

ORIGINAL ARTICLE

Hyperphosphatemia during nutrition recovery in patients with severe anorexia nervosa



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KEYWORDS

Eating disorder;
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Abstract

Introduction: Anorexia nervosa (AN) is a disorder associated with many medical complications. Regarding phosphorus metabolism, the only recognized alteration is hypophosphatemia associated with refeeding syndrome. However, in our clinical practice, we have observed a high frequency of hyperphosphatemia in late phases of nutrition therapy in severely undernourished AN patients, which has barely been described.

Materials and methods: We carried out a retrospective study of patients with AN hospitalized for severe decompensation of the disease.

Results: Eleven patients were included, all women, with a median age of 23 years [20–46] and a body mass index at admission of 12.2 kg/m² [11.7–13.1]. Hyperphosphatemia was noted in 9 of the 11 cases (81.8%) with a median time to onset of 53 days [30–75]. The median peak serum phosphorus (P) level was 5.1 mg/dl [4.9–5.4]. An inverse relationship was found between the increase in P levels and phosphorus supplementation at the onset of admission. The magnitude of the P increase was associated with the body weight gain achieved during nutrition therapy.

Conclusion: Late hyperphosphatemia during nutrition therapy in severely undernourished AN patients affects more than 80% of cases. Body weight gain throughout nutrition therapy is a predictor of increased P levels.

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PALABRAS CLAVE

Trastorno de la conducta alimentaria;
Anorexia nerviosa;
Hiperfosfatemia;
Nutrición

Hiperfosfatemia durante la renutrición en pacientes con anorexia nerviosa grave**Resumen**

Introducción: La anorexia nerviosa (AN) es un trastorno que conlleva numerosas complicaciones médicas. Respecto al metabolismo del fósforo, la única alteración reconocida es la hipofosfatemia asociada al síndrome de realimentación. Sin embargo, en nuestra práctica clínica, hemos objetivado una alta frecuencia de hiperfosfatemia en fases tardías de la renutrición en pacientes con AN severamente desnutridos, que ha sido escasamente descrita.

Material y métodos: Estudio retrospectivo de pacientes con AN que hubieran precisado ingreso hospitalario por descompensación grave de la enfermedad.

Resultados: Se incluyeron 11 pacientes, todas mujeres, con una mediana de edad de 23 años [20–46] y un índice de masa corporal al ingreso de 12.2 kg/m² [11.7–13.1]. Se objetivó hiperfosfatemia en 9 de los 11 casos (81.8%) con una mediana de tiempo hasta su aparición de 53 días [30–75]. La mediana del nivel máximo de fósforo (P) sérico fue de 5.1 mg/dl [4.9–5.4]. Se encontró una relación inversa entre el incremento en los niveles de P y el aporte de suplementos de fósforo al inicio del ingreso. La magnitud del incremento de P se asoció con la ganancia de peso corporal alcanzada durante la renutrición.

Conclusión: La hiperfosfatemia tardía durante la renutrición en pacientes con AN severamente desnutridas afecta a más de 80% de los casos. La ganancia de peso corporal a lo largo de la renutrición es un predictor del incremento en los niveles de P.

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Introduction

Phosphorus (P) is an essential micronutrient found in virtually all structural molecules.¹ Overall, 85% of P in the body is found in the bone, 14% in the intracellular space and 1% in the extracellular fluid.² Correct homeostasis of P is essential for synthesising adenosine triphosphate, nucleic acids or second messengers, among others, as well as for the formation of the phospholipids that make up cell membranes.¹

The normal concentration of plasmatic P varies between 2.5 and 4.5 mg/dl² and is determined by the complex interaction of different organs, mainly the intestine, parathyroid glands, bone and kidney. This interaction is controlled by various endocrine mediators, some classic ones such as parathyroid hormone (PTH) and vitamin D, and others that have gained prominence more recently, such as fibroblast growth factor 23 (FGF-23). Renal reabsorption of P in the proximal tubule through sodium-phosphate (Na-Pi) co-transporters¹ is ultimately considered the main determinant of phosphataemia.

Anorexia nervosa (AN) is an eating disorder (ED) characterised by an oral intake less than the requirements despite low weight, with an intense fear of weight gain and an alteration in the perception of the body image.³ AN also brings numerous medical complications derived from undernutrition itself and from compensatory behaviours,⁴ as well as an increased risk of mortality.⁵

Complications of AN have been described involving multiple body systems in the body such as the digestive, cardiovascular, neurological, endocrinological, bone and metabolic systems.⁴ Electrolyte disturbances are among the most frequent complications of AN and usually derive from repeated vomiting, compulsive water intake, laxative or diuretic abuse, or the refeeding syndrome (RS). AN is a recognised risk factor for the development of

RS, a potentially serious complication that can occur in the first few days after aggressive nutritional repletion in undernourished patients and/or after prolonged fasting.⁶ Hypophosphataemia is one of the most common anomalies in this syndrome and a key fact for diagnosis.^{6,7} Outside the context of RS, no frequent abnormalities in P homeostasis have been reported in subjects with AN. However, in our clinical practice, we have observed hyperphosphataemia in the late stages of renutrition in severely undernourished patients with AN, a finding that has been poorly described in this group so far and for which we have not found any of the recognised causes of hyperphosphataemia. In our study, we describe the incidence, magnitude and temporal pattern of this finding. We also explore the association with other variables to help predict its appearance and/or propose aetiological hypotheses.

Material and methods

A retrospective analysis of patients diagnosed with AN-type eating disorders admitted to our hospital due to severe disease decompensation was conducted between December 2010 and September 2019. Criteria for severe decompensation were a body mass index (BMI) <15 kg/m² (DSM-5)³ and/or the presence of a serious medical complication (acute pancreatitis, hepatic encephalopathy or gastrointestinal bleeding, among others).

We excluded patients under 18 years of age since serum P levels are physiologically high during childhood and adolescence,² and patients who had not had at least three P tests in a minimum period of six weeks between the first and the last test.

Demographic variables, data related to the eating disorder, nutritional status, and biochemical and hormonal parameters were collected on admission. Throughout the

follow-up, clinical data related to nutritional status and biochemical and hormonal parameters were recorded at the following time points: every week during the first month, every two weeks until the sixth month, and at 12 months. The glomerular filtration rate (GFR) was estimated in all cases using the Crockroft–Gault formula, which considers weight and height. Nutritional status was determined according to subjective global assessment (SGA).

Hyperphosphataemia was defined as a serum P level greater than 4.5 mg/dl² (in the absence of P supplementation) in at least one test throughout follow-up. P0 was designated as the serum P value at admission, P1 as the serum P value at diagnosis of hyperphosphataemia, and P2 and P3 as the following P test values.

The presence of RS in the first days of renutrition was established according to the criteria of Friedly et al.,⁷ which differentiate between *imminent* RS, if in the first 72 h after the start of renutrition only laboratory abnormalities are evident, and *manifest* RS, if it also presents with clinical symptoms.

In accordance with our usual clinical practice in very severely undernourished AN patients, RS prophylaxis was carried out in all cases, and included the following measures: (1) administration of thiamine, high-potency vitamin B complex and multivitamins for at least 10 days (Hydropolivit A Mineral®); (2) controlled caloric intake with a progressive increase to obtain a weight gain between 0.5 and 1 kg/week; (3) prophylactic individualised supplementation of P (phosphate NM 3.56 g powder®); (4) monitoring and intensive treatment of electrolyte alterations, and (5) close *clinical and analytical* monitoring.

The study was approved by the medical research ethics committee of the Puerta de Hierro-Majadahonda University Hospital.

Statistical analysis

Categorical variables are expressed as absolute and relative frequencies and quantitative variables as median and interquartile range. For the analysis of the relationship between variables, generalised estimating equation (GEE) models have been used in order to include the data from the different visits of each patient without violating the assumption of independence of the observations. When the dependent variable is binary, the identity function has been used as a link function with the Gaussian family. The estimate of the effect in each case is shown, adjusted for the follow-up time with their respective 95% confidence intervals. The statistical analysis was performed using STATA® software v.15.

Results

Baseline characteristics

Between December 2010 and September 2019, a total of 27 AN-type ED patients older than 18 years were admitted to our hospital. Of these, 16 were excluded from the study for not meeting the inclusion criteria (4 patients did not fulfill criteria for severe descompensation, and 12 patients did not have a sufficient number of P tests).

Table 1 Baseline characteristics of the global cohort (N = 11).

Sex (women) (n/N)	11/11
Age (years)	23 (20–46)
Reason for admission (n/N)	
Body mass index <15 kg/m ²	10/11
Serious medical complication	1/11
Hospitalisation duration (days)	57 (34–83)
Duration of ED (years)	2 (1–16)
Compensatory behaviours (n/N)	6/11
Vomiting	3/6
Excessive exercise	4/6
Laxative abuse	0/6
Diuretic abuse	0/6
Weight loss in the six months prior to admission	
Kilograms	11 (4–18)
Percentage	24 (14–37)
Body mass index (kg/m ²)	12.2 (11.7–13.1)
Subjective global assessment (n/N)	
A	0/11
B	0/11
C	11/11
Phosphorus at admission (mg/dl) (NV 2.5–4.5)	2.7 (1.8–3.8)
Other biochemical parameters at admission (NV)	
Glucose (mg/dl) (60–100)	78 (72–83)
Creatinine (mg/dl) (0.5–0.9)	0.5 (0.4–0.8)
Urea (mg/dl) (21–45)	30 (23–41)
Glomerular filtration rate (ml/min/1.73 m ²)	103 (90–143)
Albumin (g/dl) (3.5–5)	3.7 (3.5–3.8)
Albumin-corrected calcium (mg/dl) (8.7–10.3)	8.8 (8.4–9.1)
Parathyroid hormone (pg/mL) (14–72)	50 (44–58)
Alkaline phosphatase (IU/l) (35–104)	50 (45–60)
Vitamin D (ng/mL) (37–160)	66 (52–76)

Data are expressed as relative frequencies or median and interquartile range.

ED: eating disorder; NV: normal value.

Finally, a cohort of 11 patients was obtained, whose baseline characteristics are shown in Table 1. All the patients were women, with a median age at the admission of 23 years (20–46) and a median time with the ED of two years (1–16). Overall, 91% of the patients (10/11) remained hospitalised for at least 20 days (median 57 days, IR [34–83]).

Approximately 55% of cases (6/11) reported compensatory behaviours: three patients purging behaviours, four patients excessive exercise, and one patient both behaviours. All patients were classified as severely undernourished according to the SGA, and 91% (10/11) had a BMI <15 kg/m² at admission (median 12.2 kg/m², IR [11.7–13.1]). One patient was hospitalised for a serious medical complication (hepatic encephalopathy secondary to alcoholic liver disease) with a BMI at the admission of 16.7 kg/m² in the presence of severe ascites and oedema.

Median weight loss prior to hospitalisation was 11 kg (4–18) in absolute terms and 24% (14–37) in percentage terms.

Table 2 Prophylaxis and development of refeeding syndrome in the global cohort (N=11).

Vitamin prophylaxis (n/N)	11/11
Phosphorus supplementation (n/N)	9/11
As prophylaxis	4/9
For hypophosphataemia	5/9
Duration of supplementation (days)	22.5 (7–46)
Refeeding syndrome (n/N)	5/11
Imminent	5/11
Manifest	0/11

Data are expressed as relative frequencies or median and interquartile range.

Median P at admission (P0) was 2.7 mg/dl (1.8–3.8). The rest of the biochemical parameters at admission are shown in Table 1.

All patients (100%) received vitamin supplements to prevent RS (Table 2). Oral supplementation of P was prescribed in 81.8% (9/11) at the beginning of admission: in 55% (5/9) due to hypophosphataemia without clinical data of RS, and in 45% (4/9) as prophylaxis due to a very high risk of RS (with normal serum P). P supplementation lasted for a median of 22.5 days (17–46) (Table 2).

Incidence and temporal pattern of hyperphosphataemia

During follow-up, hyperphosphataemia was observed in 9 of 11 patients (81.8%). An additional patient presented an increase in P from 3.6 mg/dl on admission to a limit value of 4.5 mg/dl, which persisted in a test done 4 weeks later.

Table 3 shows the individual evolution of P levels throughout the follow-up, and Table 4 shows the grouped analysis.

The median P at admission (P0) in the subgroup of patients who developed hyperphosphataemia was 2.4 mg/dl (1.7–3.1). Of the 9 patients with hyperphosphataemia, 8 had received P supplementation in the form of an oral supplement at the beginning of the admission. In 6 of them, the supplement had been stopped before high levels of P were detected, and they presented hyperphosphataemia for the first time (P1) at a median of 28.5 days (13.5–39) after interruption of the supplement. The supplement was discontinued in the remaining two patients due to high P

values (4.6 mg/dl in both cases). In the first case, hyperphosphataemia of 4.7 mg/d (P1) was confirmed 42 days after discontinuation of the supplement. In the second case, hyperphosphataemia of 5.1 mg/dl (P1) was confirmed 13 days after interruption of the supplement. One patient developed hyperphosphataemia (P1 5.4 mg/dl) on day 12 of admission without receiving P supplementation.

Overall, the median time from the day of admission to detection of hyperphosphataemia was 53 days (30–75), and the median serum P at diagnosis (P1) was 4.8 mg/dl (4.7–5.1) (Table 4).

All patients had at least one P test after P1 (designated P2), performed a median of 14 days later (12–64). In 4 patients, P2 was normal. In one patient, it was lower than P1 but remained above the normal range. In another patient, it remained elevated and unchanged compared to P1, and in three patients, it was higher than P1. Three of the five patients with elevated P2 had an additional P test (P3) performed a median of 21 days later (13–178). In two cases, P3 had normalised; in the third case, it remained elevated (Table 3).

The maximum P value (Pmax) ranged from 4.7 to 5.6 mg/dl (median 5.1 mg/dl, [IR: 4.9–5.4]), with the highest value corresponding to the patient who did not receive P supplementation. Pmax was reached between 16 and 183 days (median 75 days, [IR: 53–83]) from the day of admission. In 5 patients, P1 and Pmax coincided in time, and in 4 patients, a range of 6 to 54 days (median 14 days, [IR: 12–24]) elapsed from diagnosis until Pmax was reached.

In 3 patients, it was impossible to document P normalisation since it remained high in the last evaluation, carried out at 6, 14 and 33 days after diagnosis, respectively. In the remaining 6 patients, the time from diagnosis to the documentation of normal P ranged from 7 to 362 days (median 85 [IR: 37–157]). However, the duration of hyperphosphataemia could be overestimated given the long time interval between two consecutive P tests in some cases.

Other parameters related to phosphorus-calcium metabolism

In the group of patients who developed hyperphosphataemia, the median albumin-corrected calcium level experienced a statistically significant increase from admis-

Table 3 Evolution of phosphorus in patients with hyperphosphataemia (N=9).

Patient	P0	P1		P2		P3	
	mg/dl	Time since P0 (days)	mg/dl	Time since P1 (days)	mg/dl	Time since P2 (days)	mg/dl
1	4	12	5.4	106	4.1	—	—
2	2.7	51	5.6	7	4.3	—	—
3	3.1	57	4.7	64	4.4	—	—
4	2	24	4.8	14	4.9	6	4.3
5	1.1	82	4.9	14	5.5	—	—
6	0.4	79	5.1	26	4.8	336	4.3
7	1.7	174	4.7	161	4.2	—	—
8	4	64	4.6	6	5.0	—	—
9	2.4	30	4.6	12	4.6	21	4.6

Table 4 Characteristics of hyperphosphataemia (N = 9).

Variable	No.	Result
Serum phosphorus at admission (P0) (mg/dl)	9	2.4 (1.7–3.1)
Serum phosphorus at diagnosis (P1) (mg/dl)	9	4.8 (4.7–5.1)
Maximum serum phosphorus (Pmax) (mg/dl)	9	5.1 (4.9–5.4)
Time from admission to diagnosis (days)	9	53 (30–75)
Time from admission to Pmax (days)	9	75 (53–83)
Duration (time from P1 to documentation of normal P) (days)	6	85 (37–157)
Biochemical parameters coinciding with Pmax (NV)		
Creatinine (mg/dl) (0.50–0.90)	9	0.60 (0.56–0.70) (36–50)
Urea (mg/dl) (21–45)	9	42 (79–125)
Glomerular filtration rate (ml/min/1.73 m ²) (60–120)	9	89 (3.9–4.7)
Albumin (g/dl) (3.5–5.0)	9	4.0 (9–9.5)
Albumin-corrected calcium (mg/dl) (8.7–10.3)	9	9.1 (21–31)
Parathyroid hormone (pg/mL) (14–72)	4	26 (50–88)
Alkaline phosphatase (IU/l) (35–104)	9	75 (47–83)
Vitamin D (ng/mL) (37–160)	4	62 (47–83)
Phosphorus in 24-h urine (g/24h) (0.40–1.30)	2	0.34 (0.22–0.38)

Data are expressed as median and interquartile range.

Table 5 Comparison of patients with and without hyperphosphataemia.

	Hyperphosphataemia	
	Yes (n = 9)	No (n = 2)
Baseline phosphorus	2.4	3.8
Years with ED	11	1
Weight loss prior to admission (kg)	14	3.5
Weight loss prior to admission (%)	33	10
Body mass index at admission	11.6	13.0
Compensatory behaviours	5/9	1/2
Refeeding syndrome	5/9	2/2
Phosphorus supplementation	8/9	1/2

ED: eating disorder.

sion (median 8.8 mg/dl, [IR: 8.4–9]) until the time Pmax was reached (median 9.1 mg/dl, [IR: 9–9.5]) ($p < 0.02$). The change in the levels of PTH (28 pg/ml [24–30] vs 26 pg/ml [21–31]) and vitamin D (72 nmol/l [62–150] vs 62 nmol/l [47–83]) in the same time frame was not statistically significant. However, these variables could only be reassessed in 45% of the patients since the rest of the cases only had baseline measurements.

Urinary elimination of P was quantified in two patients, coinciding with P1, and it was found to be decreased in both cases (0.29 and 0.40 g/24 h [NV 0.40–1.30]), even after correcting for the GFR.

Factors associated with the degree of hyperphosphataemia and the time until development

Table 5 compares patients with and without hyperphosphataemia throughout renutrition. Since only two patients did not develop hyperphosphataemia, it was impossible

to statistically analyse the differences between both subgroups.

In the subgroup of patients who developed hyperphosphataemia, the univariate analysis showed no association between the magnitude of the P increase and any of the baseline characteristics of the sample (Table 6). However, the magnitude of the increase in P was positively associated with the change in BMI ($p = 0.040$), and negatively associated with the development of RS ($p < 0.001$) and P supplementation ($p = 0.006$).

Likewise, the magnitude of the P increase was positively associated with the change in serum calcium levels ($p < 0.001$), and negatively with the change in vitamin D levels ($p = 0.013$), but no association was found with the change in PTH levels ($p = 0.305$). Finally, a negative correlation was demonstrated between the magnitude of the increase in P and the change in GFR ($p = 0.022$) and in AP levels ($p = 0.013$).

On the other hand, a positive association was observed between the value of Pmax and the change in BMI throughout renutrition ($p < 0.001$). No variable was associated with the time to development of hyperphosphataemia.

Discussion

This paper describes the frequent finding in our clinical practice of asymptomatic late hyperphosphataemia in patients with severe AN undergoing nutritional repletion. This phenomenon was evidenced in more than 80% of the cases. However, the incidence may be underestimated given that, in at least one case (with P levels in the upper limit of normal maintained for a long time), serum P tests were performed with long time intervals between them.

Very few studies in the literature have specifically examined P homeostasis in the context of renutrition in general and AN in particular. Gentile et al. describe plasma P levels above the normal range in 26% and 32% of severely undernourished patients with AN (mean BMI 11.3 kg/m²), on day 30 and 60 of admission for renutrition, respectively.⁸ Kil-

Table 6 Factors associated with the increase in P (univariate analysis).

	Coef.	95% CI	p-value
Baseline phosphorus	0.063	(−0.048–0.173)	0.267
Years with ED	−0.001	(−0.012–0.009)	0.784
Weight loss prior to admission (%)	−0.006	(−0.013–0.001)	0.086
BMI at admission	0.018	(−0.035–0.072)	0.501
Compensatory behaviours	0.237	(−0.061–0.534)	0.120
Refeeding syndrome	−0.348	(−0.512–0.183)	<0.0001
Phosphorus supplementation	−0.609	(−1.043–0.175)	0.006
Change in BMI	0.090	(0.004–0.177)	0.040
Corrected serum calcium increase	1.130	(0.599–1.673)	<0.001
Albumin increase	0.489	(0.168–0.810)	0.003
Change in vitamin D levels	−0.123	(−0.022–0.003)	0.013
Change in PTH levels	−0.004	(−0.01–0.003)	0.305
Change in AP levels	−0.007	(−0.013–0.002)	0.013
Change in glomerular filtration	−0.003	(−0.005–0.001)	0.022

AP: alkaline phosphatase; 95% CI: 95% confidence interval; BMI: body mass index; PTH: parathyroid hormone; ED: eating disorder.

bane et al.⁹ recently described the case of a patient with severe AN (BMI 10 kg/m²) admitted for a hip fracture who, after initially presenting with hypophosphataemia due to RS, developed hyperphosphataemia 60 days after admission. In contrast, Svedlund et al.¹⁰ found no changes in plasma P levels after 12 weeks of renutrition in a cohort of 25 patients with AN. However, in this study, the degree of undernutrition was lower than in the previous ones (mean BMI 15.5 kg/m²). Furthermore, underdetection of hyperphosphataemia is possible given that P tests were only carried out at admission and discharge. Therefore, our study is the first to specifically highlight hyperphosphataemia as a frequent finding during the late phase of renutrition in patients with AN.

In our cohort, the time elapsed from the start of nutritional support to the detection of hyperphosphataemia ranged between 4 and 10 weeks with a median of 53 days. Although this figure could be overestimated (since early P test results were not available for all cases), it coincides with those reported by Kilbane et al.⁹ and Gentile et al.⁸

The maximum P value reached a median of 5.1 mg/dl, with a maximum of 5.6 mg/dl; thus, hyperphosphataemia reached a significant degree, at least in some cases. The duration of hyperphosphataemia was difficult to estimate, given the poor uniformity in the periodicity of analytical tests. In those cases where P levels normalised, this occurred spontaneously without needing specific measures.

In line with studies that have documented elevated levels of P through nutritional recovery in patients with AN,^{8,9} the cohort in our study was severely undernourished (BMI 12.2 kg/m² [11.7–13.1]). Moreover, hyperphosphataemia was not found in the study by Svedlund et al.,¹⁰ where the degree of malnutrition was milder. This suggests a possible association between the degree of undernutrition and the development of hyperphosphataemia. Still, this extreme could not be analysed in our cohort, given the small number of patients without hyperphosphataemia. It was possible, however, to show a positive association of both the increase in P levels and the maximum value of P with the increase in BMI throughout renutrition so that those patients who increased their BMI the most presented a more pronounced increase in P and a higher maximum P value. Weight gain

induced by renutrition could therefore predict the development of hyperphosphataemia.

From the pathophysiological point of view, two ultimate mechanisms can lead to an increase in P levels: a) an increase in the influx of P (whether from endogenous or exogenous sources) into the bloodstream, and b) a defect in renal elimination.

Exogenous P overload can be ruled in our patients out since P supplementation was negatively associated with changes in P values. In addition, laxatives (a recognised source of P) were not prescribed in any of the patients, and no association was found between the magnitude of the increase in P and the abuse of laxatives before admission (which the patients could have maintained surreptitiously during hospitalisation).

Massive cell destruction, observed exceptionally in patients with AN who perform extreme exercise, leads to a release of P from cells that can cause acute hyperphosphataemia. In our case, the chronic course of hyperphosphataemia and the absence of biochemical data suggestive of muscle destruction, such as elevated creatine phosphokinase (CPK) or lactate dehydrogenase (LDH), rule out rhabdomyolysis as a possible cause of the hyperphosphataemia.

On the other hand, renal excretion of P is highly efficient in the absence of kidney disease. It allows normal levels of serum P to be maintained even with intake or supply much higher than normal. Thus, chronic hyperphosphataemia of "dietary" origin can occur only when there is a coexisting defect in the renal elimination of P. Therefore, to explain the hyperphosphataemia in our patients, a defect in the renal elimination of P must be invoked.

The process of renal P excretion includes filtration through the renal glomerulus and the subsequent reabsorption of more than 90% of the filtrated P through the Na-Pi co-transporters of the proximal renal tubule.¹ An increase in tubular phosphate reabsorption (TPR) leads directly to decreased urinary excretion of P.

Glomerular filtration (GF) of P is impaired in renal failure, but in the early stages the decrease in GF can be compensated with a decrease in tubular reabsorption. However

in advanced stages of kidney disease, this compensatory effect is insufficient and results in an increase in plasma levels of P.¹ In our study, although low muscle mass due to undernutrition limits the usefulness of creatinine and GFR as markers of renal function, a negative association was found between the change in P levels and the change in GFR with renutrition. Despite this, the involvement of GFR in the development of hyperphosphataemia seems unlikely, given that GFR remained above 60 ml/min in 90% of cases.

Therefore, the mechanism responsible for the hyperphosphataemia observed in our patients must be inappropriate reabsorption of P in the proximal renal tubule. The finding of lower than normal urinary excretion of P corrected by GFR in the two patients in whom this parameter was explored, also described by Kilbane et al.,⁹ supports this possibility.

Tubular reabsorption of P is a process subject to tight regulation. A wide range of factors participates, the most classic ones being PTH, with an inhibitory effect, and vitamin D, with a stimulatory effect.¹

Baseline vitamin D levels were normal in our sample, in line with the findings from other authors.¹¹ In hospitalised patients with AN, a decrease in vitamin D levels throughout hospitalisation has also been described, with a decrease in sun exposure during hospitalisation having been postulated as a possible cause.¹⁰ Consistent with these data, in our study, we also found a decrease, although not statistically significant, in vitamin D levels during renutrition. We also observed an inverse correlation between the change in P levels and vitamin D levels. Taken together, these data rule out the involvement of vitamin D in the aetiopathogenesis of hyperphosphataemia in our patients. In addition, PTH does not seem to be involved in the development of hyperphosphataemia either because no significant changes or associations with an increase in P were observed during renutrition.

A strong candidate to explain, at least in part, the development of hyperphosphataemia during renutrition is the growth hormone (GH)/insulin-like growth factor-1 (IGF-1) system. Activation of this system induces an increase in TPR, mainly mediated by the effects of IGF-1 on Na-Pi-IIa co-transporters.¹² In addition, hyperphosphataemia is frequently found in circumstances associated with high levels of GH and IGF-1, whether physiological, such as adolescence,² or pathological, such as acromegaly.¹³

GH and IGF-1 levels were not measured in our patients, but resistance to GH is known to occur in severely undernourished patients with AN.¹⁴ This resistance is characterized by low levels of IGF-1 and high levels of GH and tends to subside with restoring nutritional status. In fact, IGF-1 levels are exquisitely sensitive to nutritional repletion and show significant increases after three days of feeding.¹⁵

In recent years, the leading role of the FGF-23/klotho system in P homeostasis has been revealed. FGF-23 is a protein produced by osteocytes that decreases Na-Pi co-transporters and 1- α -hydroxylase activity (and thus the generation of 1,25[OH]₂D from its precursor 25[OH]D) at the kidney.¹ Consequently, it decreases tubular reabsorption and intestinal absorption of P, thereby leading to decreased plasma levels of P.¹ The effect of FGF-23 on the renal tubule is mediated by the membrane receptor FGFR1c and a co-receptor called klotho, which increases the affinity of FGF-23 for its receptor.¹

On the other hand, there are data that suggest to a relationship between the GH/IGF-1 system and the FGF-23/klotho system. Low levels of klotho have been found in children with organic GH deficiency¹⁶ and high levels in patients with GH-secreting pituitary adenomas,¹⁷ which would point to a compensatory effect of the FGF-23/klotho system in these situations.

Considering these observations, a relationship between GH/IGF-1, FGF-23/klotho and alterations in P homeostasis in AN patients would not be surprising. Some studies have begun to explore the status of the FGF-23/klotho system in this context. Kilbane et al. found elevated FGF-23 levels in their patient with severe AN with late hyperphosphataemia during renutrition.⁹ In addition, Otani et al.¹⁸ described increased levels of FGF-23 in patients with purging AN and normal levels in patients with restrictive AN (with the same P levels), although they did not detail in which phase of renutrition these parameters were evaluated. Regarding klotho, at least two studies have shown an increase in circulating levels during nutritional recovery in patients with AN.^{19,20}

Although some of the observations mentioned are very preliminary, considered together they allow us to postulate that late hyperphosphataemia associated with renutrition in AN would result from resistance to the phosphaturic effect of FGF23/klotho during renutrition, which, in turn, would lead to a compensatory response manifested by elevation in the levels of FGF23 and/or klotho. IGF-1 could be the mediator between the improvement in nutritional status and resistance to FGF-23/klotho, either through a direct effect on the Na-Pi transporters of the proximal tubule or through interference with intracellular signalling of FGF-23/ klotho at other levels.

Regardless of the responsible mechanism, it seems unlikely that hyperphosphataemia associated with renutrition would have a significant clinical impact, given its moderate severity and its transient and self-limited nature. From a teleological perspective, increasing plasma P levels could ensure a sufficient supply of P to allow bone anabolism once the organism has sufficient nutrients, perhaps analogous to what was observed during the growth stage. However, a pathological significance of renutrition-associated hyperphosphataemia cannot be ruled out. In any case, the recognition of this condition would have double importance: on the one hand, it would avoid unnecessary explorations in the search for other causes of hyperphosphataemia; and on the other hand, if an adaptive character is demonstrated, it would avoid therapeutic measures aimed at limiting the increase in P.

Among the limitations of the study is the retrospective nature, which is responsible for a lack of uniformity in the frequency of evaluation of certain parameters, and for significant variability in the duration of follow-up. An additional limitation is the small sample size, which limited the statistical analysis in some cases.

Conclusion

Late hyperphosphataemia during nutritional repletion in severely undernourished AN patients is a common finding and probably results from inappropriate tubular reabsorption of P. The increase in P levels is related to the weight

gain achieved with renutrition. The mediators of this phenomenon must be identified in the future, but the GH/IGF-1 and FGF-23/klotho systems are suggested as possible candidates. Likewise, the significance of this finding should be investigated, and whether it is an adaptive phenomenon or a phenomenon with pathological significance should be determined.

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Conflicts of interest

The authors declare that they have no conflicts of interest related to this article.

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