

# Incidence of hypophosphataemia in patients on parenteral nutrition

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— OBJECTIVE — To determine the effect of parenteral nutrition on plasma phosphate levels and to evaluate the incidence of refeeding hypophosphataemia.

— SUBJECTS AND SETTING — 250 adult patients started consecutively on parenteral nutrition (PN) were monitored at The Royal Surrey County Hospital, a 530-bed, non-teaching, secondary care trust incorporating medical and surgical care, paediatrics, intensive care, maternity services and a regional cancer centre.

— DESIGN — Data on plasma levels of magnesium and phosphate, relevant interventions performed and nutrition outcomes was collated by the Trust Nutrition Support Team.

— RESULTS — 36 patients (15 per cent) were found to be hypophosphataemic before commencing PN. 86 patients (34.4 per cent) developed refeeding hypophosphataemia within seven days after commencing PN. It was considered severe (less than 0.5mmol/L phosphate) in 10.8 per cent. Refeeding hypophosphataemia reached a nadir at three days and recovered in over 75 per cent of patients within 10 days without intervention. Cancer patients appear to be at greater risk than non-cancer patients for developing refeeding hypophosphataemia. Plasma magnesium levels did not mimic phosphate levels.

— CONCLUSION — Recognition of hypophosphataemia and the development of guidelines for its management in the care of PN patients are important.

**R**efeeding syndrome is a major cause of hypophosphataemia in hospital inpatients. It is defined as “severe electrolyte and fluid shifts associated with metabolic abnormalities in malnourished patients undergoing refeeding, whether orally, enterally or parenterally”.<sup>1</sup> After a period of fasting (the length of which is not well defined, but might be as little as 48h),<sup>2</sup> gluconeogenesis and protein catabolism are promoted and a negative protein balance occurs. When feeding with glucose is re-established (for example, when parenteral nutrition [PN] is given) the cellular uptake of phosphate, magnesium and potassium is promoted, causing the concentration of these minerals in the plasma to decrease. Plasma concentrations of thiamine are decreased and fluid and sodium balance are also affected.

Hypophosphataemia generally occurs after one to two days of PN in patients who were malnourished before being given PN, and after three to five days in those who were “normally nourished”.<sup>3</sup> Hypomagnesaemia would be expected to accompany phosphate depletion in malnourished patients,<sup>4</sup> but it is not known whether magnesium levels reduce in line with phosphate levels in those not significantly malnourished at the start of PN.

Although hypophosphataemia has long been recognised as perhaps the most important aspect of refeeding syndrome,<sup>5</sup> it is not always appreciated by prescribers of PN.<sup>6,7</sup> It would also appear that it cannot always be prevented using best current practice and serious cases continue to be reported.<sup>8-10</sup>

It should also be noted that, when a plasma sample is reported below the normal range, before refeeding hypophosphataemia is diagnosed, other causes of hypophosphataemia need to be taken into account, as do the duration of the hypophosphataemia and the temporal association with starting PN.

We were unsure of the frequency of refeeding problems among the patients in our hospital receiving PN. Moreover, guidance as to when to treat any fall in phosphate levels is lacking. There is also debate about how much phosphate to give. Since 1994, the British National Formulary has recommended, giving 9mmol phosphate every 12h, based on a small study.<sup>11</sup> However, reports of instances where a larger amount

has been given safely in certain patient groups have been published.<sup>12-14</sup>

A study was therefore undertaken in which patients receiving PN at The Royal Surrey County Hospital, Guildford (RSCH) were monitored in order to determine:

- The number of patients receiving PN who develop refeeding hypophosphataemia
- Whether any initial drop in plasma phosphate concentration in response to refeeding was sustained over the period that patients received PN
- Whether there is any correlation between plasma magnesium and plasma phosphate concentrations

Further aims of the study included the identification of risk factors for developing hypophosphataemia and the production of updated guidelines for medical staff at RSCH on the biochemical tests required before and during PN in specific patient groups.

## Method

All adult patients who were started on PN during a 28-month period between 2003 and 2005 were invited to take part in the study. When first visited by the RSCH nutritional support team, patients were given information about the process of delivering and monitoring PN and consent to use their biochemical data in the study and to hold the results (anonymised) on a database for future statistical analysis was requested. Providing consent was received, patient data from medical notes, prescribing and administration charts, dietetic records and laboratory reports (see Panel 1, p167) were recorded by a member of the nutritional support team onto the parenteral nutrition recording form and then entered anonymously onto an SPSS database (SPSS version 14). Blood samples were collected by members of the phlebotomy service and analysed by staff at the pathology laboratory service. The data contained in the laboratory reports is set out in Panel 1 (p167). Local ethics committee approval for the study was obtained.

In order to determine whether certain patient groups were more prone to hypophosphataemia, Pearson chi-squared

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## Panel 1: Data contained on laboratory reports

Baseline blood levels (ie, before starting parenteral nutrition [PN]) and blood levels during PN treatment of:

- Potassium, sodium, calcium, magnesium, phosphate, urea, creatinine, alanine transaminase, alkaline phosphatase and bilirubin — all analysed daily for five days and then three times a week.
- Albumin, C-reactive protein and triglycerides — all analysed weekly
- Glucose — analysed daily. Four-hourly blood strip analysis was also carried out at first if necessary, depending on insulin requirements.

analysis was performed for the following groups:

- Male patients, compared with female patients
- Patients on the intensive care unit, compared with those on general wards
- Patients diagnosed with cancer, compared with those who were not
- Patients who were receiving PN following surgery, compared with those receiving it for another reason

**Phosphate concentrations:** The phosphate concentrations used in the study to indicate the degree of phosphate depletion were:

- Reference range (ie, normal): 0.80–1.40mmol/L
- Mild hypophosphataemia: 0.65–0.79mmol/L
- Moderate hypophosphataemia: 0.50–0.64mmol/L
- Severe hypophosphataemia: 0.30–0.49mmol/L
- Very severe hypophosphataemia: less than 0.30mmol/L

Patients were deemed to have developed refeeding hypophosphataemia if they had had a period of 48h or more without food before PN was started and if a reduction of 0.15mmol/L or more, to <0.80mmol/L, was detected from their baseline phosphate level in the first seven days of PN. The lowest phosphate concentration recorded during the first seven days of PN was used to determine the degree of hypophosphataemia.

## Results

A total of 250 (136 male and 114 female) adult inpatients were started on PN over the study period. All gave their consent to take

part in the study. The mean age was 63 years (range 18–92 years). Almost half of patients (49 per cent) had undergone surgery during their stay, 44 per cent were diagnosed with cancer, 8 per cent were diabetic and 40 per cent were being treated in the hospital's ICU for the course of their PN. Of the ICU patients, six were also on continuous haemofiltration with phosphate-free dialysis fluid.

### Baseline phosphate concentrations

Plasma phosphate concentrations were obtained in the 48h period before starting PN (ie, baseline phosphate levels) for 236 patients. These showed that 26 patients (11 per cent) were hyperphosphataemic (ie, plasma phosphate >1.4mmol/L). A total of 36 patients (15 per cent) were hypophosphataemic (ie, plasma phosphate <0.8mmol/L). All other patients had baseline blood phosphate concentrations within the reference range before starting PN.

Likely causes of baseline hyperphosphataemia included renal failure, (12 patients), parathyroid surgery (one patient) and over-treatment with intravenous phosphate (two patients). For the remaining patients, the recorded hyperphosphataemia might have been an artefact, since a high level was found on only one occasion.

Causes of baseline hypophosphataemia were thought to include receiving glucose infusion(s) (six patients), receiving insulin infusion(s) (three patients), malabsorption (three patients) and respiratory alkalosis (one patient).

**Phosphate levels during PN** In the first week after starting PN, serial plasma phosphate results were available for 235 of the 236 patients for whom baseline phosphate concentrations were available. A total of 126 patients had low blood phosphate concentrations recorded at some time between Day 1 and Day 7 of PN. The lowest recorded phosphate concentration was 0.17mmol/L — this patient died less than seven days after PN was started. In 33 cases, the cause of hypophosphataemia was not refeeding because there had been no period (48h or more) of impaired nutrition before PN started.

Of the 110 patients with cancer, 70 had some degree of hypophosphataemia, compared with 58 of the 125 non-cancer patients. The Pearson chi-squared test indicated that a cancer diagnosis is a risk factor for hypophosphataemia in patients on PN ( $P=0.008$ ), the relative risk being 1.46 (95 per cent CI 1.09–1.95). No significant difference in the incidence of hypophosphataemia was observed between ICU/general ward patients ( $P=0.338$ ), surgical/non-surgical patients ( $P=0.116$ ) or male/female patients ( $P=0.120$ ).

In seven patients whose baseline phosphate levels had been low, plasma phosphate

concentrations actually increased after PN was started. One of these patients was developing acute renal failure, two received separate supplements of intravenous phosphate and four patients improved with only the standard (18–30mmol per 24h) phosphate in their PN bag.

### Incidence of refeeding hypophosphataemia

A total of 86 patients (34.4 per cent) were deemed to have developed refeeding hypophosphataemia. In 13 of these patients, baseline phosphate levels had been below the normal range, and fell further. All other patients had had phosphate levels above 0.8mmol/L. Further information about the degree of hypophosphataemia experienced by those patients who developed refeeding hypophosphataemia is set out in Table 1.

The median for the plasma phosphate nadir was three days after starting PN (range one to seven days). It should be noted that, for seven patients who had hypophosphataemia after PN started, baseline phosphate levels were not available, and so an assessment of whether these patients developed hypophosphataemia as a result of refeeding could not be made.

### Recovery from hypophosphataemia

Details about the pattern of recovery from hypophosphataemia are listed in Table 2, p168.

For 12 patients with moderate to severe hypophosphataemia, their plasma phosphate concentration was still low after seven to 10 days. In one of these patients, the plasma phosphate concentration remained the same (0.56mmol/L) and, in the remainder, the concentrations rose but were still within the moderately hypophosphataemic range. None of the patients with severe hypophosphataemia remained severe. However in one patient with very severe hypophosphataemia, follow-up plasma phosphate concentrations were not known because of the withdrawal of active treatment and investigations.

**Table 1: Incidence and degree of hypophosphataemia in patients who developed refeeding hypophosphataemia**

Degree of hypophosphataemia	Number of patients (%)
Mild	23 (9.2)
Moderate	36 (14.4)
Severe	25 (10.0)
Very severe	2 (0.8)

The plasma phosphate concentrations that correlate to the various degrees of hypophosphataemia are indicated in the text

**Table 2: Pattern of recovery from hypophosphataemia on PN**

Degree of hypophosphataemia (No of patients)	Number of patients in whom plasma phosphate concentrations:			
	Recovered without supplementation	Recovered after supplementation	Were unknown at 7–10 days	Remained below 0.80mmol/L
Mild (49)	28	0	21	0
Moderate (48)	30	1	11	6
Severe (27)	17	5	0	5
Very severe (2)	0	0	1	1

The plasma phosphate concentrations that correlate to the various degrees of hypophosphataemia are indicated in the text. Supplementation involved a patient receiving a phosphate infusion (50mmol over 24h). Patients who were not given separate supplementation received 18–30mmol per day of phosphate from their parenteral nutrition (PN) alone.

**Magnesium levels** Concentrations of plasma magnesium were found to be low (ie, below the reference range of 0.7–1.0mmol/L) in 30 of the 79 patients who developed refeeding hypophosphataemia and whose magnesium levels were measured. The following should be noted:

- Plasma magnesium concentrations of 10 of these 30 patients were low before PN was started
- Plasma magnesium concentrations in the two patients who developed refeeding hypophosphataemia and developed very severe hypophosphataemia were normal throughout the study
- In total, plasma magnesium concentrations fell in 20 of the 86 patients (23 per cent) who developed hypophosphataemia as a result of refeeding
- Of the 33 patients who had hypophosphataemia after starting PN, but which was deemed not to be refeeding hypophosphataemia, eight patients (24 per cent) also had hypomagnesaemia

## Discussion

**Incidence of hypophosphataemia and refeeding hypophosphataemia** Previous studies have shown a wide range of incidence of refeeding hypophosphataemia in patients receiving nutritional support. For example, in a study of 158 patients who received either enteral or parenteral nutrition following an intestinal fistula, the incidence was found to be 9.5 per cent.<sup>15</sup> Another study showed that moderate to severe hypophosphataemia occurred in 34 per cent of 62 ICU patients in a US hospital (reference range 0.84–1.58).<sup>2</sup> In addition, a Spanish research group found that the incidence of hypophosphataemia was 16 per cent.<sup>16</sup> French researchers found hypophos-

phataemia in 63 per cent of surgical patients.<sup>17</sup>

When considering severe (and very severe) hypophosphataemia only, other studies have shown an incidence of between 0.97 per cent (<0.32mmol/L)<sup>2</sup> and 1.7 per cent (<0.4mmol/L).<sup>16</sup>

The wide variation in the incidence of hypophosphataemia most likely results from a combination of factors. These include:

- Differing reference ranges used to define hypophosphataemia
- Inclusion of patients fed enterally as well as parenterally
- Inclusion of groups of patients who have putative risk factors for developing hypophosphataemia, such as cancer
- Inclusion of patients who have established risk factors for developing hypophosphataemia (eg, those taking medicines such as antacids, bisphosphonates, glucocorticoids, insulin and some antivirals)
- Selection bias (eg, studies that rely on a retrospective analysis of laboratory data might be expected to find a higher incidence of hypophosphataemia because patients with a history or risk of developing the condition are more likely to have blood samples taken for biochemistry analysis and therefore be included).
- Differing amounts of phosphate consumed or given before PN is started
- Differing amounts of phosphate contained in PN

**Risk factors for developing hypophosphataemia** We found that there was an increased risk of hypophosphataemia in cancer patients. We are unaware of any other published research about this in PN patients.

In our study, we did not find that patients on ICU were any more prone to hypophosphataemia than patients on general wards. This is possibly surprising, given that ICU patients might be more likely to have, for

example, concomitant disease associated with reduced plasma phosphate concentrations. However, ICU patients are perhaps more likely to receive timely interventions to correct any low plasma phosphate levels than those in general wards. Further analysis of data in the present study might be able to show whether this is the case and might identify other risk factors.

### Correlation between plasma magnesium and plasma phosphate concentrations

There was no clear link between plasma magnesium and phosphate concentrations, suggesting that the hypomagnesaemia developed by some patients was caused by factors other than refeeding syndrome.

### Guideline development

Local practice guidelines had previously been developed to try and prevent refeeding problems. These advocated the monitoring of electrolytes, glucose and circulatory volume before and during refeeding and, where possible, correcting any abnormalities before starting PN, (which can usually be achieved within 12–24 hours).<sup>1</sup> The problem with this approach is that deficits of potassium, magnesium and phosphate may not be corrected adequately without commencing some intake of calories, and patients remain at risk of refeeding syndrome even if their plasma levels appear “normal”. Another issue is that the fluid and sodium load necessary to deliver potassium and phosphate can add to the patient’s risk of developing cardiac symptoms with refeeding syndrome. The National Institute for Health and Clinical Excellence advocates starting PN as soon as possible and not “correcting” abnormal biochemistry first.<sup>18</sup> This advice, together with the findings from this study that hypophosphataemia is not generally prolonged and that plasma phosphate concentrations rise to normal in most patients on PN without intervention, have been taken into account in updating the local guidelines. Other changes made to guidelines and policies include:

- The section in the local clinical guidelines booklet on PN has been updated to improve the ease in which biochemical tests are ordered
- A section of the guidelines on the treatment of hypophosphataemia has been prepared
- A PN policy has been agreed by the RSCH NHS trust which contains sections on refeeding syndrome

It should be noted that a complication in developing guidelines is whether to take account of the phosphate contained within the lipid in PN (typically 6–7.5mmol). Conventionally, the phosphate content of PN, including that within lipids, is considered to be 100 per cent bioavailable.<sup>19</sup> However,

there is little evidence that patients, especially the critically ill, can use the lipid phosphate, and so it is difficult to know whether to include it in calculations. Either way, additional phosphate (ie, other than that within lipids) is necessary to provide the recommended daily amount (of 17.5mmol) and there is typically a total of 18 to 30 mmol phosphate in the majority of modern compounded solutions.

**Limitations** This study was performed in a heterogeneous group of adult patients, most of whom were receiving PN following surgery. Although the findings are generalisable, it might be difficult to link risk factors to causation.

Blood phosphate concentrations are a measure of total plasma inorganic phosphate, which generally accounts for just 0.1 per cent of total body phosphate or less. The concentrations therefore do not necessarily correlate with the development of clinical symptoms, until levels drop significantly. They are, nevertheless, seen as a useful marker of phosphate depletion.

In addition, there is no real national consensus about what concentration of plasma phosphate constitutes, for example, severe hypophosphataemia. For our study, we therefore adapted parameters used in other studies.<sup>14</sup> Had we chosen different parameters, some of our results might have been different.

**Future work** Further analysis of the data has been carried out to determine whether any risk factors could be determinant for refeeding syndrome, including the amounts of phosphate given in PN. It is hoped that analysis of the data will show how long a period of undernutrition or “nil by mouth” is determinant for refeeding syndrome.

## Conclusion

All 250 patients on PN over 28 months were recruited to the study and relevant biochemistry results were available for almost 90 per cent of patients. Over a third of patients receiving PN developed refeeding hypophosphataemia, which was severe in 10.8 per cent of cases. The nadir was found to be Day 3. Most patients did not require intervention to resolve their low phosphate levels because they rose during the next seven days with continuing PN. Cancer patients on PN may be more at risk of hypophosphataemia than others.

Falls in magnesium levels mimicked falls in phosphate levels in less than a quarter of identified cases of refeeding hypophosphataemia.

## References

1. Crook MA, Hally V, Panteli JV. The importance of the refeeding syndrome. *Nutrition* 2001;17:632–7.
2. Marik PE, Bedigian MK. Refeeding hypophosphataemia in critically ill patients in an intensive care unit. A prospective study. *Archives of Surgery* 1996;131:1043–7.
3. Brooks MJ, Melnik G. The refeeding syndrome: an approach to understanding its complications and preventing its occurrence. *Pharmacotherapy* 1995;15:713–26.
4. Weisinger JR, Bellorin-Font E. Magnesium and phosphorus. *Lancet* 1998;352:391–6.
5. Ritz E. Acute hypophosphataemia. *Kidney International* 1982;22:84–94.
6. Marinella MA. The refeeding syndrome and hypophosphataemia. *Nutrition Reviews* 2003;61:320–3.
7. Hearing SD. Refeeding syndrome. *BMJ* 2004;328:908–9.
8. Duerksen DR, Papineau N. Electrolyte abnormalities in patients with chronic renal failure receiving parenteral nutrition. *Journal of Parenteral and Enteral Nutrition* 1998;22:102–4.
9. Shadaba A, Paine J, Adlard R, Dilkes M. Re-feeding syndrome. *Journal of Laryngology and Otology* 2001;115:755–6.
10. Slodkowski M, Rubinsztajn R, Cebulski W, Krasnodebski-Ireneusz W. A case report of severe hypophosphataemia in the course of refeeding syndrome. *Polski Merkuriusz Lekarski* 2004;17(102):638–9.
11. Vannatta JB, Whang R, Papper S. Efficacy of intravenous phosphorus therapy in the severely hypophosphatemic patient. *Archives of Internal Medicine* 1981;141:885–7.
12. Terlevich A, Hearing SD, Woltersdorf WW, Smyth C, Reid D, McCullagh E et al. Refeeding syndrome: effective and safe treatment with Phosphates Polyfusor. *Alimentary Pharmacology and Therapeutics* 2003;17:1325–9.
13. Perreault MM, Ostrop NJ, Tierney MG. Efficacy and safety of intravenous phosphate replacement in critically ill patients. *Annals of Pharmacotherapy* 1997;31:683–8.
14. Charron T, Bernard F, Skrobik Y, Simoneau N, Gagnon N, Leblanc M. Intravenous phosphate in the intensive care unit: more aggressive repletion regimens for moderate and severe hypophosphataemia. *Intensive Care Medicine* 2003;29:1273–8.
15. Fan CG, Ren JA, Wang XB, Li JS. Refeeding syndrome in patients with gastrointestinal fistula. *Nutrition* 2004;20:346–50.
16. Llop Talaveron JM, Comas Sugranes D, Badia Tahull MB, Saez Fernandez A, Jodar Masanes R, Gomaz Saez JM. hypophosphataemia in parenteral nutrition: prevention and associated risk factors. *Nutricion Hospitalaria* 2004;19:362–6.
17. Zazzo JF, Troche G, Ruel P, Maintenant J. High incidence of hypophosphataemia in surgical intensive care patients: efficacy of phosphorus therapy on myocardial function. *Intensive Care Medicine* 1995;21:826–31.
18. National Institute for Health and Clinical Excellence. Nutrition support in adults. Oral nutrition support, enteral tube feeding and parenteral nutrition. Clinical Guideline. London: NICE; Feb 2006.
19. Pineault M. TPN in very low birth weight infants with Travasol blend C. *Journal of Parenteral and Enteral Nutrition* 1986;10:296–9.