Original research

Incidence of hypocalcemia and hypercalcemia in hospitalized patients: Is it changing?

A. Catalano,⁎ D. Chilà, F. Bellone, G. Nicocia, G. Martino, I. Loddo, N. Morabito, S. Benvenga, S. Loddo

Department of Clinical and Experimental Medicine, University Hospital of Messina, Messina, Italy
Department of Cognitive Sciences, Psychology, Education and Cultural Studies, University of Messina, Messina, Italy
Department of Laboratory Medicine and Advanced Biotechnologies, Mediterranean Institute for Transplantation and Advanced Specialized Therapies – ISMETT – IRCCS, Palermo, Italy
Master Program on Childhood, Adolescent and Women’s Endocrine Health, University of Messina, Italy
Interdepartmental Program of Molecular & Clinical Endocrinology and Women’s Endocrine Health, University Hospital Policlinico G. Martino, Messina, Italy

ARTICLE INFO

Keywords:
Electrolytes
Hypercalcemia
Hypocalcemia
Inpatients
Elderly
Pediatrics

ABSTRACT

Disorders of calcium metabolism are frequently encountered in routine clinical practice. However limited data are available on the epidemiology of hypocalcemia and hypercalcemia in hospitalized patients. Our aim was to evaluate the frequency of hypocalcemia and hypercalcemia in hospitalized patients. This is a retrospective study based on the laboratory results of all hospitalized subjects (n = 12,334) whose calcemia was determined between January 1st, 2011 and December 31st, 2014. Measurements of serum calcium were carried out by a single centralized laboratory. Hypocalcemia was defined as serum calcium levels < 8.2 mg/dl and hypercalcemia as serum calcium levels > 10.4 mg/dl. Albumin correction was applied to adjust serum calcium values.

Overall, hypocalcemia accounted for 27.72% (n = 3420) and hypercalcemia for 4.74% (n = 585) of the 12,334 inpatients. The highest prevalence of hypocalcemia was found in patients over 65 yr. (n = 2097, 61.31%) vs. younger subjects, while the highest prevalence of hypercalcemia was observed in patients aged 0–18 yr. (n = 380, 64.95%). Hypocalcemia was more often encountered in males (n = 1952, 57.07%) while no gender differences were found regarding hypercalcemia. Incidence of hypocalcemia changed over time varying from 35.42% (n = 1061) in 2011 to 21.93% (n = 672) in 2014 (r = −0.98; p = 0.01). Differently, incidence of hypercalcemia did not significantly increase significantly from 3.47% (n = 104) in 2011 to 6.92% (n = 211) in 2014 (r = 0.94; p = 0.052).

Despite increased awareness about electrolytes disturbance, physicians should consider calcium levels because of life-threatening consequences associated to hypo- and hypercalcemia. Patient’s gender and age could be associated to a different risk of calcium disturbance in hospitalized patients.

Introduction

Calcium is the most abundant mineral in the body and participates with phosphorus to form calcium phosphate in bones and teeth. It is involved in many biological processes since it is essential for the normal functioning of nerves and muscles and plays a role in blood coagulation and in several enzymatic processes [1,2].

As expected perturbation of calcium homeostasis may have a deep impact on human pathology [2]. Serum calcium levels are usually maintained within a normal range and ionized calcium is tightly regulated by the actions of parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D (1,25(OH)2D) on the kidney, bone and gastrointestinal tract [3,4].

PTH stimulates calcium release from bone and calcium resorption in the kidney, moreover it stimulates 1α-hydroxylation of 25-hydroxyvitamin D leading to the production of active 1,25-dihydroxyvitamin D (calcitriol) which modulates gastrointestinal calcium absorption [3].

In a clinical setting, either elevation (hypercalcemia) or reduction (hypocalcemia) of serum calcium concentrations could depend by several pathologies and could be associated with life-threatening consequences [2].

Increasing life expectancy and improvement of standard medical
Results of p < 0.05 were considered to indicate statistical significance. Linear regression was used to describe changes of incidences over time. Values calculated differences in the proportion of categorical variables. Linear regression was used to describe changes of incidences over time. Values of p < 0.05 were considered to indicate statistical significance.

Discussion

Hypo- and hypercalcemia are calcium disorders commonly observed

Materials and methods

This is a retrospective study considering all the patients whose calcium concentrations were determined during hospital recovery at the University Hospital of Messina, Messina, Italy, over the period from January 1st, 2011 to December 31st, 2014. Any age and gender were considered. Total calcium levels were detected by a Centralized Laboratory of our hospital through an automated analyzer (Roche Modular Analytics P 800). All the measurements were corrected with serum albumin levels as required. Statistical analyses were performed using MedCalc software (version 10.2.0.0; Mariakerke, 173 Belgium). The χ² test was performed to calculate differences in the proportion of categorical variables. Linear regression was used to describe changes of incidences over time. Values of p < 0.05 were considered to indicate statistical significance.

Results

In the period from January 1st, 2011 to December 31st, 2014 we evaluated a sample of 12,334 internal patients whose calcium level was measured. We found 27.72% (n = 3420) of patients showing hypocalcemia and 4.74% (n = 585) showing hypercalcemia. Concerning patients with hypocalcemia, we observed 42.93% of cases (n = 1468) in females and 57.07% (n = 1952) in males (χ² = 136, p < 0.0001). Adult subjects were more likely to exhibit low calcium levels: in fact, hypocalcemia was found in 61.31% (n = 2097) of subjects over 65 yr., in 33.3% (n = 1139) of subjects aged 19–65 yr., finally in 5.38% (n = 184) of subjects aged 0–18 yr. (χ² = 2407, p < 0.0001). At the same time, we detected 585 cases of hypercalcemia of whom 50.95% (n = 298) were observed in female and 49.05% (n = 287) in male patients (χ² = 0.34, p = 0.55). The higher incidence of hypercalcemia was found in subjects aged 0–18 (64.95%, n = 380), whereas in the age range 19–65 yr. was 16.92% (n = 99) and in patients over 65 yr. (n = 106) was 18.11% (χ² = 395, p < 0.0001).

Incidence of hypocalcemia changed over time varying from 35.42% (n = 1061) in 2011 to 21.93% (n = 672) in 2014 (r = −0.98; p = 0.01); differently, incidence of hypercalcemia increased from 3.47% (n = 104) in 2011 to 6.42% (n = 211) in 2014 (r = 0.94; p = 0.052); normocalcemia cases increased from 61.10% (n = 1830) in 2011 to 71.13% (n = 2180) in 2014 (r = 0.93; p = 0.06) (Fig. 1). Incidence of hypocalcemia according to gender was reduced during the observation period in both genders (r = −0.96, p = 0.03 and r = −0.99, p = 0.006 in females and males respectively) (Fig. 2). Differently, incidence of hypercalcemia increased over time in males (r = 0.99, p = 0.006) but not in females (r = 0.67, p = 0.32) (Fig. 3).

Distribution of cases of hypocalcemia according to age remained unchanged over time in the group of subjects in the age range 0–18 yr. (r = −0.52, p = 0.47) while in subjects between 19 and 65 yr. and in those ones over 65 yr. a reduction of cases was observed (r = −0.96, p = 0.04 and r = −0.99, p = 0.007, respectively) (Fig. 4). A tendency of increasing incidence of hypercalcemia was observed in the age ranges 0–18 yr. (r = 0.92, p = 0.07) and 19–65 yr. (r = 0.97, p = 0.02), while incidence of hypercalcemia remained unchanged in the subjects aged over 65 yr. (r = 0.17, p = 0.82) (Fig. 5).
in hospitalized patients, due to several causes as summarized in Tables 1 and 2 [14–26].

Prevalence of hypocalcemia was previously reported to rank to 18% of all hospitalized patients and to be represented in 85% of patients in the intensive care units [5].

In our population the prevalence of hypocalcemia was 27.72%. A common cause of hypocalcemia in primary care is vitamin D deficiency which is, irrespective of latitude, a frequent condition often resulting in secondary increased levels of PTH [3]. Mild and slowly developing hypocalcemia could be an asymptomatic laboratory finding, but hypocalcemia could be also a life-threatening metabolic disturbance and acute hypocalcemia can provoke severe symptoms which requires hospitalization [4,5]. Hypocalcemia is frequently encountered in hospitalized patients and could be also empathized by low dietary calcium intake.

We noticed a tendency to a decreasing incidence of hypocalcemia over the observation period, with a reduction of cases of 13.49% from 2011 to 2014. Our findings are consistent with the wide attention recently attributed to vitamin D deficiency, especially in the elderly. As vitamin D is a key regulator of calcium absorption, adequate vitamin D status could contribute to maintain eucalcemia [27–29]. Incidence of hypocalcemia decreased of 14.35% in particular in females. This is at least in part due to more frequent prescriptions of vitamin D and/or calcium in accordance with the prevention of osteoporosis [30]. However a significant decreasing incidence of hypocalcemia was also observed in males as shown in Fig. 2.

Fig. 2. Incidence of hypocalcemia according to gender over the period from January 2011 to December 2014.

Fig. 3. Incidence of hypercalcemia according to gender over the period from January 2011 to December 2014.

Fig. 4. Incidence of hypocalcemia according to age over the period from January 2011 to December 2014.
The prevalence of hypercalcemia in our hospital was 4.74%. Our findings are consistent with previous data by Aishah et al. who found a smaller prevalence of 2.4% in hospitalized patients [31]. No relevant gender differences was found about prevalence of hypercalcemia, but an increased incidence of hypercalcemia in males and younger subjects was detected over the observation period. Although we did not investigate the causes of calcium abnormalities, we speculated that in the younger subjects an iatrogenic effect (e.g. thiazide diuretics, lithium, theophylline) could not be ruled out, in addition to the other causes of hypercalcemia in young individuals [32].

Despite increased awareness about electrolyte disturbances, physicians should consider calcium levels because of life-threatening consequences associated to hypo- and hypercalcemia. Gender and age of patient could be associated to a different risk of this electrolyte disorder in hospitalized patients.

Declarations of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcte.2018.05.004.

References

[1] Espay AJ. Neurologic complications of electrolyte disturbances and acid-base balance. Handb Clin Neurol 2014;119:365-82.
[2] Akirov A, Gorshstein A, Shraga-Slutzky I, Shimon I. Calcium levels on admission and before discharge are associated with mortality risk in hospitalized patients. Endocrine 2017 Aug;57(2):344-51. http://dx.doi.org/10.1007/s12020-017-1353-y. Epub 2017 Jun 30.
[3] Holick MF. Vitamin D deficiency. N Engl J Med 2007;357(3):266-81.
[4] Body JJ, Bouillon R. Emergencies of calcium homeostasis. Rev Endocr Metab Disord 2003;4(2):167-75.
[5] Cooper MS, Gittoes NJ. Diagnosis and management of hypocalcemia. BMJ 2008;336(7656):1298-302.
[6] Ralston SH, Gallacher SJ, Patel U, Campbell J, Boyle IT. Cancer associated hypercalcemia: morbidity and mortality. Clinical experience in 126 treated patients. Ann Intern Med 1990;112:499-504.
[7] Egbuna OI, Brown EM. Hypercalcemia and hypocalcemia conditions due to calcium-phosphate disturbances. J Clin Endocrinol Metab 2005;90(8):4379-86.
[8] Lizzio G, Milionis HJ, Eliaf M. A review of drug-induced hypercalcemia. J Bone Miner Miner Metab 2009;27(6):635-42.
[9] Palmér M, Jakobsson S, Akerström G, Ljunghall S. Prevalence of hypercalcaemia in a health survey: a 14-year follow-up study of serum calcium values. Eur J Clin Invest 2008;38(10):756-62.
[10] Frolich A. Prevalence of hypercalcaemia in normal and in hospital populations. Dan Med Bull 1998;45:436-9.
[11] Catalano A, Raitile G, Lasco A. Hypocalcemia: a sometimes overlooked cause of heart failure in the elderly. Aging Clin Exp Res 2012;24(4):400–3.
[12] Labriola L, Wallemacq P, Gulbis B, Jadoul M. The impact of the assay for measuring albumin on corrected calcium concentrations. Nephrol Dial Transplant 2009;24(8):2071-6.
[13] Riancho JA, Arjona R, Sanz J, Olmos JM, Valde R, Barcelo JR. Is the routine measurement of ionized calcium worthwhile in patients with cancer? Postgrad Med

Table 1
Main causes of hypocalcemia.

| Category          | Cause                                                                 |
|-------------------|----------------------------------------------------------------------|
| PTH-Dependent     | 1. Primary Hyper-PTH                                                  |
|                   | a) Primary Hyper-PTH                                                  |
|                   | b) Secondary Hyper-PTH                                                |
|                   | a) Renal failure                                                      |
|                   | b) Aluminum intoxication                                             |
|                   | 1. Primary Hypo-PTH                                                  |
|                   | a) Renal failure                                                      |
|                   | b) Aluminum intoxication                                             |
|                   | 1. PTH-Independent                                                   |
|                   | a) Paraneoplastic syndrome                                            |
|                   | b) Iatrogenic (thiazide diuretics, lithium, theophylline)             |
|                   | c) Vitamin D intoxication                                             |
|                   | 1. Absent-PTH                                                         |
|                   | a) Tumor lysis                                                        |
|                   | b) Rhabdomyolysis                                                    |
|                   | c) Acute renal failure                                                |
|                   | 1. Ineffective-PTH                                                    |
|                   | 1. Acute hyperphosphatemia                                            |
|                   | a) Tumor lysis                                                        |
|                   | b) Rhabdomyolysis                                                    |
|                   | c) Acute renal failure                                                |
|                   | 1. Abolished-PTH                                                      |
|                   | a) Tumor lysis                                                        |
|                   | b) Rhabdomyolysis                                                    |
|                   | c) Acute renal failure                                                |

Table 2
Main causes of hypercalcemia.

| Category          | Cause                                                                 |
|-------------------|----------------------------------------------------------------------|
| Absent-PTH        | 1. Primary Hypo-PTH                                                  |
|                   | a) Tumor lysis                                                        |
|                   | b) Rhabdomyolysis                                                    |
|                   | c) Acute renal failure                                                |
|                   | 1. Secondary Hyper-PTH                                                |
|                   | a) Renal failure                                                      |
|                   | b) Aluminum intoxication                                             |
|                   | 1. PTH-Independent                                                   |
|                   | a) Paraneoplastic syndrome                                            |
|                   | b) Iatrogenic (thiazide diuretics, lithium, theophylline)             |
|                   | c) Vitamin D intoxication                                             |
|                   | 1. Absent-PTH                                                         |
|                   | a) Tumor lysis                                                        |
|                   | b) Rhabdomyolysis                                                    |
|                   | c) Acute renal failure                                                |
|                   | 1. Ineffective-PTH                                                    |
|                   | 1. Acute hyperphosphatemia                                            |
|                   | a) Tumor lysis                                                        |
|                   | b) Rhabdomyolysis                                                    |
|                   | c) Acute renal failure                                                |
|                   | 1. Abolished-PTH                                                      |
|                   | a) Tumor lysis                                                        |
|                   | b) Rhabdomyolysis                                                    |
|                   | c) Acute renal failure                                                |

Fig. 5. Incidence of hypercalcemia according to age over the period from January 2011 to December 2014.
Bilezikian JP, Khan A, Potts Jr JT, ML Brandi, Clark IL, Shoback D, et al. Hypoparathyroidism in the adult: epidemiology, diagnosis, pathophysiology, target-organ involvement, treatment, and challenges for future research. J Bone Miner Res 2011;26(10):2317–37.

Rosen CJ, Brown S. Severe hypocalcemia after intravenous bisphosphonate therapy in occult vitamin D deficiency. N Engl J Med 2003;348(15):1503.

Mishra A, Wong L, Jonklaas J. Prolonged, symptomatic hypocalcemia with pamidronate administration and subclinical hypoparathyroidism. Endocrine 2001;14(2):159–64.

Tohem JF, Bilezikian JP. Diagnosis and treatment of hypocalcemic emergencies. Endocrinologist 1996;6(1):10–8.

Lasco A, Catalano A, Morabito N. Are physicians ready to prevent osteoporotic fractures in hemodialysis patients? Int J Endocrinol Metab 2012;10(4):634–5. Fall.

Stewart AF. Clinical practice. Hypercalcemia associated with cancer. N Engl J Med 2005;352:373–9.

Brown EM. Familial hypocalciuric hypercalcemia and other disorders with resistance to extracellular calcium. Endocrinol Metab Clin North Am 2000;29:503–22.

Eftekhar F, Yousefzadeh D. Primary infantile hyperparathyroidism: clinical, laboratory and radiographic features in 21 cases. Skeletal Radiol 1982;8:201–8.

Sargent JTS, Smith OP. Haematological emergencies managing hypercalcemia in adults and children with haematological disorders. Br J Haematol 2010;149:465–77.

Endelson GW, Kleerekoper M. Hypercalcemic crisis. Med Clin North Am 1995;79:79–92.

Nusbaum SR, Gaz RD, Arnold A. Hypercalcemia and ectopic secretion of parathyroid hormone by an ovarian carcinoma with rearrangement of the gene for parathyroid hormone. N Engl J Med 1990;323:1324–8.

Chen YC, Sonnoki DM, Mastro AM. Breast cancer metastasis to the bone: mechanism of bone loss. Breast Cancer Res 2010;12:215–26.

Clines GA. Mechanisms and treatment of hypercalcemia of malignancy. Curr Opin Endocrinol Diabetes Obes 2011;18:339–46.

Catalano A, Morabito N, Di Stefano A, Morini E, Basile G, Faraci B, et al. Vitamin D and bone mineral density changes in postmenopausal women treated with strontium ranelate. J Endocrinol Invest 2015;38(8):859–63.

Catalano A, Morabito N, Basile G, Cucinotta D, Lasco A. Calcifediol improves lipid profile in osteopenic/osteoporotic postmenopausal women. Eur J Clin Invest 2015 Feb;45(2):144–9.

Catalano A, Morabito N, Atteritano M, Basile G, Cucinotta D, Lasco A. Vitamin D reduces musculoskeletal pain after infusion of zoledronic acid for postmenopausal osteoporosis. Calcif Tissue Int 2012;90(4):279–85. http://dx.doi.org/10.1007/s00223-012-9577-6.

Catalano A, Morabito N, Basile G, Fusco S, Castagna G, Reitano F, et al. Fracture risk assessment in postmenopausal women referred to an Italian center for osteoporosis: a single day experience in Messina. Clin Cases Miner Bone Metab 2013;10(3):191–4.

Aishah AB, Foo YN. A retrospective study of serum calcium levels in a hospital population in Malaysia. Med J Malaysia 1995;50(3):246–9.

Tasian GE, Ross ME, Song L, Sas DJ, Keren R, Denburg MR, et al. Annual incidence of nephrolithiasis among children and adults in South Carolina from 1997 to 2012. Clin J Am Soc Nephrol 2016;11(3):488–96.

Catalano A, Basile G, Ferro C, Bellone F, Scarcella C, Benvenuto S, et al. Hyponatremia as a leading sign of hypopituitarism. J Clin Transl Endocrinol: Case Rep 2017;5:1–3.