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Hypercalcemia in patients with rheumatoid arthritis: a retrospective study

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Summary
Objetive: To investigate the prevalence of hypercalcemia in patients with rheumatoid arthritis (RA) and analyze the clinical features and causes of hypercalcemia.
Material and methods: Retrospective case-based review study that included 500 patients with RA. Patients with increased calcium levels on at least two occasions were identified.
Results: Hypercalcemia was present in 24 of the 500 RA patients (4.8%). The age ranged between 50 and 80 years, with a mean of 68±10 years. The mean duration of the disease was 10±7 years. Of the patients with hypercalcemia, 22 were postmenopausal women (92%) and only two were men (8%). Hyperparathyroidism was found in 9 patients in the series; only one patient had malignant hypercalcemia due to multiple myeloma, and one case was a consequence of vitamin D intoxication. In one patient, hypercalcemia appeared to be related to calcium-alkali syndrome. In the remaining patients, hypercalcemia was idiopathic (8/24) or the study was incomplete (4/24). No obvious relationship was found between disease activity and the appearance of hypercalcemia.
Conclusion: As in the general population, primary hyperparathyroidism is the most common cause of hypercalcemia in patients with RA. In some patients, no other disorders causing hypercalcemia were identified, raising the possibility of a causal relationship between RA and hypercalcemia.

Key words: hypercalcemia, rheumatoid arthritis, hyperparathyroidism, vitamin D.

Introduction
Hypercalcemia is a relatively common clinical problem and a frequent laboratory finding, both in hospital and out-of-hospital practice. Calcium ions play a critical role in many cellular functions. Parathyroid hormone (PTH) and vitamin D are the most important hormones for regulating calcium. The main sources of serum calcium are intestinal absorption, stimulated by active vitamin D metabolites, and bone resorption, usually stimulated by PTH. Therefore, hypercalcemia can be classified as PTH-dependent (due to increased secretion of PTH by the parathyroid glands) and independent of PTH. The latter cases are attributable to increased bone resorption and/or increased intestinal absorption of calcium, induced by factors other than PTH. Among them, PTH-related protein (PTHrP) and locally produced cytokines are factors that often cause hypercalcemia in cancer patients[1]. Unregulated extrarenal synthesis of 1,25-dihydroxyvitamin D can also cause hypercalcemia, particularly in patients with chronic granulomatous disorders and in some patients with lymphoma[2].

Most reported cases of hypercalcemia are due to primary hyperparathyroidism or malignant neoplasms; together, these causes account for more than 90 percent of cases. Less common causes include granulomatous disorders, vitamin D poisoning, lithium or thiazide therapy, familial hypocalciuric hypercalcemia, etc. Among musculoskeletal diseases, sarcoidosis and metastatic bone tumors are well-known causes of hypercalcemia. However, the relationship between rheumatoid arthritis (RA) and hypercalcemia is unclear and conflicting results have been reported[3-5]. Thus, while Ralston et al. found only 1 patient with hypercalcemia among 102 patients with RA[5], a much higher frequency, up to 30%, has been reported in some series[3]. Therefore, our study aims to determine the frequency of hypercalcemia and its origin in unselected patients with RA.

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Patients and methods

We investigated 500 unselected patients with a diagnosis of RA[6], seen in the Rheumatology consultation of the Marqués de Valdecilla Hospital. This tertiary hospital serves a population of about 350,000 people.

A computerized search of the blood tests carried out on these patients over a 15-year period (2002-2016) allowed us to identify total and ionized calcium values. Hypercalcemia was defined as a total serum calcium concentration greater than 10.4 mg/dl, and/or ionized calcium greater than 1.35 mmol/l (the limits of the normal range), in at least two determinations. The clinical records of patients with hypercalcemia were reviewed and clinical and biochemical data were extracted according to a standard protocol. The protocol was approved by the Cantabria Clinical Research Ethics Committee, which did not consider the written consent of the patients necessary due to the retrospective observational nature of the study.

A Pubmed search was done on the terms "rheumatoid arthritis" and "hypercalcemia". Secondary references of relevant documents were also checked.

Results

Patients' characteristics

A total of 476 patients (95.2%) presented normal serum calcium levels, while 24 patients (4.8%) had hypercalcemia, according to the definition above.

The demographic, clinical and laboratory characteristics are listed in table 1. In summary, the RA sample with hypercalcemia (n=24) showed a preponderance of female gender (22 of 24, 92%) and had a mean age of 68±10 years (50-80). Most of the patients had long-standing RA (mean duration of the disease at the time of identification of hypercalcemia, 10±7 years; range 2-21), but in 5 cases the diagnosis of RA and hypercalcemia were simultaneous. Globally, 72% patients had positive rheumatoid factor and/or positive anti-citrullinated peptides. Not unexpectedly, the clinical spectrum was quite varied. Globally, 11 of the 24 patients with hypercalcemia (46%) had elevated inflammatory markers (CRP or ESR) at that time. Only 10 patients (42%) had evidence of arthritis at the time of hypercalcemia, and only 6 of them had arthritis and increased inflammatory markers. Four patients were taking vitamin D supplements and 9 were receiving calcium supplements. In all but one case, the doses were low and could not be considered as the cause of hypercalcemia.

Causes of hypercalcemia

After diagnostic studies, primary hyperparathyroidism was found in 9 patients (Figure 1). This represents 1.8% of the 500 RA patients, and 37% of the 24 hypercalcemia patients. Serum PTH levels ranged between 73 and 283 pg/ml (normal range <65 pg/ml). In 6 patients, a parathyroid adenoma was identified by scintigraphy or during surgical exploration. Three patients rejected the imaging studies. Two patients underwent surgery, 4 received antiresorptives and 3 did not receive any specific therapy.

Only one of the patients had a malignant hypercalcemia, due to multiple myeloma. In another patient, the hypercalcemia was due to vitamin D intoxication. In one patient, hypercalcemia could be due to the calcium-alkaline syndrome, a situation similar to the milk-alkaline syndrome. This diagnosis was based on the fact that hypercalcemia was associated with renal failure and the patient had been treated with calcium carbonate and thiazide supplements.

Table 1. Characteristics of patients with hypercalcemia

Parameter	Value
Age at detection of hypercalcemia	68 ± 10 years
Duration of RA	10 ± 7 years
FR+	12/24 (50%)
ACCP+	12/24 (50%)
Total serum calcium	10.8 ± 0.5 mg/dl
Serum ionic calcium	1.41 ± 0.1 mmol/l
PCR	2.3 ± 4.8 mg/dl
VSG	31 ± 33 mm/h
Creatinine	1.2 ± 0.7 mg/dl
PTH	87 ± 80 pg/ml
25-OH-vitamin D	46 ± 66 ng/ml

Variables expressed as mean ± standard deviation (SD) or number and percentage. RA: rheumatoid arthritis; RF: rheumatoid factor; ACCP: anti-citrullinated cyclic peptide antibodies.

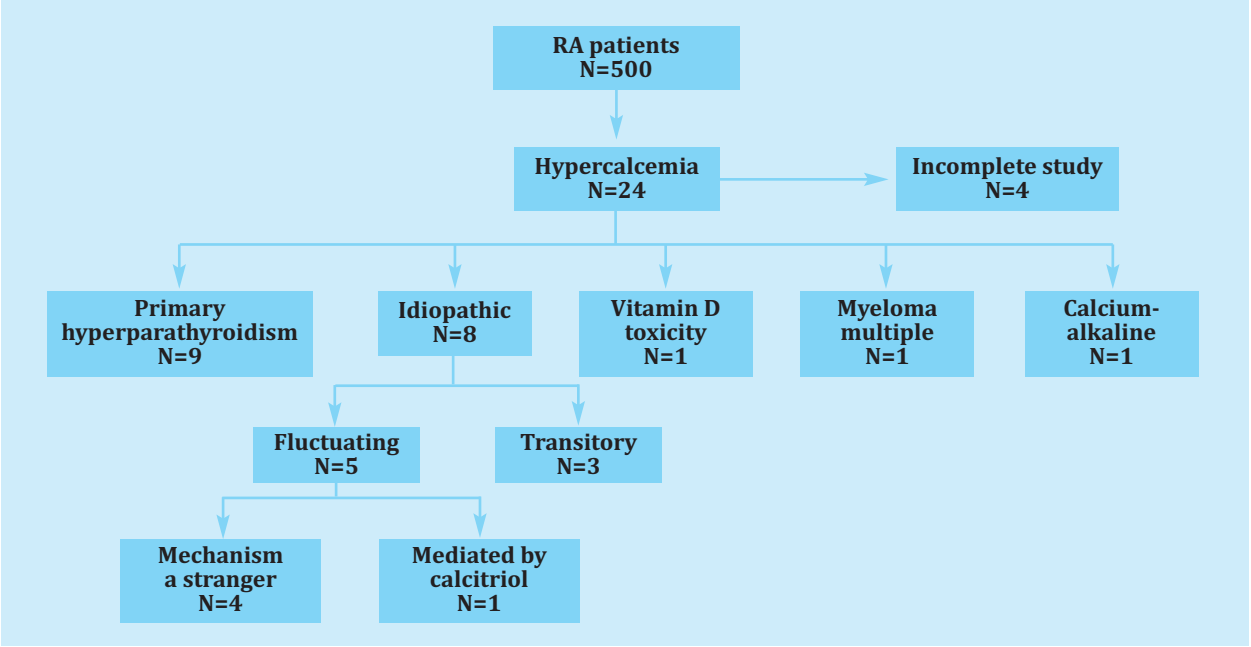
In the other patients in our series (8/24), the cause of hypercalcemia was unknown and, therefore, it can be considered idiopathic. Among this group, hypercalcemia was fluctuating (alternating normal and increased levels) in 5 patients, while in the other 3 it was transient. Hypercalcemia was always mild and asymptomatic. Although some patients showed elevated markers of inflammation, review of the cases did not reveal a relationship between calcaemia and clinical outbreaks of the disease. In 4 patients, follow-up studies and follow-up excluded disorders known to be associated with hypercalcemia (such as cancer, hyperparathyroidism, hyperthyroidism, adrenal insufficiency, etc.). However, in 4 other patients the study was limited, insufficient to establish with certainty the etiology of hypercalcemia.

None of the patients presented hypercalcemia secondary to granulomatous diseases (such as tuberculosis and sarcoidosis) or solid organ neoplasia. However, one patient had hypercalcemia mediated by increased 1,25-dihydroxyvitamin D levels, with suppressed PTH and increased angiotensin converting enzyme (ACE). Neither in the initial study (which included CT, PET and bone marrow biopsy), nor during follow-up were signs of neoplasia, adenopathy or granulomatous disease found. Corticosteroid treatment achieved full normalization of biochemical parameters, but the source of 1,25-dihydroxyvitamin D could not be identified.

Discussion

RA is a chronic systemic inflammatory disorder. Although joint tissues are the main target of the inflammatory process, the disease also has consequences for bone tissue, both locally and systemically. In particular, RA causes increased bone resorption, which results locally in erosions and juxta-articular osteopenia, and systemically in reduced bone mass and increased risk of osteoporotic fractures. However, the association of RA with hypercalcemia is discussed (Table 2).

Figure 1. Causes of hypercalcemia in this series



Almost 4 decades ago, Kennedy et al. noted the presence of hypercalcemia in 23 of 50 patients with RA (46%). In 7 cases (14%) the hypercalcemia was permanent. The cause was unclear. Many patients had active disease and some biochemical characteristics that suggested hyperparathyroidism, but serum PTH levels were within the normal range[4]. However, Scott et al. reported a very low frequency of hypercalcemia among RA patients, 0.5% among outpatients and 0-2% among hospitalized patients[7]. These findings are similar to those of Ralston et al., who found only one case of hypercalcemia in a group of 102 RA patients studied over a 3-month period[5]. On the other hand, in a more recent study by Oelzner et al. which included 146 German RA patients, the frequency of hypercalcemia was 30%. Since high calcium levels were correlated with higher ESR and CRP values, as well as lower levels of PTH and 1,25-dihydroxyvitamin D, they suggested that hypercalcemia was probably due to increased bone resorption related to disease activity[3].

In our study, the frequency of hypercalcemia among RA patients was 4.8%, which is intermediate between those reported in previous studies. It is interesting to note that, unlike previous studies, we did not observe a clear association between RA activity and hypercalcemia. However, differences in patient characteristics, and specifically the availability of more potent disease-modifying drugs in recent years, make it difficult to compare the older series with the more recent ones.

Regarding the etiology of hypercalcemia, primary hyperparathyroidism seems to be the most common cause in patients with RA, similar to what happens in the general population. The prevalence of hyperparathyroidism in the Caucasian population is approximately 0.2-0.9%[8,9]. Therefore, the 1.8% frequency that we found in RA may be somewhat higher than expected. However, the limited sample size does not allow us to firmly establish that the frequency of primary hyperparathyroidism is higher in RA than in the general population. However, a higher prevalence of hyperparathyroidism has recently been published in other RA cohorts, with a mean frequency of around 2.8%[10]. On the other hand, it is worth mentioning that patients with hyperparathyroidism can have a variety of musculoskeletal manifestations, including pain and chondrocalcinosis[11-13], which must be properly interpreted and not be confused with the consequences of RA or other rheumatic disorders.

In the general population, cancer is the second most common cause of hypercalcemia[14,15]. In our RA series, only one patient had hypercalcemia related to a malignancy, which is reassuring in the context of the increased cancer risk reported in RA[16].

The calcium-alkaline syndrome, an update of the picture previously known as milk-alkaline syndrome, characterized by the triad of hypercalcemia, metabolic alkalosis and kidney failure, secondary to the ingestion of variable amounts of calcium together with an absorbable alkaline, represents, according to data recent, the third most common cause of hypercalcemia[17-19]. One patient in our cohort presented a picture consistent with this syndrome.

In a significant proportion of patients, the cause of hypercalcemia remained unclear. Patients with lymphoma and granulomatous disorders (such as tuberculosis or sarcoidosis) may have hypercalcemia due to unregulated extrarenal synthesis of 1,25-dihydroxyvitamin D[20,21]. In the current series, one patient had recurrent hypercalcemia associated with high levels of 1,25-dihydroxyvitamin D. Consistent with an extrarenal source, 1,25-dihydroxyvitamin D and calcium levels normalized with glucocorticoid therapy. However, after a large study, which included repeated PET scans, CT scans, and bone marrow biopsies, no evidence of granulomatous disorder or cancer could be found. On the other hand, the patient's age and the time course of serum calcium and 1,25-dihydroxyvitamin D levels do not fit within the spectrum of genetic deficiency of CYP24A1, an enzyme that metabolizes 25 and 1,25-dihydroxyvitamin D[22,23]. Therefore, RA, although inactive, was the most likely explanation for the abnormal synthesis of 1,25-dihydroxyvitamin D. It should be noted

Table 2. Hypercalcemia studies in patients with rheumatoid arthritis (RA)

Author, year (reference)	N hypercalcemia/total	Sex, female/male	Age, years	Maximum calcium, mg/dl	Cause of hypercalcemia
Kennedy, 1979[4]	7/50	7 /0	NI	11.2	RA
Bramble, 1980[30]	2/50	NI	NI	NI	NI
Scott, 1981[7]	2/20 (ambulatory) 2/193 (hospitalized)	NI	NI	11.2	NI
Gates, 1986[24]	Only case	0/1	35	13.4	RA
Ralston, 1990[5]	1/102 21/-	1/0 NI	NI	NI	Hyperparathyroidism, 15 Thiazides, 4 Cancer, 2
Oelzner, 2006[3]	44/146	NI	NI	NI	RA
Mudge, 2012[31]	Only case	1/0	60	11.1	RA
Abrar-Ahmad, 2016[32]	Only case	1/0	77	11.5	Hyperparathyroidism
Current series	24/500	22/2	50-80 (mean 68)	12.3	Hyperparathyroidism, 9 Multiple myeloma, 1 Calcium-alkali, 1 Vitamin D poisoning, 1 Idiopathic, 8 Incomplete study, 4

NI: not included.

that Gates published the case of a patient similar to this[24]. The mechanisms that relate RA to 1,25-dihydroxyvitamin D synthesis are unclear, but could depend on cytokine-mediated macrophage activation. Whatever the mechanisms involved, these appear to be very rare cases. In fact, RA was not among the underlying disorders in a series of 101 patients with 1,25-dihydroxyvitamin D[25] mediated hypercalcemia.

Future epidemiological studies, with larger cohorts of RA patients, would help to clarify whether the frequency of hyperparathyroidism increases in RA. Furthermore, careful clinical studies of patients in whom diagnostic analysis does not reveal causes of hypercalcemia other than RA can help to better understand the pathophysiology of these rare cases.

Treatment of hypercalcemia in RA must take into account the cause and the mechanisms responsible for the increase in serum calcium. General measures should include the withdrawal of calcium supplements and other drugs that induce hypercalcemia (such as lithium or thiazides) and maintaining adequate hydration. In acute severe cases, intravenous fluids, bisphosphonates such as zoledronic acid, and sometimes calcitonin are indicated[26]. For patients with a parathyroid adenoma, surgical removal is the therapy of choice, but non-invasive procedures can be useful in patients with very high surgical risk[27,28]. In these patients, drug treatment with cinacalcet or antiresorptive agents can help control hypercalcemia[9]. In 1,25-dihydroxyvitamin D-mediated hypercalcemia, corticosteroids are usually very effective, but ketoconazole or antimalarials can also help control extrarenal vitamin D hydroxylation and, consequently, normalize levels[2,29].

Conclusion

In this study of a cohort of 500 RA patients, hypercalcemia was present in 4.8%. As in the general population, primary hyperparathyroidism was the most common cause. In some patients, no other disorders causing hypercalcemia were identified, raising the possibility of a causal relationship between RA and hypercalcemia. However, in these cases we did not find a clear link between disease activity and calcium levels.

Although limited by its retrospective nature, our study thus adds useful information on the epidemiology of hypercalcemia and RA. These results suggest that hypercalcemia has a similar frequency in RA and in the general population and that the causes are similar. Although the study was incomplete in some cases, our data support that most patients have another underlying diagnosis as the cause of hypercalcemia. Therefore, if hypercalcemia is discovered in a patient with RA, a search should be made for underlying causes, particularly hyperparathyroidism and cancer.

Conflict of interests: The authors declare no conflict of interest.

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