OPEN

Reducing Metabolic Bone Disease Burden in Intestinal Failure Children on Home Parenteral Nutrition

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ABSTRACT

Objective: To determine the prevalence of secondary hyperparathyroidism in a cohort of pediatric patients receiving home parenteral nutrition.

Methods: For a service review, a population-based cohort of 37 pediatric intestinal failure patients receiving long-term parenteral nutrition that underwent serial biochemical monitoring during a study period of approximately 4 years were examined. Following the production of an algorithm, a follow-up audit was carried out (n = 33) after approximately 6 months.

Results: Of the 37 patients examined in the initial service review, 22 (59%) were found to have an elevated parathyroid hormone (PTH) during the period of monitoring and 5 (14%) had a persistently elevated PTH. In the follow-up audit following the implementation of an algorithm, the number with elevated PTH reduced to 6 (18%) and no patients had persistently high levels.

Conclusion: Elevated PTH is a common biochemical finding in pediatric intestinal failure patients receiving home parenteral nutrition and its presence should alert clinicians to the need to optimize nutritional parameters such as calcium to phosphate molar ratio and vitamin D status; failure to do so may increase the future burden of metabolic bone disease in such patients. We propose that an algorithm may help in this endeavor.

Key Words: children, intestinal failure, home parenteral nutrition, calcium: phosphate molar ratio in parenteral nutrition, metabolic bone disease, vitamin D

What Is Known

- Parathyroid hormone regulates calcium homeostasis.
- Secondary hyperparathyroidism can result from calcium deficiency and may lead to metabolic bone disease (MBD).
- MBD results in reduced bone mineral density, osteomalacia and/or rickets.
- MBD is known to occur in children with intestinal failure.

What Is New

- Parathyroid hormone can be used to monitor the development of a calcium deficiency state in children with intestinal failure receiving parenteral nutrition.
- We propose an algorithm that may help to adjust the molar ratio of calcium to phosphate in parenteral nutrition and thereby reduce the incidence of secondary hyperparathyroidism.

INTRODUCTION

Intestinal failure (IF) in children occurs when there is a reduction in small bowel length due to the result of infection, surgery, or poor function of the gut. The gut is unable to absorb what is nutritionally required, and parenteral supplementation is needed (1). Therefore, to achieve adequate nutrition for growth and development and fluid intake, long-term home parenteral nutrition (HPN) is used, often in conjunction with enteral nutrition.

An important complication of IF is metabolic bone disease (MBD) (2), first described in pediatric patients in 2010 (3) although it has been recognized in adult patients receiving parenteral nutrition (PN) for decades before this (4). MBD is a disturbance of skeletal homeostasis which results in defective bone mineral density (BMD) (2). MBD in the context of IF refers to the presence in isolation or combination of rickets and/or osteomalacia and reduced bone density predisposing children to osteoporosis. Rickets involves deficient mineralization of the growth plates, seen in growing children only, and occurs in combination with osteomalacia which involves the accumulation of undermineralized osteoid, resulting in the softening of bones. Dual-energy X-ray absorptiometry (DXA) measures bone mineral content and BMD, however, it cannot differentiate osteomalacia. Osteoporosis in children is defined as the presence of low BMD with a history of nontraumatic fractures (5). As the gold standard approach of bone biopsy (2) is not widely available and involves an invasive procedure, osteomalacia is traditionally identified by biochemical parameters of the derangement of mineral homeostasis and clinical features associated with secondary hyperparathyroidism (2).

To aid in quality improvement we carried out a service review to establish the prevalence of hyperparathyroidism in a cohort of children receiving HPN. Following this exercise, we identified a need to develop an algorithm to help adjust the calcium and phosphate levels in PN depending on the blood levels of calcium and parathyroid hormone (PTH) (Fig. 3) and audited the prevalence of secondary

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hyperparathyroidism after approximately 6 months post implementation of the algorithm.

METHODS

The rationale for the initial service review was that we were increasingly seeing elevated PTH in our cohort of patients with IF. The need to develop an algorithm stemmed from the service review and thereafter was subjected to clinical audit. No ethical approval was therefore deemed necessary.

We did not include information on any vitamin D and calcium received orally/enterally because vitamin D acts in the gut and patients with IF are not likely to have a significant contribution to calcium absorption via this mechanism.

Clinical Data Collection

Clinical data including age and biochemical results were collected from the electronic patient record covering up to approximately 4.5 years for the initial service review and 4 months for the follow-up audit. For establishing an average vitamin D level for patients, the mean value across the study time period was calculated. The mean time on PN in Figure 1 could only be approximated owing to incomplete records in the pharmacy. The approximation represents the best estimation of the start time from the information the pharmacy were able to provide.

Patients

37 IF children receiving HPN were included in the initial service review (Fig. 1).

33 IF children receiving HPN were included in the follow-up audit (Fig. 1). Additionally, we excluded any results from time points where the patient was admitted to the hospital and therefore unlikely to be biochemically stable, as well as any patients in the original cohort who hadn't had any blood results in the second study period.

The population of patients was slightly different between the initial service review and the follow-up audit. 26 of the 37 patients from the initial service review were included, as well as 7 additional new patients. The 11 patients who were not included were excluded because they had either discontinued HPN, transitioned to adult services, or had no results.

We excluded from the audit any patient with kidney disease, as this would be an independent cause of secondary hyperparathyroidism.

Laboratory Testing

Adjusted calcium, phosphate, creatinine, and PTH results were all obtained from serum samples analyzed on an automated Roche Cobas (Roche Diagnostics, Mannheim, Germany) platform. Estimated GFR was calculated using the CKD-EPI equation (6). Vitamin D levels were quantified using an in-house tandem mass spectrometry assay and levels quoted in this study refer to measured total 25-hydroxyvitamin D. We decided not to include alkaline phosphatase (ALP) because it wasn't possible to unpick any increase in levels from the impact of PN on the liver.

Development of the Algorithm

The algorithm for adjusting the molar ratio of calcium to phosphate in PN (Fig. 3) was initially drafted by a pediatric chemical pathologist with an interest in pediatric IF. Following this, a pediatric endocrinologist with an interest in MBD reviewed and revised the algorithm. The revised algorithm was then reviewed by 2 pediatric gastroenterologists and a pediatric dietician, all with an interest in pediatric IF.

RESULTS

Initial Service Review

Elevated PTH was observed at least once in 22 (59%) of patients, with 5 (14%) having a persistently raised PTH. Persistently raised PTH was defined as those in whom >50% of PTH measurements in the time period were above the reference interval. 15/22

	Initial Service Review		Follow up Audit	
Number of patients	37		33	
Average age (years)	7.4 (1.1 – 18)		7.3 (0.9 – 16.4)	
Gender	M - 18	F - 19	M - 18	F- 15
Raised PTH (age specific reference ranges available on request)	22		6	
Persistently raised PTH	5		0	
Average 25-hydroxyvitamin D level (normal range >50 nmol/L)	67.6 nmol/L		71.8 nmol/L	
Approximate mean duration on PN (years)	5.1		5.9	
Mean number of PTH measurements per patient	9.8		2.2	

FIGURE 1. Patient characteristics and biochemical markers of bone homeostasis in intestinal failure (IF) patients receiving home parenteral nutrition (HPN).

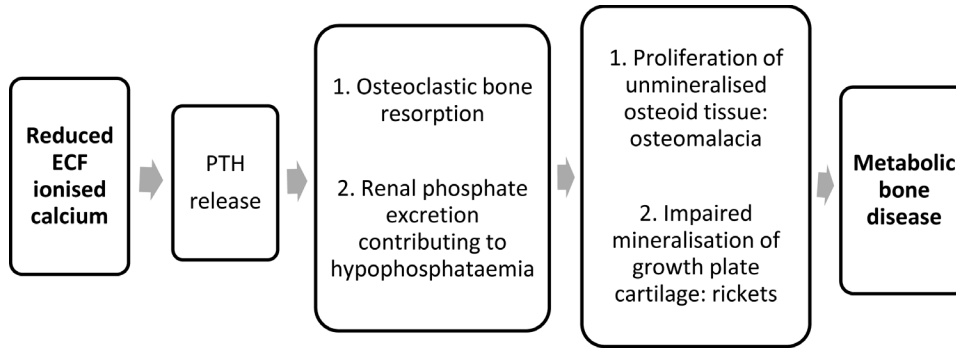

FIGURE 2. Schematic showing how persistent hyperparathyroidism can drive contribute to calcipenic metabolic bone disease, unless measures to address calcium levels are instituted. ECF = extracellular fluid; PTH = parathyroid hormone.

(68%) of the patients with raised PTH had normal serum-adjusted calcium throughout the timed study period; this also applied to 3 out of the 5 patients with persistently raised PTH. There were 7/22 (32%) patients who had calcium levels outside the reference range at the same time as a raised PTH, however, of these 6 had hypocalcemia (and therefore appropriate high PTH).

Within the 22 patients in whom PTH was elevated the mean vitamin D concentration was 67 nmol/L. Within the 15 in whom PTH was not elevated, the mean vitamin D concentration was 66 nmol/L; although 2 of these patients had insufficient measurements of vitamin D to create an average. Two patients in the normal PTH cohort had suboptimal individual vitamin D measurements and 3 patients had suboptimal vitamin D (<50 mmol/L) in the high PTH cohort.

Thirteen individual patients had low (n = 7) or lower third normal (n = 13) phosphate at the time of a high PTH. 11 of these had low (n = 7) or lower third normal (n = 11) phosphate on multiple occasions. The remaining 24 patients had serum phosphate values greater than the lower third of the reference range at all times during the period of study.

Follow-up Audit

Six (18%) patients had secondary hyperparathyroidism at some point and no patients had persistent hyperparathyroidism; in all patients, this was transient and resolved. Importantly, all patients were normocalcaemic at all times. This highlights the importance of PTH levels in assessing calcium balance status.

Seven (21%) patients had suboptimal (<50 nmol/L) vitamin D, and the mean vitamin D was 72 nmol/L, however only 1 patient from the high PTH group had suboptimal vitamin D.

No patients had low or lower third normal phosphate at the time of a high PTH. All 33 patients had serum phosphate values greater than the lower third of the reference range, at all times, during the period of study.

DISCUSSION

The etiology of MBD in pediatric IF is thought to be a combination of inadequate calcium and phosphate provision, vitamin D deficiency, inflammation from an underlying disease, medical treatments (eg, corticosteroids), inactivity as well as genetic factors. Historically, aluminum toxicity from the PN solution itself became a recognized factor in the development of MBD (2). Generally, aluminum toxicity tends to be a problem in associated renal failure where the child is unable to excrete aluminum. In children with IF, osteopenia occurs in approximately 45% with 16%–25% having osteoporosis (2). History of fracture is important in diagnosing osteoporosis in children. 90% of peak bone mass is accrued by the age of 18 (7). Therefore, failing to optimize bone health for pediatric IF patients on HPN risks a lifetime of reduced BMD, which carries with it a risk of fragility fractures and subsequent morbidity. This is not to mention the negative symptoms that may accompany MBD such as bone pain, which in 1 study of pediatric IF patients, was present in almost 20% of the cohort (8).

PTH is the principal regulator of calcium homeostasis. Four parathyroid glands are situated at each pole of the thyroid gland, and these respond within seconds to a low or falling calcium level by secreting PTH (9). PTH is an 84-amino-acid single-chain peptide that mobilizes calcium through increased osteoclastic resorption of bone, stimulating renal activation of 25-hydroxy (25 OH) vitamin D to its active form, 1,25 $(OH)_2$ vitamin D and by promoting renal phosphate loss as well as calcium reabsorption. Activated 1,25 $(OH)_2$ vitamin D then acts to promote intestinal absorption of calcium (9,10), however since the distal intestine accounts for 70%–80% of ingested calcium absorption (11), this particular mechanism may be compromised in pediatric IF patients with a reduced gut length.

In the calcium deficiency state (calcipenic state) PTH concentration increases and the end result of the combined actions of PTH is a normalization of blood calcium levels, reduction in serum phosphate and elevation of ALP. Osteoclastic bone resorption and low blood phosphate levels cause rickets and osteomalacia (Fig. 2). The specific type of hyperparathyroidism described herein is secondary hyperparathyroidism, which is a normal physiological response; as opposed to primary and tertiary hyperparathyroidism which both represent an inappropriate release of PTH, resulting from, most commonly parathyroid adenoma and long-standing CKD, respectively. It is important to note that an increase in PTH is the earliest biomarker to suggest a calcium deficiency state is evolving before the reduction of serum phosphate and elevation of ALP ensues. Therefore, monitoring PTH concentration is important to evaluate calcium balance.

As can be seen from our results, involving 37 patients within our initial service review cohort, of the 22 (59%) in whom PTH was elevated, a considerable number; 5 of the 22 (23%) had a persistently raised PTH. Interestingly we did not observe a significant difference in the vitamin D levels of those with and without raised PTH in either the service review or the follow-up audit. However, the retrospective nature of this work meant that the cohorts were not directly comparable, and the time duration of the study differed between them. In another study of 51 HPN-dependent adult patients, 81% were found to have reduced BMD on DXA, despite 35% displaying normal vitamin D levels (12). This would suggest that although vitamin D is likely to play a role in MBD, there are other factors involved. However, it should be remembered that DXA measures BMD, whilst secondary hyperparathyroidism being investigated here causes osteomalacia which, DXA can't differentiate from bone mineral content and density.

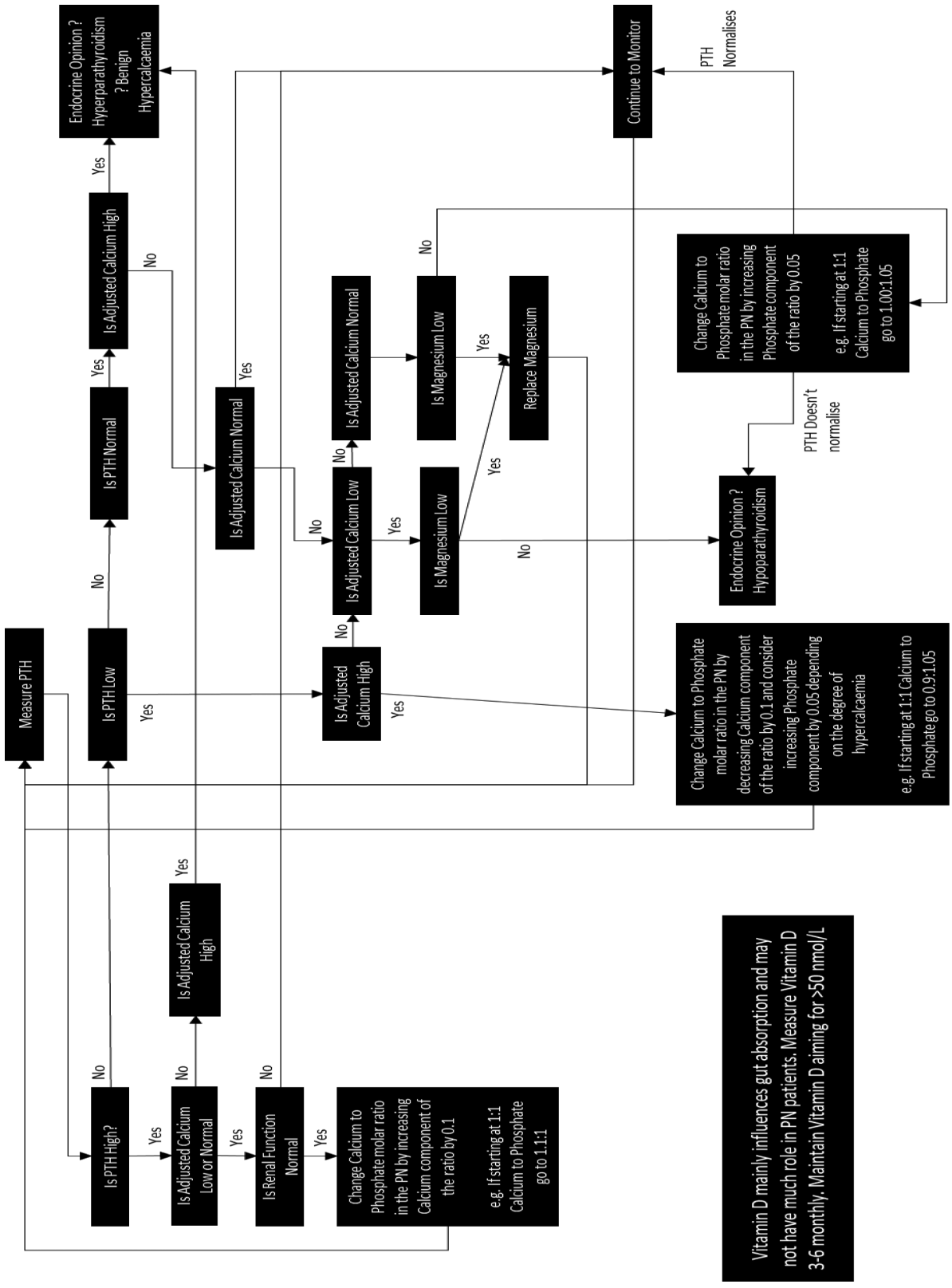

FIGURE 3. Proposed algorithm for adjustment of the calcium to phosphate molar ratio in pediatric home parenteral nutrition (HPN).

One study of pediatric IF patients receiving HPN (13), found sufficient levels of 25 (OH) vitamin D in both those with IF versus healthy controls; these authors did however identify lower 1,25 $(OH)_2$ vitamin D levels in the IF patients compared with the healthy group. Several potential mechanisms were proposed for this including increased elimination of 1,25 $(OH)_2$ vitamin D, inflammation leading to reduced hydroxylation, and fibroblast growth factor 23 mediated downregulation of 1,25 $(OH)_2$ vitamin D production. In this study, vitamin D was administered parenterally and therefore another suggestion was that the mode of vitamin D administration may play a role in 1,25 $(OH)_2$ vitamin D metabolism. It was concluded that the intestine may be more important in the metabolism of vitamin D than earlier recognized and raised the question of whether the oral or parenteral provision of vitamin D was superior for its metabolism into 1,25 $(OH)_2$ vitamin D. We did not measure 1,25 $(OH)_2$ vitamin D levels within our cohort although perhaps this would help to better understand an individual's particular calcium and vitamin D homeostasis. This would however be limited by assay availability as 1,25 $(OH)_2$ vitamin D assays are less widely available than those quantifying 25 (OH) vitamin D.

Secondary hyperparathyroidism in HPN patients should serve as a reminder to the clinician, that interventions to address the low body store of calcium (as calcium levels are generally normal) should be instituted; without doing so, bone resorption will continue to occur, driving bone mineral loss and the elevated PTH will drive renal phosphate wasting leading to hypophosphatemia, which can result in hypertrophic growth plates as part of Rickets (14). This cycle if untreated over time will contribute to the development of MBD (Fig. 2) (7). We note that in our initial service review, there was a higher prevalence of low or lower third normal phosphate than in the follow-up audit post implementation of the algorithm, although the shorter time period of study poses a significant limitation.

As mentioned above, the parathyroid glands respond on a minute-by-minute basis to low or falling ionized calcium levels, by releasing PTH. The serum-adjusted calcium may not pick up these subtle changes in calcium balance and therefore measuring PTH is an accurate way for the clinician to gauge a patient's calcium status. We have proposed an algorithm for correcting secondary hyperparathyroidism in pediatric home PN patients (Fig. 3) which aims to increase the calcium-to-phosphate molar ratio in the PN over time, followed by repeat assessment of PTH. By providing a greater molar ratio of calcium to phosphate, the drive to secrete PTH can be reduced and therefore over time the deleterious effect of untreated hyperparathyroidism on bone health can be lessened. Although mechanistically it is understood that treating secondary hyperparathyroidism will reduce bone mineral loss, further research is needed to confirm this particular treatment approach is effective within the pediatric home PN cohort. Low bone mass is multifactorial and PTH may have a limited role in contributing to this. The follow-up audit following the establishment of the algorithm showed a reduction from 59% to 18% of patients having secondary hyperparathyroidism at some point and no patients having persistently elevated PTH. Owing to the shorter duration time of the audit, it is difficult to be sure if the algorithm had a positive impact, however, we feel it adds value to the management of these patients.

In cases where the PTH is found to be low with accompanying low or normal adjusted calcium, it is important to exclude magnesium deficiency. Chronic magnesium deficiency can lead to a reduction in PTH secretion, resulting in hypocalcemia. Indeed, since magnesium is principally absorbed by the small intestine, those with IF are particularly susceptible to this electrolyte deficiency which can then disrupt calcium homeostasis (15). Vitamin D assessment has not been included within our proposed algorithm since vitamin D mainly influences gut absorption of calcium and may not have as much of a role in calcium status within IF patients. Studies in adults receiving long-term home PN failed to reveal a significant association between vitamin D status and BMD results (16). Therefore, although important to bone health and insufficiency and deficiency should be treated, it does not appear to be a principal determinant in this cohort and therefore our approach has been to monitor levels and aim for concentrations greater than 50 nmol/L (17).

Hyperparathyroidism is a direct response to the parathyroid glands sensing hypocalcemia. In patients in whom a raised PTH is detected alongside a low phosphate, simply aiming to correct the low phosphate alone will not rectify the biochemical picture. In fact, pharmacological treatment with phosphate will reduce ionized calcium, exacerbating hypocalcemia, driving increased PTH production and further increasing renal phosphate loss (14). Thus, in response to a raised PTH, it is important to direct treatment towards restoring calcium levels, which in turn will help correct any associated PTH-induced hypophosphatemia. In restoring calcium balance and therefore addressing secondary hyperparathyroidism, the risk of associated MBD development can be ameliorated (18).

CONCLUSION

Secondary hyperparathyroidism is a common finding within pediatric patients receiving HPN. Long-term, untreated hyperparathyroidism is a well-recognized driver of BMD loss, as skeletal calcium stores are mobilized to maintain serum calcium levels. MBD is a well-recognized complication of HPN in pediatric patients. Although its origins are multifactorial, the deleterious effects of untreated hyperparathyroidism are likely to exacerbate its development and therefore more research is needed to establish treatment approaches to improve this commonly seen biochemical disturbance, thereby helping to reduce the future burden of disease posed by MBD, as these patients enter adulthood. Following identifying a need via service review, we have proposed an algorithm for optimizing the PN calcium-to-phosphate molar ratio in pediatric PN patients with secondary hyperparathyroidism, to reduce the risk of future MBD. However, further research is needed to establish robust evidence-based strategies to address this common biochemical finding within this cohort of patients in prospective studies. The retrospective nature of the methods used meant that we were restricted to available biochemical data and a prospective piece of research would be of value to explore this issue in more detail.

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