

Original Paper

Correlations between Hypercalcemia and Endoscopic Findings in HD Patients - A Prospective Study

D. Baboi^{1,2}, Cristiana David^{3,4}, Ileana Peride^{3,4}, A. Niculae^{3,4}, I.A. Checheriță^{3,4}, I. Dina^{1,2}

¹Department of Internal Medicine, "St. John" Emergency Clinical Hospital, Bucharest, Romania

²Clinical Department No 1, "Carol Davila" University of Medicine and Pharmacy Bucharest, Romania

³Department of Nephrology and Dialysis, "St. John" Emergency Clinical Hospital, Bucharest, Romania

⁴Clinical Department No 3, "Carol Davila" University of Medicine and Pharmacy Bucharest, Romania

REZUMAT

Rolul hipercalcemiei în apariția hemoragiilor digestive la pacientul hemodializat cronic

Hemoragiile digestive reprezintă complicații redutabile, potențial cauzatoare de deces la o categorie de pacienți tratați, cu factori de risc multipli, așa cum sunt renalii cronici aflați în tratament de suplere a funcției renale prin hemodializă. La acești pacienți, baza fiziopatologică a leziunilor generatoare de pierderi de sânge, pe o mucoasă afectată de uremie și hipervolemie cvasipermanentă, este hipersecreția de acid clorhidric produsă nu numai pe căile clasice cunoscute (gastrină, histamină și acetil-colină) ci și prin acidoza metabolică interdigitală și prin stimularea unor receptori calciu-dependenți situați și la nivelul celulei parietale.

Obiectivul studiului: ne-am propus studierea relației dintre nivelul calcemiei la pacientul dializat cronic și riscul de apariția hemoragiilor digestive prin leziuni ale mucoasei tubului digestiv acid-induse.

Material și metodă: studiu prospectiv, ce a cuprins un număr de 59 de pacienți cunoscuți cu boală renală cronică, hemodializați de cel puțin 6 luni, împărțiți în funcție de manifestările digestive în trei loturi, astfel: Lotul I – bolnavi cu hemoragie digestivă superioară evidentă; Lotul II – pacienți cu hemoragie digestivă ocultă și Lotul III – lot martor de pacienți fără pierderi de sânge la nivelul tractului digestiv.

Rezultate: Valorile mari ale calcemiei s-au corelat semnificativ cu frecvența hemoragiilor digestive exteriorizate prin hematemeză, melenă, precum și cu frecvența hemoragiilor oculte. Valoarea medie a calcemiei a fost semnificativ superioară în lotul I față de lotul II ($p=0.00006$) și față de cea calculată în lotul III ($p=0.000004$); corelația dintre media calcemiilor în loturile II și III este nesemnificativă ($p=0.039$).

Concluzie: Efectele perturbării severe și de durată a metabolismului fosfo-calcic la dializații cronice sunt complexe, influențând nu numai sistemul cardiovascular, ci și sistemul digestiv, uneori cu consecințe cel puțin la fel de grave.

Cuvinte cheie: calcemia, hemoragie digestivă superioară, CaSR

Corresponding author: Lecturer Ileana PERIDE*, MD, PhD
Clinical Department No 3, "Carol Davila" University of Medicine and Pharmacy Bucharest
37th Dionisie Lupu Street, Sector 1, 020022, Bucharest, Romania
e-mail: ileana_peride@yahoo.com

ABSTRACT

Digestive hemorrhages are fierce complications, with high death risk in deficient patients with multiple risk factors, such as chronic hemodialyzed patients. In group of individuals, the pathophysiological basis of the hemorrhagic lesions on a mucosa quasi-permanently affected by uremia and hypervolemia consists of hydrochloric acid oversecretion not only through the known classical paths (gastrin, histamine and acetylcholine), but also induced by interdialytic metabolic acidosis and stimulation of certain calcium-dependent receptors of the parietal cells. Objective: to determine the relation between serum calcium level in chronic dialyzed patients and the risk of digestive hemorrhages as a result of acid-induced lesions of the digestive mucosa.

Method: prospective study on 59 patients with chronic renal disease, under hemodialysis for at least 6 months. The lot was split in 3 groups according to digestive symptoms: Group I – patients with evident superior digestive hemorrhage; Group II – patients with occult digestive hemorrhage and Group III – control group with patients without digestive hemorrhage.

Results: the high values of serum calcium significantly correlate with the frequency of superior digestive hemorrhages expressed by hematemesis and melena, and also with the frequency of occult hemorrhages. Serum calcium levels was significantly higher in group I than in group II ($p = 0.00006$), or in group III ($p = 0.000004$); the correlation between mean calcium values in groups II and III is weaker ($p = 0.039$).

Conclusions: the effects of severe and prolonged disturbances of the phosphorus and calcium metabolism in chronic dialyzed patients are complex, influencing not only the cardio-vascular system, but also the digestive system, sometimes with at least comparable consequences.

Key words: serum calcium, superior digestive hemorrhage, CaSR

INTRODUCTION

Patients with chronic renal disease frequently display eso-gastro-duodenal associated pathology: anorexia, heartburn, nausea, vomiting, abdominal pain, gastric motility disorder so far as gastroparesis; some of these symptoms decline once the substitution therapy of the renal function is initiated through hemodialysis, and some persist because of the interdialytic metabolic acidosis, used anticoagulant in dialysis or complementary therapies.

The most severe clinical manifestation is superior digestive hemorrhage, with multiple intricate causes (mucosal lesions induced by gastrin, angiodysplasia including GAVE – gastric antral vascular ectasia, treatments with lesion potential – NSAIDs, corticoids, oral iron drugs, mucosa inflammation under uremic toxins or oxygen radicals, gastric and intestinal wall edema due to interdialytic hypervolemia, malnutrition). The gastric hyperacidity induced injuries in renal patients are often esophagitis, gastritis, duodenitis and gastro-duodenal ulcer.

Gastric hydrochloric acid secretion, physiologically crucial for the beginning of digestion and food sterilization, occurs in parietal cells of gastric

body and bottom glands (1). Secretion stimulation is the result of a hormonal, paracrine and nervous complex process. Classically described paths are: neuronal path, mediated by acetylcholine that is secreted by vagal stimulation, endocrine path, hormonal, mediated by gastrin and paracrine path, mediated by histamine (2,3). The most important stimulus for priming proton secretion is gastrin. Food ingestion determines antral distension which stimulates G cells of the median area of the antral, pyloric and proximal duodenal glands, releasing gastrin in blood. Gastrin has the following effects:

- hormonal effect on parietal cells and
- stimulation effect on histamine synthesis and release from ECL cells (enterochromaffin) (4); histamine also stimulates acid secretion, but through paracrine mechanism.

Gastrin is glomerular filtered and then degraded in proximal contour tubes. Therefore, in hemodialyzed patients, an excess of circulatory gastrin, that might explain gastric hyperacidity, may occur. This theory has not been supported by all studies, some of them showing a lack of increased gastric values (5). What has been undoubtedly proven is the correlation between infection with *Helicobacter pylori* and

increased levels of gastrin through feedback mechanism as a result of mucosa atrophy and secondary hypochlorhydria (6,7).

The current researches focus on identifying a new path of gastric hyperacidity in renal chronic patients, especially in those patients who display hypercalcemia. Hypercalcemia occurs by stimulating calcium-sensing receptor – CaSR. These receptors are an essential link in calcium homeostasis, being detected both in parathyroids (stimulate and modulate the secretion of PTH) (8) and in all the organs on the axis PTH-vit D (gastro-intestinal, kidneys and bones) (9).

The integrity of gastro-duodenal mucosa results from the balance between defensive and offensive mechanisms; thereby, any defect of mucosal barrier and/or of mechanisms that modulate acid secretion will result in erosions or ulcerations of esophagus, stomach or duodenum (2). Superior digestive endoscopy may detect one or several mucosa alterations: edema, erosions, ulcerations, bleeding.

Objectives

We intended to perform a prospective study regarding the correlation between serum calcium values and the occurrence of digestive manifestations linked to acid hypersecretion, complicated or not by digestive hemorrhages, endoscopically detected in a group of chronic hemodialyzed (HD) patients.

METHOD

Our prospective study was performed between October 2011 and August 2014 within the Department of Nephrology and Dialysis, and Department of Internal Medicine, “St. John” Emergency Clinical Hospital, Bucharest and included a number of 59 hospitalized hemodialyzed patients with chronic renal disease that met the below criteria.

Inclusion criteria:

- diagnostic of chronic renal disease and under dialysis for at least 6 months;
- digestive manifestations that led to investigations through superior digestive endoscopy;
- capacity of signing an informed consent.

Exclusion criteria:

- recent oral treatments (within last month) with NSAIDs, anticoagulants, martial therapy;
- Kt/V under 1.2 (indicator of inadequate dialysis);

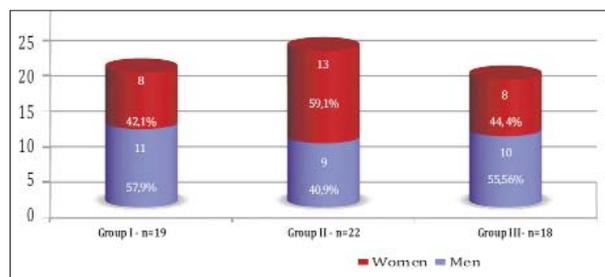


Figure 1. Gender distribution

- albumin under 3.5g/dL (indicator of malnutrition, hepatic decompensation);
- Helicobacter pylori antibodies presence;
- absolute contraindications of endoscopy (e.g.: severe respiratory insufficiency, recent myocardial infarction, refuse to undergo endoscopy);
- simultaneous diseases that might influence calcium homeostasis (e.g.: sarcoidosis, multiple myeloma, neoplasia).

The patients were split into 3 groups, depending on the digestive manifestation and bioumoral expression (**fig. 1, table 1**):

- Group I – evident digestive hemorrhage at submission, resulting in hematemesis, melena or hematochezia.
- Group II – occult digestive hemorrhage, identified by positive hemocult test of microcytic deficiency anemia.
- Group III – chronic HD patients with only dyspeptic symptomatology.

RESULTS

Superior digestive endoscopic examination of all the groups detected the following lesions (**table 2**).

The distribution of biochemical parameters evaluated by this study were included in **table 3**.

Statistical analysis determined that mean serum calcium level in group I is significantly higher than in groups II and III. The higher the serum calcium levels, the greater the risk of digestive bleeding (**fig. 2**).

Comparing serum calcium levels in group I with those in group II or III we obtained:

- group I – group II: $S_d = 0.30$ $T_{I-II} = 4.25$
($p = 0.00006$)
- group I – group III: $S_d = 0.28$ $T_{I-III} = 5.60$
($p = 0.0000004$)
- group II – group III: $S_d = 0.13$ $T_{II-III} = 2.10$
($p = 0.039$)

Table 1. Overall features of the groups

Parameters	Group I	Group II	Group III
Number	n=19	n=22	n=18
Gender			
Male/Female	11/8	9/13	10/8
Age	59.89±12.51	53.77±13.39	52.77±13.93
Primary renal disease			
Diabetes	7	4	3
Hypertension	6	9	4
PKD	2	1	0
Chronic glomerulonephritis	1	2	3
Chronic pyelonephritis	2	3	4
Collagen diseases	1	1	1
Multiple Myeloma	1	2	3
Unknown etiology	0		
Others	0		
Hemoglobin g/dl	9.50±1.55	9.65±1.20	11.65±0.70
over 11.5	4	1	10
10-11.5	3	7	8
8-10	7	10	0
under 8	5	4	0

Table 2. Type of endoscopic lesions observed in the studied groups

Endoscopic Lesions	Group I n-19	Group II n-22	Group III n-18
Esophagitis	1	3	5
Hiatal hernia	0	-	-
Hemorrhagic Gastritis	7	1	-
Erythematous Gastritis	2	6	7
Hemorrhagic duodenitis	4	-	-
Erythematous duodenitis	0	5	5
Gastric Ulcer	2	3	1
Duodenal Ulcer	2	3	-
GAVE	0	1	-
Dieulafoy lesion	1	-	-

Table 3. Biochemical characteristics of the groups

Biochemical Parameter	Group I n-19	Group II n-22	Group III n-18
Serum calcium mg/dl (mean values)	9.8±0.70	9.05±0.41	8.9±0.27
under 8.5	2	1	2
8.5-9.5	6	18	15
over 9.5	11	3	1
PTH µg/dl			
under 150	5	2	1
150-300	2	13	11
over 300	12	7	6
Dialysis adequacy Kt/V*	1,3	1,4	1,5

$$*Kt/V = -\ln(R-0.03) + [(4-3.5R) \times (UF \div W)]$$

Concluding: As $t_{n_1+n_2-2;1-\alpha} = 1.30$ and $T > 1.30$ it rejects the hypothesis H_0 , so serum calcium values in group I are statistically significantly higher than in

group II and group III (fig. 3).

Comparing serum iPTH levels in group I with those in group II or III we obtained:

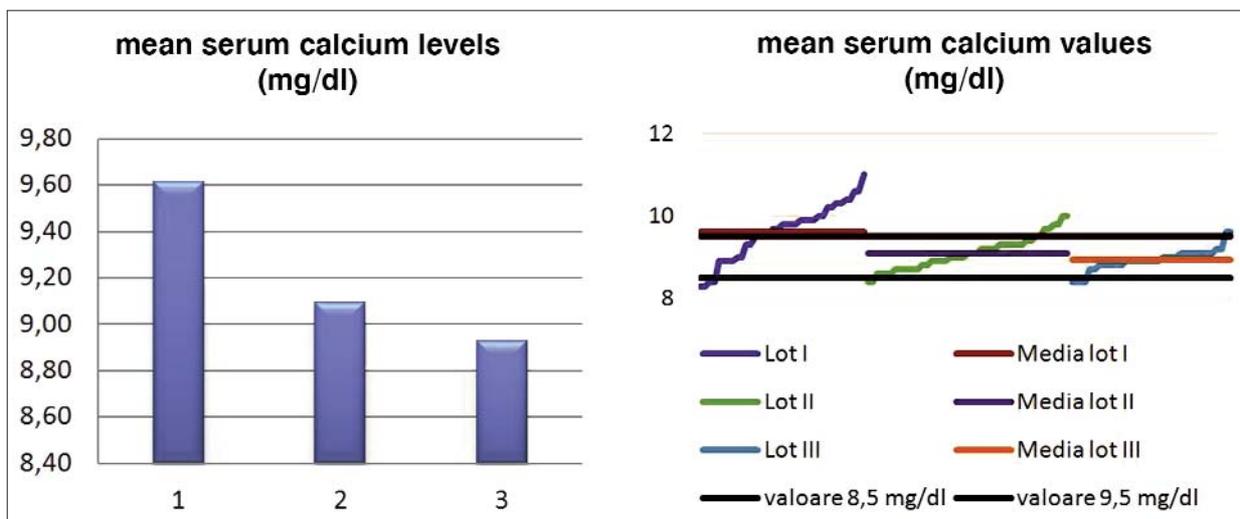


Figure 2. Serum calcium values distribution according to the severity of digestive bleeding

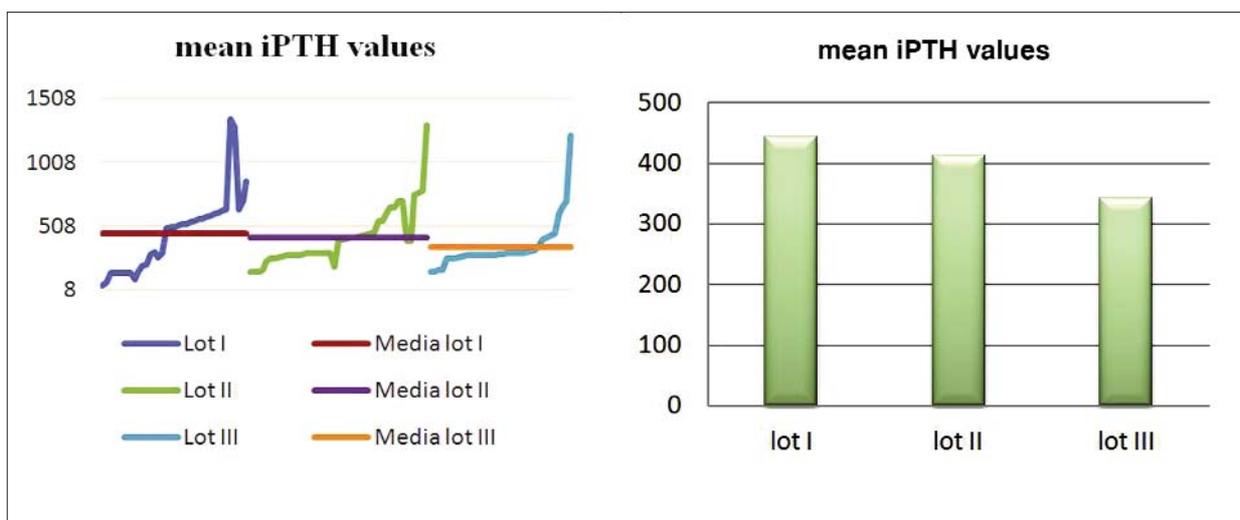


Figure 3. iPTH values distribution according to the severity of bleeding

- group I – group II: $S_d = 68608$ $T_{I-II} = 0.56$
($p = 0.5787$)
- group I – group III: $S_d = 65280$ $T_{I-III} = 1.72$
($p = 0.0899$)
- group II – group III: $S_d = 43964$ $T_{II-III} = 1.50$
($p = 0.1371$)

Concluding: In group I and in group II of patients with overt and occult digestive bleedings the values of iPTH are significantly higher than group III. There is no difference between the values of iPTH in group I and II.

The most important biochemical parameter studied turns out to be serum calcium level (fig. 4).

DISCUSSIONS

Hypercalcemia detected in patients under chronic dialysis occurs via several possible mechanisms (10):

1. secondary hyperparathyroidism and exceptionally rare tertiary hyperparathyroidism;
2. iatrogenic through phosphate chelators that contain calcium, and vitamin D overdosing;
3. aluminum intoxication (the aluminum from the dialysis solution decreases ionic calcium, which results in mobilizing bone calcium); calcium concentration of the dialysis solution may influence calcium balance.

Secondary hyperparathyroidism of the chronic

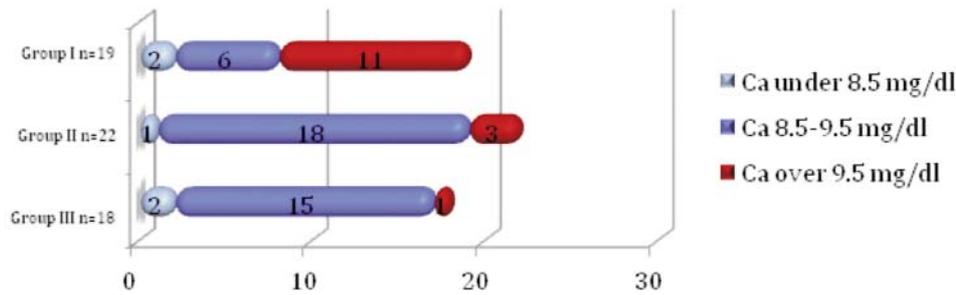


Figure 4. Calcium levels in the studied groups

renal patient occurs as a result of the parathyroid gland stimulation via 3 triggers: hypocalcemia, hyperphosphatemia and hypovitaminosis D [25(OH) D3 deficiency] (11). In order to avoid the clinical manifestations associated with hyperparathyroidism (e.g.: mineral bone disease of chronic renal patient (CKD-MB) (12), cardio-vascular and neurologic complications, pulmonary fibrosis, medular fibrosis) measures to combat hyperphosphatemia have to be implemented from the incipient stages of the chronic renal disease. These measure, according to current guides (K/DOQI – 2009) are:

- low phosphate diet (max 900 mg/day); foods with high phosphorus content must be avoided (venison, veal, viscera, fish, lactates and processed products with high phosphorus content), but, in the meantime by preserving protein intake. The recommended protein intake of 1-1.2g/kg body weight/day can be achieved using foods with phosphorus/protein ration of under 12, but acceptable up to 17 (13,14);
- phosphate chelators – calcium, aluminum and magnesium salts. Aluminum chelators have been replaced, due to their side effects, with calcium chelators (calcium acetate and carbonate); there are calcium- and aluminum-free products, but their costs are prohibitive (sevelamer hydrochloride, lanthanum carbonate). Calcium containing phosphate chelators display the disadvantage of increasing serum calcium with the aforementioned consequences. Therefore, according to a study on 53 hemodialyzed patients, calcium acetate induced hypercalcemia in 18% of the cases, while calcium carbonate in 31% (15);
- serum calcium level control by altering the

calcium concentration in dialysis solution is risky; by using a dialysis liquid with low calcium concentration (1.25-1.3 mmol/L (16)), solution that has been proposed for the patients with iatrogenic hypercalcemia as a result of high doses of active vitamin D and calcium chelators, is not viable, since it can induce the risk of intradialytic hypotension;

- treatment with vitamin D metabolites - calcitriol or 1-alfa-calcidiol that will be metabolized in liver to calcitriol. Standard doses, even if they may be able to control PTH level, can have as side effects hyperphosphatemia, hypercalcemia and calciuresis. (17). In order to compensate these undesirable effects, vitamin D3 (paricalcitol) and D2 (doxercalciferol) non-hypercalcemic analogues have been introduced (18).

The mortality risk increases in chronic renal insufficiency parallel to the increase of the calcium-phosphorus multiplication over 72 mg²/dl² mainly by cardio-vascular events; these are augmented by the anemia as a result of the blood loss in digestive hemorrhage (19).

Multiple studies and meta-analyzes proved the independent association between the serum calcium, phosphate, and parathyroid hormone level increase and mortality (20,21), and inside a study, a level of serum calcium outside the interval of 9-10 mg/dL (both ways) has been proven to increase mortality risk (22). While the effect of hypercalcemia on cardio-vascular mortality is already well-known (vascular and valvular calcifications, rhythm disorders etc.), we studied the relationship between calcemia level and the lesions of the superior digestive mucosa and the presence of digestive hemorrhage in the context of excluding the patients

with lesion potential on eso-duodenal mucosa. The extent of the bleeding varied from light (occult) proved through positive hemocult test and anemia to severe (evident), from which certain cases needed endoscopic hemostatic procedures.

In our prospective study 59 patients with chronic renal disease under hemodialysis for at least 6 months have been comprised; 30 men and 29 women aged average 53 ± 13.6 years, (age limits 30 and 82), split in 3 groups according to clinical and biochemical digestive manifestations: one group with evident superior digestive hemorrhage, one group with occult hemorrhage and one group without digestive hemorrhage.

The most frequent causes of the chronic renal disease were hierarchically: diabetes, essential hypertension, chronic pyelonephritis and glomerulonephritis, with no significant differences between groups. There is no significant difference between demographic characteristics of the groups as well.

In group I of 19 patients that were admitted for evident superior digestive hemorrhage (hematemesis or melena) emergency endoscopy was performed in the first 12 hours. In this group, the median of calcium serum level was 9.9 g/dL and 16 lesions complicated with digestive hemorrhage were identified: 7 hemorrhagic gastritis (43.75%), 4 hemorrhagic duodenitis (25%), 2 gastric ulcer (12.5%), 2 duodenal ulcer (12.5%) and 1 Dieulafoy lesion (6.35%); in the last 3 patients no fresh bleeding or clots have been detected, but endoscopic lesions have been found: class C esophagitis Los Angeles (1 case) and erythematous gastritis (2 cases).

In group II of 22 patients, with the median of serum calcium values of 9.05 g/dl, only one lesion with light diffuse capillary bleeding has been detected - hemorrhagic gastritis, the other lesions in order of frequency being: erosive gastritis (6 patients - 27.27%), duodenitis (5 patients - 22.72%), gastric ulcer Forrest III (3 patients - 13.63%), uncomplicated duodenal ulcer (3 patients - 13.63%), esophagitis (3 patients - 13.63%), GAVE (1 patient - 4.54%).

In group III of 18 patients, with the median of calcemia of 8.9 g/dl, the endoscopic lesions were minimal: 5 patients with hiatal hernia and esophageal reflux, 7 patients (38.88%) with erythematous gastritis, 5 patients (27.77%) with duodenitis and only 1 patient with gastric ulcer (Forrest III).

The mean calcium values in the groups formed according the gravity of bleedings are statistically different. Mean serum calcium level in group I is

significantly higher than in groups II and III. Group III has a low mean calcium value - we can assume that the digestive manifestations of these patients are linked to neurotic vegetative disorders.

Statistics showed in all 3 groups the direct proportionality between the severity of the lesions and the calcium serum level.

Gastric CaSRs are situated within latero-basal membrane of the parietal cell (23,24) and of the antral G cells (25) and, once stimulated, they determine the increase of acid secretion via apical ATPase $H^+ - K^+$. This explains why maintaining a high calcemia in hemodialyzed patients determines acid hypersecretion both directly by CaSRs stimulation in parietal cells and indirectly through gastrin: physiological defense mechanisms are overwhelmed and acid-induced lesions occur.

CONCLUSIONS

The high values of serum calcium significantly correlate with the frequency of superior digestive hemorrhages expressed by hematemesis and melena, and also with the frequency of occult hemorrhages. We consider that the effects of severe and prolonged disturbances of the phosphorus and calcium metabolism in chronic HD patients are complex, influencing not only the cardio-vascular system (as proved by numerous studies performed in the last decades), but also the digestive system, sometimes with at least comparable consequences.

Our possibilities for intervention in the course of renal bone disease are still limited, and the current used medication has unknown side effects, which we just began to identify.

While we experienced by turn euphoria, excess, decline and ponderation in the treatment of renal anemia with synthetic erythropoietin, the therapy of renal osteodystrophy is still in it's early. We know little of the puzzle of the metabolism of phosphorus and calcium and of the ways the organism adapts itself in the relation kidney - metabolic acidosis - bone; therefore, our interventions should be more cautious, attempting to minimize the side effects.

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