrome (RFS) is a life-threatening and unfortunately under-diagnosed condition and this may be defined as 'severe electrolyte (including hypophosphataemia) and fluid shifts associated with metabolic abnormalities in malnourished patients undergoing refeeding whether orally, enterally or parenterally'.[2,3] More recently the associated refeeding hypophosphataemia (RH) has been described.[4–8] Refeeding hypophosphataemia (RH) can be defined as the hypophosphataemia following refeeding and in our laboratory, the lower cut-off limit for serum phosphate is 0.80 mmol/L. The aim of this current study was to assess biochemical monitoring for hypophosphataemia during parenteral feeding including incidence and clinical outcomes.

This retrospective case review study was approved by the hospital audit committee (ethics committee approval was not necessary) and was carried out on all hospitalised adult patients newly receiving PN (Braun or Kabi nutrition suppliers) from January 2008 to September 2010. Patients on PN were identified from pharmacy and also dietician referral records or the laboratory results system. Access to patient case files and dietetics records provided details pertaining to diagnosis, indications for PN, the level of biochemistry monitoring and any complications incurred as well as biochemical data and also fluid balance. The RFS was defined as by Crook et al. [3] and more specifically hypophosphataemia <0.80 mmol/l and hypomagnesaemia (<0.7 mmol/L) and hypokalaemia (<3.5 mmol/L) with fluid balance changes.

The study institution is a large inner city district general hospital and the nutrition team consisted of a dietician, pharmacist, gastroenterologist and metabolic/biochemistry physician. All routine biochemical analyses were performed on an Abbott Architect analyser; assay coefficients of variation (CV) <5%. All statistical analyses were performed in Microsoft Excel 2010 and SPSS version 17.0. Categorical data were analysed by Fisher's exact test. Parametric and non-parametric data were analysed using Student t-tests and Mann–Whitney U tests, respectively. Between-group comparisons of quantitative data were analysed using ANOVA tests followed by *post hoc* Games–Howell tests. Statistical significance was set at $p < 0.05$.

From an original total of 62 adult patients referred to the nutritional support team, 5 (8.1%) were considered inappropriate (as based upon NICE guidelines 1) at the time of assessment and were not started on PN, giving a total of 57 patients eligible for the study. The mean age was 59.1 years (SD = 16.9) with a male preponderance of 61.4% ($n = 35$, $p = 0.112$). PN requests originated mainly from intensive care unit (ITU); ($n = 33$, 57.9%), followed by warded surgical patients ($n = 15$, 26.3%) and medical patients ($n = 9$, 15.8%).

An increased risk of RFS was specifically documented during PN assessment in 40.4% ($n = 23$) of cases, all of whom had a reduced rate of PN infusion given as a result. Prophylactic vitamins, including thiamine, in the form of Pabrinex as prescribed in the British National Formulary were documented in 59.6% ($n = 34$) of cases.

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The median duration of patients on PN was 7.5 days (range 1 – 89 days). At baseline or day 0, the monitoring rates for serum sodium, potassium, phosphate and magnesium were 98.2% (*n*=56), 98.2% (*n*=56), 89.5% (*n*=51), and 87.7% (*n*=50), respectively. By day 3, daily consecutive monitoring of serum sodium, potassium, phosphate and magnesium had declined to rates of 87.7% (*n* = 50), 87.7% (*n* = 50), 66.7% (*n* = 38) and 26.3% (*n* = 15), respectively.

Serum phosphate concentrations fell significantly within the first day of starting PN, from a median value of 1.04 mmol/L at baseline (range 0.51–2.05 mmol/L) to 0.89 mmol/L (range 0.47–1.74 mmol/L, $p = 0.013$). The fall in serum phosphate persisted at day 2 (median 0.84mmol/L, range 0.38–1.75 mmol/L) and day 3 (0.84 mmol/L, range 0.43–1.56 mmol/L) upon starting PN. At baseline, 15.8% (*n* = 9) of our patients were already hypophosphataemic (normal range 0.8–1.5 mmol/L). The exclusion of these patients from analysis did not alter the above findings, indeed it accentuated the reduction in the serum phosphate concentrations, from a baseline median value of 1.13 mmol/L to 0.91 mmo/L ($p = 0.004$), to 0.84 mmol/L at day 3 ($p < 0.001$, Figure 1).

In our data-set, 45.6% of patients (*n* = 26) on TPN eventually died during their hospital stay. They were all included in the analysis. Patients who died had a higher starting serum phosphate compared to the survivors group (median 1.18 mmol/L vs. 1.03 mmol/L, respectively although not statistically significant). We highlighted the significant drop in serum phosphate which was observed from day 1 onwards for all patients (see Figure 1, where * refers to statistically significant drop in serum phosphate compared to day 0). Upon splitting the data-set into survivors vs. died groups, the drop in serum phosphate in day 1 when compared to baseline, was no longer statistically significant ($p = 0.103$ in died group, $p = 0.08$ in survivor group). The drop in serum phosphate becomes statistically significant only on day 2 and day 3.

We did not find any documented evidence of severe hypophosphataemia (serum phosphate <0.30 mmol/L) occurring in any of the study cohort throughout their stay in hospital.

None of our study cohort (*n* = 57) had daily consecutive serum phosphate monitoring up to day 7. Indeed we saw a sharp decline in the rates of serum phosphate monitoring at day 4 (28.1%, *n* = 16) compared to day 3 (66.7%, *n* = 38). Excluding patients who were hypophosphataemic prior to starting PN (*n* = 9), the incidence of refeeding hypophosphataemia within 3 days of starting PN (defined as serum phosphate <0.80 mmol/L) in our study was 39.6% (19 out of 48). No specific group appeared to be at risk of developing refeeding hypophosphataemia upon starting PN. Patients identified earlier as at risk of developing RFS during pre-PN assessment were no more likely to develop refeeding hypophosphataemia

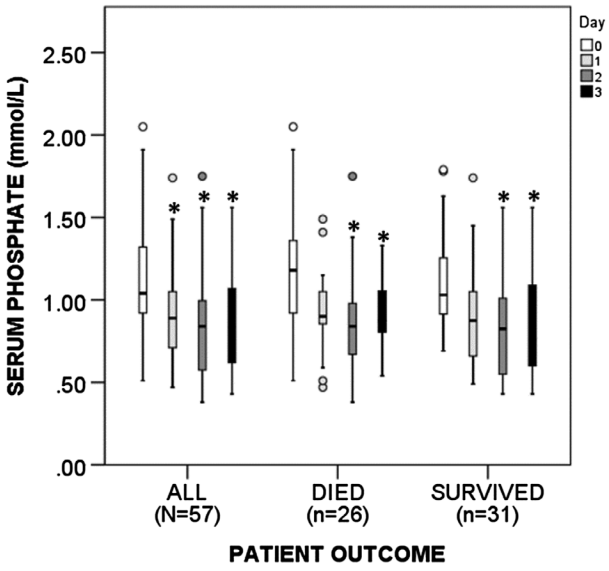


**Figure 1.** Serum phosphate levels during the study period.

($p = 0.566$), but as we noted earlier, they all had their PN cautiously infused at a lower rates in the outset.

In addition to hypophosphataemia, hypomagnesaemia (<0.7 mmol/L), hypokalaemia (<3.5 mmol/L) and hyponatraemia (<133 mmol/L) were present at 28.1% (*n* = 16), 7.0% (*n* = 4) and 8.8% (*n* = 5) of patients, respectively. There was no documented evidence of RFS in the 57 patients on PN. The mortality rate in our cohort of patients was 49.1% (*n* = 28). Of the survivors, 82.8% (*n* = 24) were discharged on a normal oral diet. The remaining group (17.2%, *n* = 5) were transferred to a different hospital on PN. The current study also showed that >90% of NICE [1] recommended biochemical monitoring tests were carried out in these patients and we believe that the presence of a multi-discipline nutrition team helped achieve this high take-up.

In this study, we have shown that hypophosphataemia occurs in PN patients and as such our findings are novel and add to the literature on this topic. PN was considered appropriately and used in a majority of the cases (91.9%) referred to the nutrition support team according to NICE guidance [1] and is in keeping with other studies although these did not report specifically on RH.[9–11] As a complication of PN, RFS lacks clear, universally accepted, operational definition that which seriously hampers research into the subject.[3,12,13] A hospital PN policy and nutrition support team may also play a role in identifying those at risk and reducing the incidence of RFS.

Most of the reported cases of RFS tend to occur within 3–5 days of starting PN.[3] Since hypophosphataemia is generally accepted as an early manifestation of RFS, it can be used to monitor the condition.[2] Even so, hypophosphataemia in the event of PN or EN, or refeeding hypophosphataemia as it is called, have different cut-offs of serum phosphate concentration in different

studies with no universally accepted definition at the time of writing. Our incidence rate for patients developing hypophosphataemia within 3 days of starting PN was 39.6%. By ascribing a different criterion for RH (a fall by more than 0.16 mmol/L to below 0.65 mmol/L) used by another study,[14] our RH rate was 29.2% compared to 34% reported by that study. This similarity existed despite the different methodology used (prospective vs. retrospective) and case-mix (ICU patients vs. ICU and ward patients) between their study and ours. Indeed, hypophosphataemia during PN is typically sub-clinical; its detection relies heavily on serum phosphate monitoring. Another factor that may overestimate the incidence of RH in our audit was the incidence of hypophosphataemia independent to PN being erroneously classified as RH during the period of monitoring. ICU patients may have a number of factors predisposing to hypophosphataemia such as sepsis, mechanical ventilation, respiratory alkalosis and medication (including insulin, adrenaline, salbutamol and dextrose containing intravenous fluids).[15,16] Nonetheless, the presence of these factors particularly in the presence of hypophosphataemia may indicate the patient is at an increased risk of developing RFS.[4]

We observed 15.8% of all our PN patients were hypophosphataemic before starting their PN. None of our patients developed severe hypophosphataemia (<0.3 mmol/L) during the course of their PN. Rapid correction of hypophosphataemia is indicated by the presence of severe hypophosphataemia, or any hypophosphataemia accompanied by symptoms and signs such as arrhythmias, heart failure, muscle weakness, seizures and haemolysis.[17–20] However, hypophosphataemia per se does not appear to be an independent predictor of in-hospital mortality in ICU patients [17] and there is no study to date that has shown correction of RH by phosphate supplementation that has an impact on hard patient outcomes.

There were limitations of this study aside of the relatively small number of heterogeneous patients. The retrospective nature may also introduce an under-reporting bias in events surrounding the PN. Factors promoting phosphate retention such as acute or chronic kidney disease may also mask RH, which was not examined in this study.

In summary, we did not encounter any RFS but we found incident hypophosphataemia in 39.6% of our patients. An increased awareness of RFS and the involvement of a nutrition support team may play a role in reducing the incidence of RFS. Recommendations for improvements include closer monitoring of serum biochemistry tests in ward patients started on PN and input by a multi-disciplinary nutrition team.[19] As Zeki et al. [20] showed RH is more common in adults with enteral feeding than PN feeding possibly due to the incretin response due to glucose gastrointestinal absorption. We conclude that biochemical abnormalities should be carefully monitored for in PN patients and in particular hypophosphatemia should be looked out for and treated appropriately.

## Abbreviations

EN: enteral nutrition
NCEPOD: National Confidential Enquiry into Patient Outcome and Death
NICE: National Institute for Health and Clinical Excellence
PN: parenteral nutrition
RFS: refeeding syndrome

## Disclosure statement

The authors declare that there are no conflicts of interest.

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