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Hypercalcemia and autoimmune diseases

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Hypercalcemia is a very common water-electrolyte imbalance found in daily clinical practice. It is defined as the presence of a serum calcium concentration greater than 2 standard deviations from the mean laboratory value, which is usually 10.6 mg/dL[1].

From the pathophysiological point of view, high levels of calcium in the blood increase the difference in electrical potential between cell membranes, which increases the depolarization threshold. Clinically, hypercalcemia may present a very wide spectrum that can range from a certain muscle weakness to depression and even coma and death, and this depends on several factors such as the severity of hypercalcemia, the speed of its onset and other circumstances specific to the patient, such as age, comorbidity and medication received[1]. Therefore, it is not surprising that two patients with the same high serum calcium values present completely different symptoms.

The causes of hypercalcemia may vary considerably. In our environment, the most frequent is the existence of primary hyperparathyroidism[2-4], a very common endocrine disease that has an incidence in the United States with 230 cases per 100,000 inhabitants in women and 85 cases per 100,000 in men[3]. Furthermore, rheumatoid arthritis is an autoimmune-based rheumatic disease, which is also very frequent[5]. In Spain, it constitutes an estimated prevalence of 0.9% of the population[6]. In a recent review of the comorbidity described in rheumatoid arthritis, depression appears as the most frequent condition, not always considered a priority, reaching figures that range from15% to 29%[6]; curiously, hypercalcemia is not among them.

Some years ago, several studies suggested that hypercalcemia could be a marker of the activity of rheumatoid arthritis. In the series by Oelzner et al., 30.1% of the patients who suffered rheumatoid arthritis presented hypercalcemia and these patients had higher ESR and CRP levels[7], as well as lower PTH and 1.25 dihydroxyvitamin D values. In another series, the same authors suggest that low levels of 1,25 dihydroxyvitamin D could cause osteoporosis associated with rheumatoid arthritis[8]. However, other authors have described that the prevalence of hypercalcemia and its causes are similar in rheumatoid arthritis as in the general population[9]. Thus, there is a controversy and data have been published that would support both points of view, that hypercalcemia is part of the clinical spectrum *per se*, perhaps as a marker of its activity, and also the opposite, one that suggests that the causes of hypercalcemia in patients with rheumatoid arthritis are the same as in the rest of the population[7-9].

Delving deeper into the study of this dilemma, in this issue of the Revista de Osteoporosis y Metabolismo Mineral, Córdoba et al.[10] report a study carried out in 500 patients with rheumatoid arthritis, among which 24 patients of both sexes have hypercalcemia. In them, possible causes of hypercalcemia were found in several cases (9 patients with primary hyperparathyroidism, multiple myeloma, vitamin D intoxication, etc.) but in a third of them (8 of 24) no cause was found that justify it. Moreover, they could not establish a relationship between the activity of rheumatoid arthritis and hypercalcemia. Thus, the authors suggest that in the presence of hypercalcemia in a patient with rheumatoid arthritis a search for some other cause is required. This search may be unsuccessful in a high proportion of patients and, furthermore, hypercalcemia is not related to the activity of the disease.

In other words, the results of the Córdoba et al. study[10] show data that coincide with those of previous studies in both directions, without being conclusive in any of them. So, there is no doubt that the often repeated phrase "further studies are required" is perfectly valid in this case.

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