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Chronic constipation in hypercalcemic patients with primary hyperparathyroidism

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Abstract. – BACKGROUND, Chronic constipation (C), among gastrointestinal symptoms, is commonly associated with primary hyperparathyroidism (PHPT) and probably attributable to hypercalcemia.

OBJECTIVE OF THE STUDY, To evaluate in patients affected with PHPT the prevalence of C utilizing a validated questionnaire and the current prevalence of C compared to that observed in the past and to evaluate the relationship between C and the severity of PHPT.

METHODS, 55 outpatients affected with PHPT, admitted to our Department of Internal Medicine and Medical Specialities in the years (2006-2009) were studied (group 1: 50 postmenopausal women and 5 men, mean age 61.9 ± 9.4 years), together with 55 sex and age matched controls (group 2). Also considered were a group of PHPT patients observed, in the same ambulatory, during the years '70-'80 (group 3). A questionnaire, Rome II criteria, was administered and used to define C, whereas only anamneses were used to define C in group 3.

RESULTS, The prevalence of C in patients with PHPT was 21.8% in group 1 vs 12.7% in group 2 (n.s.) and 32.7% in group 3. There is a decreasing trend in the prevalence of C in patients with PHPT as observed from 1970-89 to 2006-2009 ($p < 0.05$). The reduction of C was associated together with a significant reduction in the serum calcium level ($p < 0.001$). The presence of C vs its absence in patients with PHPT is characterized by higher values of calcemia ($p < 0.001$), ionized calcium ($p < 0.001$), and parathyroid hormone ($p = 0.019$).

CONCLUSION, The actual prevalence of C in patients with PHPT is not significantly different from that found in the control group and is decreasing with respect to the past years. Moreover, C seems to be associated with the severity of the disease rather than with the diagnosis of PHPT per se.

Key Words:

Primary hyperparathyroidism, Hypercalcemia, Constipation.

Introduction

According to most case studies, chronic constipation due to hypercalcemia is one of the most common gastrointestinal symptoms associated with primary hyperparathyroidism (PHPT). Hypercalcemia is, in fact, recognized as one of the numerous causes of C[1].

The prevalence of C in PHPT is extremely variable, ranging from 4.3% and 40%[2-6]. Analyses in the literature indicate that this prevalence has been decreasing over the years, in concomitance with the increase in the asymptomatic and/or "mild" form of the disease[7]. Given the few and contradictory works aimed at evaluating the actual prevalence of C, this investigation has used criteria, established by a Committee of experts to characterize it, that go beyond the subjective interpretation of the symptom itself[8].

The aim of the study has thus been to evaluate the prevalence of C, defined according to standardized criteria, in patients with PHPT-associated hypercalcemia, by means of a questionnaire filled out and validated by the patient. This is due to the fact that up to now, C has been reported exclusively on the basis of patient history and is therefore "subjective". A further objective of the work has been to compare the present prevalence of C with respect to past observations, when the most frequent clinical picture of PHPT was "symptomatic" as opposed to the finding of the so-called asymptomatic and/or "mild" form of the disease. Finally, the study has attempted to correlate the symptom of C with the endocrine-metabolic picture to ascertain if the finding is effectively linked to the seriousness of PHPT.

Patients and Methods

From January 2006 to January 2009, 55 patients with PHPT (50 females, 5 males, average

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age 61.9 ± 9.4 years) were observed consecutively in the Department of Internal Medicine and Medicial Disciplines, "Sapienza" University, Rome, Italy (group 1).

Fifty-five subjects of comparable age and female-to-male ratio (50 women and 5 men, average age 62.1 ± 7.5 years), who had come to our Outpatient Clinic for osteoporosis screening, were used as a control group (group 2). None of the subjects were taking drugs able to interfere with the common parameters of mineral metabolism or lead to other causes of secondary constipation. All female subjects were postmenopausal.

In group 1 and group 2, a questionnaire was used for the definition of C[9-10], standardized and validated according to the "Committee on Functional Bowel Disorders and Functional Abdominal Pain (Rome II)" criteria. The diagnostic criteria were the presence (for at least 12 weeks, but not necessarily consecutive, in the preceding 12 months) of two or more of the following: (1) straining > 1/4 of defecations; (2) lumpy or hard stools > 1/4 of defecations; (3) sensation of incomplete evacuations > 1/4 of defecations; (4) sensation of anorectal obstruction/blockage > 1/4 of defecations; (5) manual manoeuvres to facilitate > 1/4 of defecations (e.g. digital evacuation support of the pelvic floor); and/or (6) < 3 defecations per week. Loose stools were not present, and there were insufficient criteria for irritable bowel syndrome [8].

In both the study and control group, the following principal parameters of phosphoric-calcium were measured in our laboratory by routine methods. They included: serum calcium, ionized calcium, phosphoremia, serum alkaline phosphatase, parathyroid hormone plasma level, and 24hr urinary calcium level using laboratory methods previously described[11-14]. For each patient, the bone mineral density was measured by Dual energy X-ray absorptiometry (Hologic QDR 4500, Hologic Inc., Waltham, MA, USA) in the lumbar spine (L1-L4) level and femoral neck (FN).

Finally, a further group, made up of patients with PHPT diagnosed prior to 1990, was studied (group 3). They consisted of the first 50 postmenopausal females and the first 5 males (average age – 59.0 ± 8.2 years – did not differ significantly) taken from a case group of about 430 PHPT patients. The presence of C as a symptom in this group was based only on case-history criteria derived from a review of their clinical records, as the validated questionnaire could not be used for these subjects.

Statistical Analysis

The statistical elaboration of the data was carried out with Sigma Stat for Windows version 2.30 (SPSS Inc. 1992-1997) and Microsoft Excel 2000 2.0.28.12 (Microsoft Corporation 1985-1999). The ± standard mean deviation was calculated for each group of variables; the comparative analysis was made between the resulting means using the Mann-Whitney test and the analysis of variance. The differences in percentages were calculated using the chi square test. The results were considered significant if a probability of less than 0.05 was obtained.

Results

The prevalence of C in PHPT (group 3) was 32.7% of the cases for the years 1970-89 and 21.8% of the cases for the years 2006-2009 (group 1). This is higher than what was observed in the group 2 of control subjects (12.7%). Significant differences between the percents in the group 1 and group 3 patients were not observed, even though when they were compared to the group of "normal" subjects (group 2), the decreasing "trend" was significant ($\chi^2 = 6.34$; $p < 0.05$).

The decreasing trend over time in the prevalence of C is confirmed in the various cases of PHPT reported in the literature, from 1959 up to 2005. In fact the prevalence of C in these studies varies from 60-80% in the '50-'60 years, with a stabilization at around 20% at the beginning of 1980s[15-17].

The average calcemia ± SD of the three groups we studied was 11.72±1.07; 11.25±0.85; 9.59 ± 0.34 mg/dL, respectively; it was significantly reduced in patients observed in 2006-2009 with respect to those in the 1970-1989 group ($p = 0.002$) and higher in both groups with respect to the controls ($p < 0.001$). When the serum calcium levels of the 1970-1989 and the 2006-2009 groups are compared in function of the presence or absence of C, the average calcemia in patients with C is similar in the two groups (respectively, 12.18 ± 1.14 vs. 12.21 ± 0.98 mg/dL n.s.), while it differs significantly in C-free subjects (11.52 ± 0.99 vs. 10.93 ± 0.44 mg/dL, $p < 0.001$) (Figure 1). In the 1970-89 case group, the patients with C had higher calcemia (12.18 ± 1.14 vs 11.52 ± 0.99 mg/dL, $p = 0.0001$), as well as higher

parathyroid hormone (113.4 ± 51.2 vs 87.1 ± 27.5 pg/mL, $p = 0.02$). In the 2006-2009 case group, in which C was evaluated with a questionnaire, the patients with C had higher calcemia and ionized calcium values than those in the C-free group (respectively: 12.2 ± 0.98 vs. 10.93 ± 0.44 mg/dL, $p < 0.001$, and 1.60 ± 0.16 vs. 1.43 ± 0.09 mmol/L, $p < 0.001$), in accord with the average value of more highly elevated plasma parathyroid hormone (111.53 ± 62.52 vs. 82.12 ± 40.39 pg/mL, $p = 0.019$). Table I also reports the results and statistical significance of the differences of other parameters, such as phosphoremia, alkaline phosphatase, 24-hour urinary calcium level and bone mineral density (BMD) measured at the femoral (FN) and lumbar levels (L1-L4).

To establish a threshold value above which hypercalcemia in PHPT is associated with C, we used (comparable to that of Consensus Conference on asymptomatic PHPT) the limit of 11.5 mg/dL, that is, 1.0 mg/dL over the uppermost limit of the norm, as the criterion of choice for the indication for surgery[18]. We noted that in patients with serum calcium level > 11.5 mg/dL, C was present in 61.5% of the cases vs. 9.5% in subjects with a value of ≤ 11.5 mg/dL ($\chi^2 = 15.75$; $p < 0.001$) (Figure 2).

Considering the various criteria for the definition of C [8], the most frequent was the number of evacuations; 33, 13 and 9 patients with PHPT presented respectively 1 or more evacuations per day, 3-5 and < 3 evacuations per week. A serum calcium level of < 11.5 mg/dL was observed, respectively in 9.1%, 30.8% and 57.7 percent of the cases ($\chi^2 = 13.5$, $p < 0.01$).

Discussion

The current presence of C in the course of PHPT, objectively defined by administration of a validated questionnaire[9,10], is 21.8% and, although this value is not statistically significant, it is higher than the value observed (12.7%) in the control population. This prevalence is lower than the percentage observed in the older cases, but similar to the more recent cases from 1980 onwards, which demonstrates percentages around 20%[3,15-17]. The findings agree with the results we obtained by comparing the first cases of PHPT observed for the years 1970-1989 and the last ones, from 2006-2009. While not significant, the percentage of C has, in fact, decreased from 32.7% to 21.8%. The prevalence of C is significantly reduced in con-

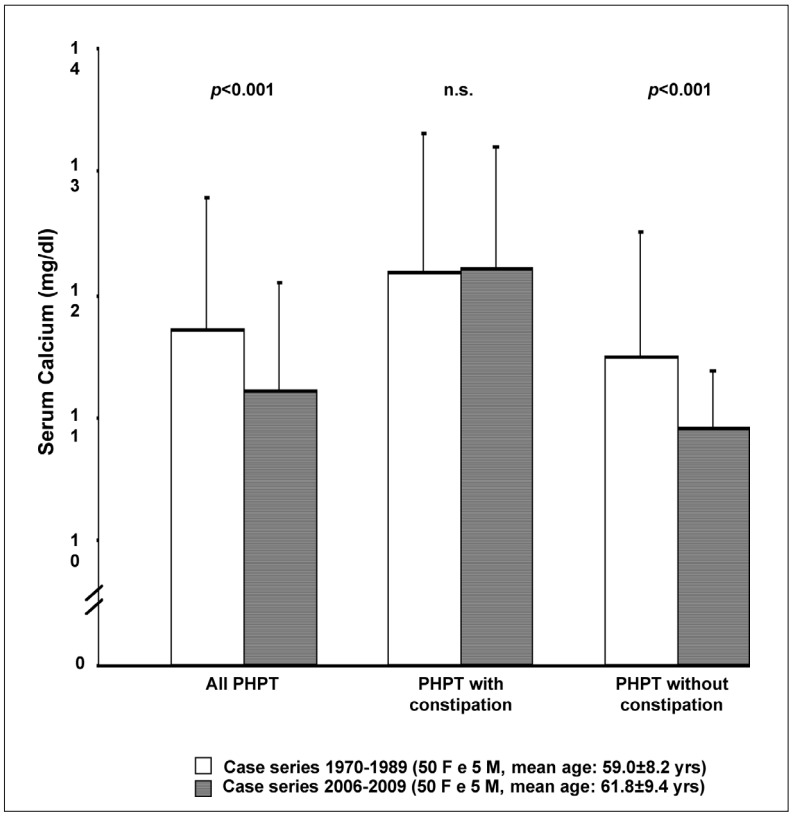

Figure 1. Mean ± SD of serum calcium in the two series of patients with primary hyperparathyroidism observed from 1970-1989 and from 2006-2009, subdivided by the presence or not of chronic constipation.

Table I. Main parameters of mineral and bone metabolism (mean + SD) in hypercalcemic patients with primary hyperparathyroidism distinguished on the basis of the presence or absence of chronic constipation.

	Constipation (n = 12)	Non constipation (n = 43)	Constipation vs non constipation
Age (years)	62.33 ± 9.33	61.81 ± 9.52	n.s.
Body Mass Index (Kg/m^2)	26.82 ± 6.21	27.7 ± 5.09	n.s.
Serum calcium (mg/dL)	12.21 ± 0.98	10.93 ± 0.44	$p < 0.001$
Ionized calcium (mmol/L)	1.60 ± 0.16	1.43 ± 0.09	$p < 0.001$
PTH (pg/mL)	111.53 ± 62.52	82.12 ± 40.39	$p = 0.019$
Serum phosphorus (mg/dL)	2.25 ± 0.39	2.74 ± 0.47	$p = 0.002$
Serum alkaline phosphatase (U/L)	107.0 ± 23.52	89.87 ± 30.09	$p = 0.047$
Urinary calcium (mg/24 hours)	351.0 ± 136.28	275.16 ± 187.03	$p = 0.021$
L1-L4 BMD (g/cm^2)	0.740 ± 0.143	0.806 ± 0.130	n.s.
FN-BMD (g/cm^2)	0.646 ± 0.158	0.648 ± 0.108	n.s.

PTH: parathyroid hormone, BMD: bone mineral density, L1-L4: lumbar spine, FN: femoral neck.

comitance with the reduction of average calcemia values observed in the two groups, those with PHPT and the normal subjects.

In both cases of patients with hyperparathyroidism, it was observed that the average value of the serum calcium level was significantly higher in patients with C as opposed to those without C. Unfortunately, we don' t have ionized calcium levels of patients in group 3, (1970-1989 yrs), which have might give us additional information in this group.

The fact that the average of the serum calcium level present in the older cases is higher than those of the more recent cases is easily explained by the current prevalence of milder forms of the disease (asymptomatic and/or "mild" PHPT) up to 80% of the new cases of PHPT diagnosed are characterized by a modest increase in both calcemia and parathyroid hormone[19]. This also takes into account the reduction in time of the prevalence of C, given that the average calcemia values of patients with C are comparable in both case groups, while those of C-free subjects are significantly different[3,15-17].

The physiopathological mechanisms at the base of C are not fully clear. Probably hypercalcemia plays a fundamental role in the onset and worsening of the symptoms[20,21]. It has been reported in the literature that also in neoplasia-associated hypercalcemia, the greater the average serum calcium value, the higher the prevalence of C. The symptom can, in fact, have a frequency of 69% for an average level of calcemia over 12 mg/dL[21]. This percent is similar to what we observed in PHPT with a value of calcemia above 11.5 mg/dL

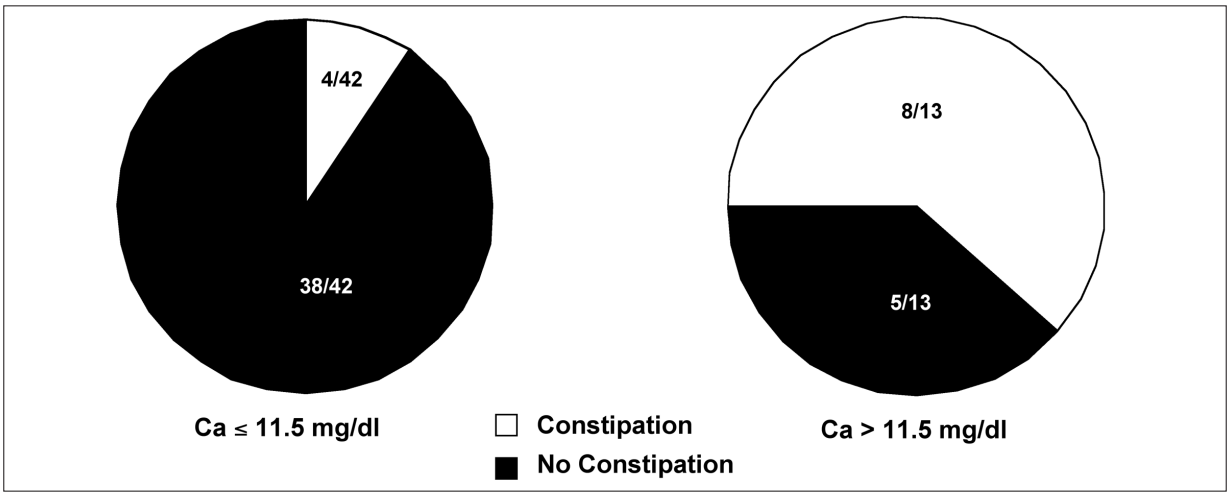

Figure 2. Frequency of chronic constipation in hypercalcemic patients with primary hyperparathyroidism related to a threshold value of serum calcium of 11.5 mg/dL.

(61.5%). Below this value, frequency is not significantly different from that observed in normal subjects (9.5%) usually going from 10%-20% (12.7% in our case group)[22]. In patients affected by cancer, it was demonstrated that for values of calcemia from 10.5 to 12.9 and from 13.0 to 14.9 and > 15.0 mg/dL, C was present respectively, in 15.8%, 46.9% and 66.7% of the cases[20].

On the other hand, in PHPT almost all of the metabolic parameters indicating a major severity of the disease (increase in parathyroid hormone, decrease in phosphoremia, increase in serum alkaline phosphatase, increase in 24hr urinary calcium) are associated with an increase in the frequency of C.

The role played by calcium in the activation of and interaction with the endocellular contractile protein apparatus has been known for a long time. The smooth musculature has, however, generally less sarcoplasmatic protein for calcium accumulation than do the striated muscles. Therefore, contraction depends primarily on extracellular concentrations of the ion. In smooth muscle the majority of Ca^{++} that initiates contraction comes from the external milieu and is supplied by cellular membrane voltage-dependent Ca^{++} channels[23].

The contractility of the smooth muscle depends on numerous factors among which are the autonomic nervous system and the interstitial cells of Cajal, truly the pacemakers of the smooth muscles of the gastrointestinal tract [24].

It has been well documented experimentally that an increase in calcium ions impedes the transmission of the afferent stimuli and decreases the efferent stimuli at the level of the parasympathetic ganglia in the presence of constant concentrations of acetylcholine[25].

It is also known that an increase in the concentration of the calcium ions reduces the neuromuscular excitability[26] and causes atonia in the gastrointestinal muscles[27]. The observation that the number of weekly defecations in PHPT patients decreases as the calcemia level increases accords with the preceding findings. In fact, 66.7% of the subjects with calcemia > 11.5 mg/dL have fewer than 3 evacuations per week compared to 9.1% of the cases that evacuate 1 or more times a day.

On the contrary, other studies have demonstrated that, after incubation with pure parathyroid extracts, the intestinal motility increases[28-29] and that the presence of chelating substances, calcium decreases intestinal tone and peristalsis[26,30]. These results are in apparent contradiction with those obtained in other studies carried out on smooth intestinal muscle cells; where the activation of membrane parathyroid hormone receptors, would mediate, thanks also to the interaction with the PTHrP (Parathyroid Hormone-Related Peptide), the release of the fibers previously subjected to contraction[31-32]. It still remains to be seen if parathyroidectomy in PHPT patients with calcemia > 11.5 mg/dL is able to correct C. In the case in which C is effectively linked to hypercalcemia, regularization of the alvus should take place together with normalization of serum calcium level.

However, in some studies it is documented how parathyroidectomy reduces the level of calcemia and the prevalence of C of about 15%[1,3], reconfirming the fundamental role of calcium in initiating C.

Conclusions

The results of our study demonstrate that:

- The actual prevalence of C in primary PHPT, while high, is not significantly different from that observed in a control population;
- A decreasing trend in the predominance of C with respect to past case studies is evident due to the prevalence, in recent years, of asymptomatic and/or "mild" forms of the disease;
- The presence of C is correlated with the degree of hypercalcemia and the overall metabolic picture of PHPT; so it may suggest that C is associated with the severity of the disease rather than with the diagnosis of PHPT *per se.*

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