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(RESEARCH ARTICLE)

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An audit on the management of hypophosphataemia on the wards in a district general hospital in the UK

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Abstract

Hypophosphataemia or low serum phosphate, if severe can be life-threatening. However, mild hypophosphataemia is quite common and usually asymptomatic. Symptomatic hypophosphataemia (normal: 0.8-1.5 mmol/L) is usually observed when serum phosphate falls below 0.3 mmol/L. Complications may include myopathy, rhabdomyolysis, respiratory failure. cardiac arrhythmias, cardiomyopathy, acute heart failure. delirium, seizures, metabolic encephalopathy and coma. Severe hypophosphataemia can also be related to anaemia, infection, osteomalacia, insulin resistance, ileus and renal tubular failure. Therefore, an audit was carried out for 1 month at the beginning of 2024 to find out whether hypophosphataemia was properly managed on the wards in accordance with the prevailing Guidelines. The findings suggested that although blood tests for Parathyroid hormone (PTH), Cortisol and 24 hours urinary phosphate were done in a small number of patients, in most cases, the management of hypophosphataemia was adequate.

Keywords: Hypophosphataemia; Hypomagnesaemia; Parathyroid hormone; Fibroblast Growth Factor 23; Calcitriol

1. Introduction

80-85% of the body phosphate is in the bones and the remaining amount in the soft tissues and blood. Parathyroid hormone, FGF23 and calcitriol (renal calcitriol synthesis is both dependent on and independent of PTH) play the key mechanisms in maintaining the phosphate levels.

There are four major mechanisms by which hypophosphataemia can occur (1):

(1). Intracellular redistribution of phosphate from extracellular fluid (respiratory alkalosis, refeeding syndrome, drugs such as insulin, adrenaline, sepsis, malignancy, diabetic ketoacidosis, surgery, liver failure), (2). Reduced absorption of phosphate- inadequate intake, chronic diarrhoea, vitamin D deficiency, use of antacids and phosphate binders, (3). Phosphaturia (hyperparathyroidism, alcohol abuse, drug therapy e.g. Diuretics, Aminoglycosides, Steroids, Theophylline, Antiretrovirals, Ferinject), (4). Dialysis and Haemofiltration, and (5) X-linked hypophosphataemic rickets- loss of function or mutation of PHEX gene resulting in excess Fibroblast Growth Factor 23 (FGF23) production with increased phosphaturia and decreased calcitriol production (2).

Ferinject or ferric carboxymaltose may disproportionately inhibit degradation of fibroblast growth factor 23 (FGF23), which can result in increased FGF23 activity and ultimately greater renal phosphate wasting (3). Hypomagnesaemia by means of renal tubular dysfunction, elevated PTH levels and cellular redistribution can contribute to hypophosphataemia. Targeted molecular therapy, bone modifying agents and metastases to bone in advanced cancer account for hypophosphataemia in cancer.

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Aim of the audit

Hypophosphataemia is frequently encountered on the wards. Severe hypophosphataemia can cause serious health problems and therefore it was necessary to find out whether the patients while being on the wards with hypophosphataemia were adequately managed.

2. Material and methods

Patients who were on different wards between the end of December 2023 and the end of January 2024 and had low serum phosphate levels were studied on HIS (Health Information system) for the purpose of the audit. The latest Guidelines of Royal Cornwall Hospital, Gloucester and Greater Glasgow and Clyde were considered while preparing the audit (1,4,5). No National Guideline is available.

Criteria for the audit (1,4,5,6):

- Check U&E and serum magnesium Useful initial tests include checking serum electrolytes (potassium, bicarbonate, magnesium, and calcium) to assess for renal tubular disease or extrarenal causes. Hypokalaemia and Hypomagnesaemia can cause hypophosphataemia
- Check Vitamin D and PTH
- Document if the Hypophosphataemia is mild, moderate or severe
- To establish the cause of hypophosphataemia: Check whether the patients are on Diuretics, Ferinject, Theophylline or have Chronic Alcoholism or Malabsorption
- Measure Morning Cortisol/Exclude Cushing's (hypophosphataemia is present in 17% cases)
- Check 24 hours urinary Phosphate
- Look for the symptoms and signs of hypophosphataemia
- Document if the patient has Cardiac failure, peripheral oedema or renal impairment
- Consider Preanalytical cause or analytical interference cause: Postprandial sample, Respiratory alkalosis and Paraproteinaemia/Multiple Myeloma- Pseudohypophosphataemia (Multiple Myeloma can also cause true hypophosphataemia secondary to acquired Fanconi syndrome)
- If the correct dose of phosphate- oral or IV is given
- Serum phosphate, potassium, calcium, magnesium and sodium levels should be monitored every 12-24 hours during IV phosphate administration
- Monitoring BP (for hypotension) and ECG for Cardiac arrythmias during IV phosphate replacement
- Referral for specialist management is advised if the cause of hypophosphataemia remains uncertain, severe (<0.3 mmol/L), or symptomatic, or if there is a family history or the patient has short stature or skeletal deformities consistent with rickets- Genetic Referral is required (if X-linked hypophosphataemic rickets is suspected); referral may be needed to Gastro or Renal as appropriate.

3. Results

- Total: 25 patients
- Age: 40-49 =3, 50-59 =5, 60-69 =1, 70-79 =6, 80-89 =9, >90 =1

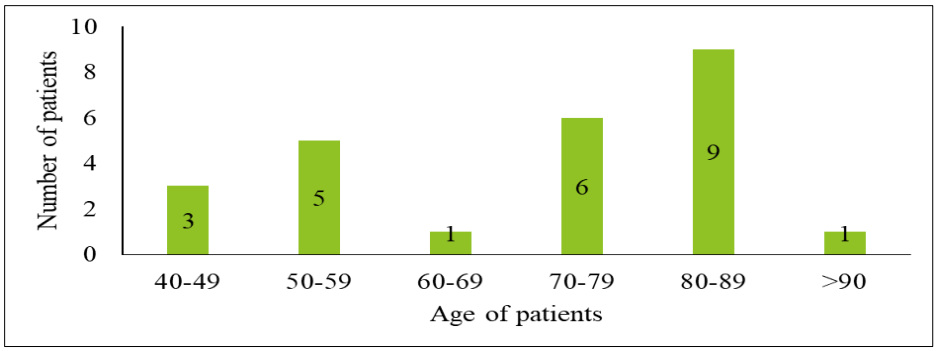

Figure 1 Age Distribution

- Gender distribution. Male: Female – 11:14

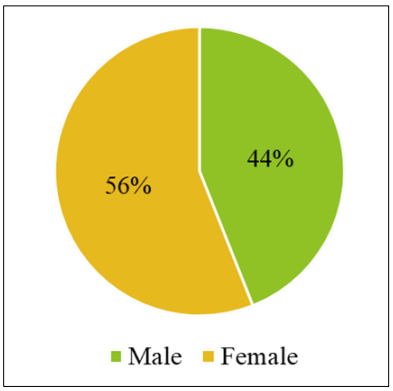

Figure 2 Gender Distribution

- Classification: Mild (>0.6), Moderate (0.3-0.6), Severe (<0.3) = 14 (56%), 9 (36%), 2 (8%)

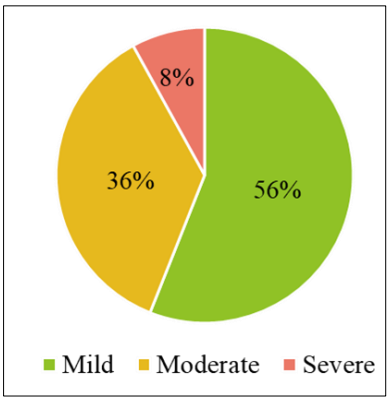

Figure 3 Classification of hypophosphataemia

- Whether Potassium, Magnesium and Calcium were checked: 25 patients (100%); Magnesium was low in 12 patients
- Whether bicarbonate was checked: 2 patients (8%)
- Whether Vitamin D and PTH (Parathyroid hormone) were checked: Vitamin D: 21 patients (84%), PTH: 8 patients (32%); Vitamin D was normal in 8 patients

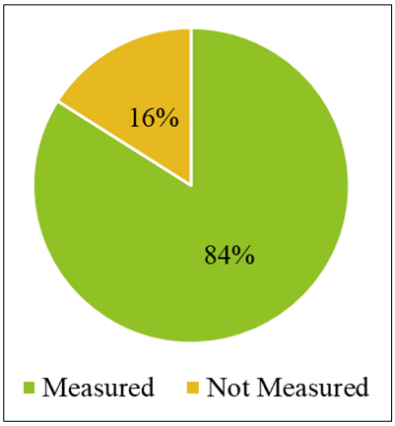

Figure 4 Measurement of Vitamin D

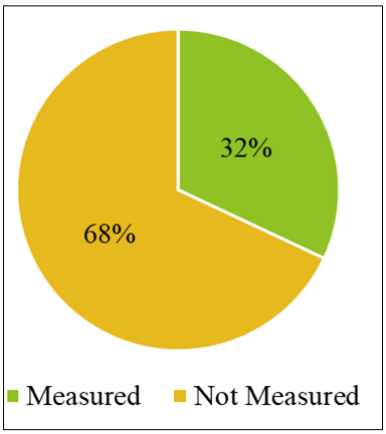

Figure 5 Measurement of parathyroid hormone

- Whether Morning Cortisol was checked to exclude Cushing's: 2 patients (8%)
- Symptoms and signs of hypophosphataemia present: 5 patients (20%)
- Whether it was documented if the patients had Cardiac failure, peripheral oedema or renal impairment: HF: 5 patients (20%), eGFR <30: 2 patients (8%)
- Whether 24 hours urinary Phosphate was measured: 2 patients (8%)- levels were 72.8 mmol/24 hrs and 20.3 mmol/L/24 hrs (N: 15-50) respectively

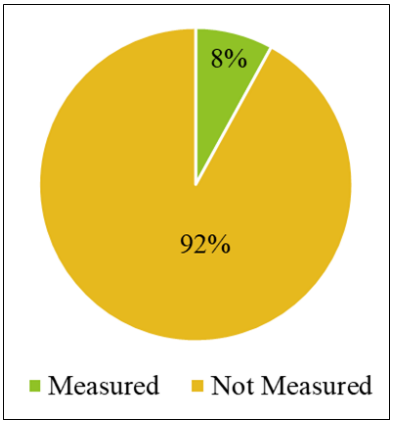

Figure 6 Measurement of 24 hours urinary phosphate

- If the cause of hypophosphataemia was mentioned: on Diuretics, Ferinject, Antacids, Theophylline for Asthma – Not accurately documented but there were reasons for hypophosphataemia in all cases (100%)- Diuretics: 4 patients, Ferinject: 1 patient, Theophylline:1 patient, Primary Hyperparathyroidism:2 patients, Gaviscon: 2 patients
- If the patients had Chronic Alcoholism: 5 patients (20%)

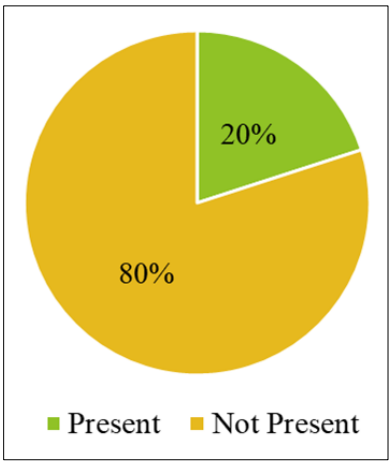

Figure 7 Patients with Chronic alcoholism

- If it was documented whether the blood sample was Post prandial or Paraproteins were measured (Spurious Hyponatraemia): None (0%)
- No of patients requiring oral or IV Phosphate- Oral: 11 patients (44%), IV: 8 patients (32%); others either required no phosphate treatment or treated with Vitamin D supplements

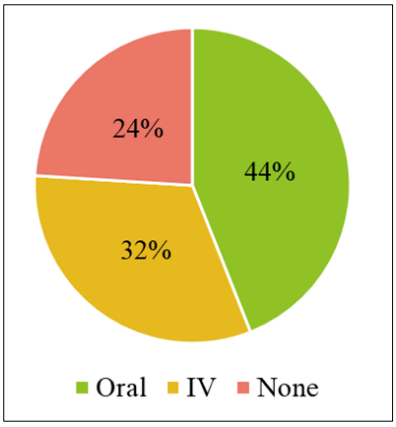

Figure 8 Route of Phosphate supplementation

- If the correct dose of phosphate- oral or IV was given: Oral phosphate correct dose- 11/11 (100%), IV phosphate correct dose given -Severe 2/2 (100%), Moderate 4/6 (67%)
- If serum phosphate, potassium, calcium and magnesium and sodium levels were monitored every 12-24 hours during IV phosphate administration- all the electrolytes were checked after 24 hours: 8/8 (100%)
- Whether BP (for hypotension) was monitored, and ECG done (for Cardiac arrythmias) during IV phosphate replacement: BP monitored in all cases 8/8 (100%), Mention of ECG the next day- 4/8 patients (50%)
- Referral for specialist management was advised if the cause of hypophosphataemia remained uncertain, severe (<0.3 mmol/L), or symptomatic: Endocrinology: 5 patients (either symptomatic or phosphate very low)
- If there was a family history or the patient had short stature or skeletal deformities (consistent with X linked hyphosphataemic rickets) - Genetic Referral was thought to be required- None documented
- Whether a referral had been done to Gastroenerology/Renal as appropriate: Gastroenterology: 8 patients (32%), Renal: none (0%)

4. Discussion

Treatment of hypophosphataemia is as follows (1,4,5,6,7): (a) Mild hypophosphataemia (0.6-0.8 mmol/L): If the patient is asymptomatic- no treatment is required; if the patient is symptomatic- oral phosphate replacement is necessary, (b)

Moderate hypophosphataemia (0.3-0.6 mmol/L): If the patient is asymptomatic- oral phosphate replacement is necessary; if the patient is symptomatic- IV phosphate replacement is necessary and (c) Severe hypophosphataemia (<0.3 mmol/L): IV phosphate replacement is necessary.

Oral Phosphate Sandoz tablet contains Phosphate (16.1 mmol), Sodium (20.4 mmol) Potassium (3.1 mmol) Dose is 1 to 2 tablets three times a day; Phosphate Sandoz Effervescent Tablets should be dissolved in 50- 70ml of water and taken orally.

Intravenous phosphate replacement is required in: symptomatic moderate hypophosphataemia (0.3 - 0.6 mmol/l), severe hypophosphataemia (< 0.3mmol/l) and in patients unable to tolerate oral supplements or if oral phosphate is unlikely to be absorbed (e.g., diarrhoea, patients with short bowel syndrome). Doses for intravenous phosphate replacement vary in the literature. Suggested regimens include a range of 0.2 - 0.5mmol/kg/day up to a maximum of 50mmol in 24 hours. Increased doses are normally only necessary in critically ill patients. Phosphate is renally cleared and therefore Phosphate (especially via the intravenous route) should be used with caution in patients with renal impairment. Phosphate Polyfusor IV 500ml comprises of Phosphate 50 mmol, Sodium 81mmol and Potassium 9.5 mmol and therefore should be administered with caution to patients with cardiac failure, peripheral or pulmonary oedema, impaired renal function or conditions predisposing to hyperkalaemia due to the potassium and sodium content of Phosphate Polyfusor. Patients with hypocalcaemia should have their calcium corrected before replacing phosphate to prevent further hypocalcaemia. Repetition of the dose is necessary if within 24 hours an adequate level (>0.6 mmol/L) has not been achieved. Hypotension, hyperphosphataemia, hypocalcaemia, hypernatraemia, dehydration and metastatic calcification are possible adverse effects of intravenous phosphate therapy. Sodium Glycerophosphate 21.6% IV is the second line choice if Phosphate Polyfusor is not available and 20ml has 20 mmol of phosphate and 40 mmol of sodium (5).

5. Summary and Conclusion

- In our study out of 25 patients-14 had mild, 9 had moderate and 2 had severe hypophosphataemia
- Serum Magnesium was checked in all cases, Vit D was checked in 21(84%) patients, PTH in 8 (32%) patients and Bicarbonate in 2 (8%) patients
- Signs and Symptoms in relation to hypophosphataemia were mentioned in 5 patients
- 24 hours Urine phosphate excretion was measured in 2 patients (8%)
- All patients had one or multiple causes of hypophosphataemia- 1 was on Ferinject, 2 had Primary Hyperparathyroidism
- 5 patients had history of Chronic Alcoholism
- 8 patients- required IV phosphate- 2 patients with phosphate below <0.3mmol/L received phosphate polyfusor infusion, out of 9 patients with moderate hypophosphataemia, 6 received IV infusion of which 4 received the correct dose
- There was no mention of ECG monitoring in 4 patients who received IV phosphate
- In 5 (20%) patients, Endocrine referrals and in 8 (32%) patients Gastroenterology referrals were done
- Serum hypophosphataemia, can co-exist with other metabolic and electrolyte abnormalities, and if severe unless treated can lead to life threatening complications. This audit aims to help the society in understanding the aetiology, significance and complications of low serum phosphate, and the way forward to managing such patients as mentioned above.

Recommendations

- In all cases of hypophosphataemia, together with serum calcium, check serum magnesium, potassium and bicarbonate
- In all cases check Vitamin D and PTH levels
- To establish the cause of hypophosphataemia, check if the patient is on Diuretics, Ferinject, Theophylline, Antacids or has Chronic Alcoholism and Malabsorption
- Measure Morning Cortisol/Exclude Cushing's
- Measure 24 hours urinary Phosphate
- Look for the symptoms and signs of hypophosphataemia
- Note if the patient has cardiac failure, peripheral oedema or renal impairment
- Document if the Hypophosphataemia is mild, moderate or severe
- Consider Preanalytical cause or analytical interference cause: Postprandial sample, Respiratory alkalosis and Paraproteinaemia

- Consider IV phosphate if the level is <0.3 mmol/L or if the patient has symptoms with the level between 0.3-0.6 mmol/L
- Monitor Electrolytes, BP (for hypotension) and ECG for Cardiac arrythmias during IV phosphate replacement and ensure that the correct dose is administered
- If there is a family history or the patient has short stature or skeletal deformities consistent with rickets- Genetic referral is required; referral should be done to Gastro/Renal/Endocrine as appropriate
- Re-audit in 1 year
- Develop our own hospital Guideline for the management of hypophosphataemia.

Compliance with ethical standards

Acknowledgments

We would like to acknowledge all Endocrine colleagues and the Secretaries for helping us with the data collection towards preparation of the audit.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

Disclosure of Conflict of Interest

No Conflict of Interest to be disclsoed.

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