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Characteristics and outcome of severe hypercalcemia on admission to the emergency department: a retrospective cohort study

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Summary

AIMS OF THE STUDY: To investigate the prevalence of hypercalcemia (>2.60 mmol/l) and severe hypercalcemia (≥2.80 mmol/l) on admission. Symptoms, causes, course of serum calcium, treatment and outcome of severe hypercalcemia were evaluated and compared to historical data from previous studies.

METHODS: In this retrospective cohort study, all patients presenting to the interdisciplinary emergency department of the Buergerspital Solothurn between 01 January 2017 and 31 December 2020 with measurements of serum calcium were included. Chart reviews were performed for patients with calcium ≥2.80 mmol/l to assess clinical presentation, course of disease and treatment for severe hypercalcemia.

RESULTS: Of 31,963 tested patients, 869 patients (2.7%) had hypercalcemia on the admission, of which 161 had severe hypercalcemia. Non-albumin corrected calcium was 3.07 (0.32) while albumin corrected calcium was 3.34 (0.44). Calcium was higher in patients with malignancy-related hypercalcemia (3.18 [0.34] versus 3.00 [0.3], p <0.001). Neuropsychiatric (35%) and gastrointestinal (24%) were the leading symptoms. Malignancy was the most common identifiable cause of hypercalcemia (40%), with lung cancer (20%), multiple myeloma (14%) and renal cell carcinoma (11%) being the main cancer types. 36% of patients with severe hypercalcemia took calcium supplements. Bisphosphonate treatment was an independent predictor of a fall in calcium until day 5 (regression coefficient: –0.404, standard error 0.11, p <0.001). Hypercalcemia was not mentioned in the final discharge report in 38% of cases.

CONCLUSION: Severe hypercalcemia is common and malignancy-related in almost half of the cases. Neuropsychiatric and gastrointestinal symptoms were most prevalent. Awareness of hypercalcemia, particularly in cancer patients and those with known triggering factors, should be raised in order to identify and treat this harmful disorder early.

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Introduction

Electrolyte disorders are common and relevant findings in patients presenting to the emergency department [1]. While dysnatremias, especially hyponatremia, and dyskalemias are rather well investigated, evidence on disorders of serum calcium is scarce, even though abnormal calcium levels on admission were associated with increased mortality in hospitalised patients [2, 3].

Calcium is the most abundant cation in the extracellular space, with approximately 99% being bound in bones and teeth [4]. On the contrary, only 1% of the body's calcium is found in the blood, of which 40% is bound to protein, 10% to organic anions and approximately 50% freely circulating in its ionised form [4]. Normal levels for ionised blood calcium are defined as 1.10–1.40 mmol/l and total calcium is often defined between 2.20 and 2.60 mmol/l [5]. Consequently, hypercalcemia can be defined by a rise in serum calcium >2.60 mmol/l, whereas severe hypercalcemia was defined by a rise in serum calcium >2.80 mmol/l [2].

Besides the crucial function of giving and maintaining form to teeth and bone, calcium acts as a cofactor for enzymes such as the adenosine-triphosphatase. [4]. It also acts as a second messenger to stimuli from surface cell receptors [6]. Additionally, calcium is an important cofactor in muscle contraction, the coagulation cascade and the cardiac conduction system [7, 8]. Given the multiple central functions of calcium in the body, it comes as no surprise that disorders of serum calcium can be highly symptomatic and have several potentially life-threatening effects. Gastrointestinal symptoms of hypercalcemia range from nausea, anorexia and constipation to peptic ulcers and pancreatitis [9–11]. Neuropsychiatric symptoms of hypercalcemia include mood disorders and cognitive changes, disorientation and somnolence [11, 12]. Hypercalcemia also shortens the cardiac QT interval and ST segment elevations have been described [13, 14]. Muscular weakness is a common symptom associated with hypercalcemia, which has also been shown to be reversible in patients with primary hyperparathyroidism after surgery [15]. Other consequences of hypercalcemia include nephrolithiasis and renal insufficiency [16–18].

Unfortunately, although hypercalcemia is frequently encountered in daily clinical practice and despite the fact that it has potentially dangerous consequences for the patient, there is a scarcity of data from larger case series. In several case reports, severe hypercalcemia was associated with dihydrotachysterol intoxication [19], the combination of vitamin A and hydrochlorothiazide [20], hematologic malignancies [21], sarcoidosis [22] and severe dehydration [23].

This study aimed to evaluate the prevalence of hypercalcemia and severe hypercalcemia on admission to the emergency department. Furthermore, the main symptoms, clinical findings, etiologies and initial management of hypercalcemia in the emergency department were investigated. Finally, as an outcome measure, hospital course in terms of calcium correction rate, need for ICU admission, length of hospital stay and in-hospital mortality were assessed along with an assessment of the various treatments for hypercalcemia.

Patients and methods

Study design and setting

In this retrospective analysis, all adult patients admitted to the interdisciplinary emergency department of the Buergerspital Solothurn between January 1st 2017 and December 31st 2020 with measurements of serum calcium were eligible for analysis. Patients with hypercalcemia defined by serum calcium >2.60 mmol/l on admission to the emergency department were included in the analysis [2]. Of those with severe hypercalcemia, defined as a serum calcium ≥2.80 mmol/l, detailed chart reviews were performed. Exclusion criteria were age <18 years and written or verbal withdrawal of consent.

Measurements

Data on age, sex, on-admission medication, medical history and clinical findings, serum sodium, calcium, creatinine and albumin, parathyroid hormone (PTH), ICU admission, length of hospital stay and in-hospital mortality were assessed by chart reviews. Treatment of hypercalcemia was assessed within 24 hours after emergency department admission and serum calcium levels were analysed daily from hospitalisation day 1 to 5 and at discharge. Detailed chart reviews were performed by the same two persons in order to gather details on the treatment as well as course of disease. Correction of serum calcium for serum albumin was performed as suggested previously [24].

Symptoms attributable to hypercalcemia

Symptoms attributable to hypercalcemia were classified as neuropsychiatric (disorientation, delirium, somnolence, coma), gastrointestinal (nausea, emesis, constipation) or musculoskeletal (weakness, pain).

Statistical analysis

Data are presented as mean and standard deviation (SD) or median and interquartile range as appropriate. Between-group comparisons of continuous variables were performed using Mann-Whitney U tests. Categorical variables were compared using the χ^2 test or Fisher's exact test. Linear regression was used to evaluate the effect of different treatments on delta serum calcium. A p-value <0.05 was considered significant. All statistics were calculated using SPSS version 28 by IBM, Armonk, NY.

Ethical considerations

The study was approved by the local ethics committee Ethikkommission Nordwest- und Zentralschweiz and the need for individual patient consent was waived (EKNZ 2021-02186).

Results

During the study period, 31,963 patients had measurements of serum calcium on admission, of which 869 (2.7%) had serum calcium levels exceeding 2.60 mmol/l.

During the observation period, 170 cases of severe hypercalcemia were identified with on-admission serum total calcium levels of ≥2.80 mmol/l. Albumin levels were measured in 120 cases and after application of the albumin correction formula (24), 9 patients were excluded in the final analysis due to corrected serum calcium levels <2.80 mmol/l.

Of the 161 presentations from 142 patients, 126 patients had one episode of hypercalcemia, 14 patients had two and one patient had three and four presentations with hypercalcemia, respectively. The mean age of the patients with severe hypercalcemia was 69 years (15) and 89 (63%) were women.

Of all 161 episodes with severe hypercalcemia, mean non-albumin corrected calcium on admission was 3.07 (0.32) while albumin corrected calcium was 3.34 (0.44). PTH level measured during hospitalisation was available in 66 patients with a mean of 10.1 (13) pmol/l. The characteristics of patients with severe hypercalcemia on admission are given in table 1.

Symptoms attributable to hypercalcemia

In 57 episodes (35%) of severe hypercalcemia, neuropsychiatric symptoms were present on admission. Gastrointestinal symptoms were leading in 39 episodes (24%) and musculoskeletal symptoms in 7 (4%) episodes. 58 episodes (36%) were characterised by unspecific general deterioration characterised by malaise or other symptoms not clearly attributable to hypercalcemia.

Causes of hypercalcemia

In 145 episodes (90%), a cause for hypercalcemia could be identified, while in 22 episodes (14%) two and in two episodes three different causes (2%) were identified.

In 64 cases, malignancy was the identifiable cause for severe hypercalcemia (40%) with lung cancer in 13 (20%), multiple myeloma in 9 (14%) and renal cell carcinoma in 7 (11%) patients. Primary hyperparathyroidism could be identified in 35 patients (22%) as the leading cause for hypercalcemia. The next most prevalent provoking factors for hypercalcemia after malignancy were thiazide (-like) diuretics in 29 (18%) and dehydration in 14 (9%) cases.

In addition, 58 patients (36%) had vitamin D substitution and 26 (16%) had calcium supplements as a regular medication.

Patients with hypercalcemia due to malignancy had significantly higher serum calcium levels on admission (3.00 (0.32) versus 3.20 (0.34), p <0.001). Serum calcium levels along with available PTH levels stratified for the cause of hypercalcemia for the 5 most prevalent etiologies are given in table 2.

Course of serum calcium and treatment of hypercalcemia

Follow-up serum calcium levels were available for 107 patients for day 1, 85 for day 2, 77 for day 3, 54 for day 4 and 55 for day 5. Mean serum calcium on admission was 3.07 (0.32) mmol/l, while the mean last measured serum calcium before discharge available in 121 cases was 2.41 (0.27) mmol/l. Mean decline in serum calcium from admission to the last measurement was 0.35 (0.31). 8 out of 121 patients (7%) with serum calcium controls had no decline in serum calcium or even a slight increase. 23 patients (19%) still had serum calcium levels ≥2.80 mmol/l at the last measurement before discharge.

Calcium on admission was significantly higher in patients with malignancy versus those with non-malignancy-related hypercalcemia (3.18 (0.34) versus 3.00 (0.3), p <0.001). There was no difference in delta serum calcium between patients with malignancy-associated hypercalcemia and those with other causes (0.36 (0.3) versus 0.35 (0.32) mmol/l, p = 0.63). There was also no difference in the proportion of patients with serum calcium remaining ≥2.8 mmol/l between malignancy- and non-malignancy-associated hypercalcemia (24 versus 15%, p = 0.35).

Data on the course of serum calcium is given in table 3.

In terms of treatment, 148 patients (92%) received intravenous hydration during the first 24 hours after admission. The mean volume substitution administered intravenously during the first 24 hours was 1595 (1453) ml. An isotonic, balanced crystalloid was used for hydration in 118 patients (73%), 0.9% saline in 24 (15%), 1.4% sodium bicarbonate in two (1%) and a combination of a balanced crystalloid and 1.4% sodium bicarbonate in two patients (1%).

In addition to hydration, 26 patients (16%) received a bisphosphonate (24 zoledronate, 2 ibandronate) at a dose of 4 mg intravenously. 25 patients (16%) were treated with loop diuretics (furosemide) at a mean daily dose of 37 mg (19) during the first 24 hours after admission. Calcitonin was applied in 17 patients (11%) at a dose of 331 units (210). Table 4 gives an overview of the treatments used for severe hypercalcemia.

In the linear regression using delta serum calcium after 24 hours as the dependent variable, administration of a loop diuretic was an independent predictor of a higher fall of serum calcium (regression coefficient: –0.135, standard error 0.061, p = 0.033). When using delta serum calcium until day 5 after admission as a dependent variable, administration of bisphosphonates was an independent predictor of a fall in serum calcium (regression coefficient: –0.404, standard error 0.11, p <0.001).

Table 1:
Characteristics of patients with severe hypercalcemia on admission.

Parameter	Mean (SD)	N
Age (years)	69 (15)	161
Blood pressure systolic (mm Hg)	136 (24)	149
Blood pressure diastolic (mm Hg)	80 (18)	149
Pulse rate (beats/min)	90 (21)	152
Temperature (°C)	36.5 (0.7)	147
SpO2 (%)	95 (4)	152
Serum calcium (mmol/l)	3.07 (0.32)	161
Albumin-corrected calcium (mmol/l)	3.34 (0.44)	111
Hemoglobin (g/l)	131 (25)	156
Serum sodium (mmol/l)	137 (11)	161
Serum potassium (mmol/l)	4.1 (0.9)	161
Creatinine (µmol/l)	137 94)	161
TSH (mIU/l)	1.96 (1.6)	118

Table 2:
Serum calcium and PTH levels of patients with the five most common causes of hypercalcemia.

	Cases	Serum calcium (SD)	PTH (SD)
Malignancy	64	3.18 (0.34)	3.6 (12.7) (N=29)
Thiazide (-like) diuretics	29	3.02 (0.38)	7.6 (16.2) (N=12)
Dehydration	14	3.02 (0.3)	3.3 (0.1) (N=2)
Oral calcium supplements	11	3.03 (0.3)	6.2 (5.0) (N=7)
Sarcoidosis	5	3.52 (0.3)	1.2 (0.6)

Table 3:
Course of serum calcium (in mmol/l) during hospitalisation.

	Admission	Day 1	Day 2	Day 3	Day 4	Day 5	Last measurement before discharge
N	161	107	84	76	54	55	121
Serum calcium (SD)	3.07 (0.32)	2.92 (0.38)	2.80 (0.38)	2.72 (0.31)	2.64 (0.33)	2.60 (0.32)	2.41 (0.27)
Serum calcium fall (SD)	–	0.16 (0.18)	–0.08 (0.12)	0.14 (0.22)	0.15 (0.08)	0.03 (0.06)	0.35 (0.31)

Outcome of hypercalcemia

27 patients (17%) received intermediate/intensive care unit treatment during their hospital stay. 25 patients (16%) died during the course of hospitalisation. In addition, recurrent visits with hypercalcemia were noticed in 47 cases (29%) during the following 365 days after the initial presentation. Hypercalcemia was not mentioned in the discharge report in 61 cases (38%).

Discussion

In the present study, the prevalence of hypercalcemia on admission to the emergency department was 2.7% and approximately 20% of hypercalcemic patients had severe hypercalcemia defined as a serum calcium exceeding or equaling 2.8 mmol/l after correction for serum albumin. Neuropsychiatric and gastrointestinal symptoms were the leading presentations of severe hypercalcemia. However, one-third of all patients with severe hypercalcemia had a rather unspecific clinical presentation. Malignancy was the main cause of severe hypercalcemia in our case series. Treatment mainly consisted of intravenous hydration and bisphosphonate, loop diuretics and calcitonin were used frequently. As to be expected, mortality was high in patients with severe hypercalcemia.

Although hypercalcemia is a common phenomenon in certain patient populations, there is a lack of studies on its prevalence, associated symptoms and optimal therapy. Oncologic studies indicated that that about 2–3% of all cancer patients were affected by hypercalcemia, with rates as high as 10% in patients with multiple myeloma [25]. In a retrospective study on an unselected population of hospitalised patients, the prevalence of hypercalcemia was 4.7%, with more cases in the group of patients aged over 65 years [26].

Concerning the causes of hypercalcemia, the present finding that 40% of cases with severe hypercalcemia were related to malignancy stands in line with previous studies [11, 27]. Interestingly, in the present study, more than one-third of the patients with severe hypercalcemia had oral calcium substitution on admission to the emergency department, and 16% had vitamin D supplements. Moreover, the use of thiazide (-like) drugs was common, potentially further aggravating hypercalcemia in these patients. The phenomenon of hypercalcemia in patients on thiazide (-like) diuretics is well described and it was found to be often related to underlying primary hyperparathyroidism [28]. However, taking a thiazide (-like) diuretic in combination with oral calcium supplements can induce hypercalcemia without underlying hyperparathyroidism [29]. Regarding the findings of the present study, the level of suspicion for hypercalcemia should be high in patients with otherwise unexplained symptoms and underlying malignancy or a combination of provoking factors for increased serum calcium. Thus, the determination of serum calcium or alternatively ionised calcium by blood gas analysis should be performed more liberally in patients presenting to the emergency department.

Another interesting finding of the present study is that although serum calcium was higher on admission in patients with malignancy-related hypercalcemia, the correction rate was comparable to non-malignancy-related cases.

Concerning the treatment of hypercalcemia, only bisphosphonate use was independently associated with a higher fall in serum calcium until day five, although loop diuretic use during the first 24 hours was a significant predictor of higher 24 hour delta serum calcium, this stands in line with a previous study [10].

Intriguingly, hypercalcemia was not mentioned in 38% of all cases in the final medical report. This indicates a relevant lack of awareness of this common and potentially harmful electrolyte disorder.

Comparing the current results to a previous work of our group ten years ago in a comparable setting, several differences are notable: Firstly, the current study aimed to focus on more severe cases of hypercalcemia with a cut-off of ≥2.8 mmol/l. Secondly, in the previous work, the prevalence of hypercalcemia on admission was lower at 0.7% compared to 2.7% today [11]. However, it is of interest, that today with close to 50% by far a higher proportion of patients received measurement of serum calcium than in the past, where we found a proportion of approximately 20% [11]. As outlined above, the causes for hypercalcemia found in the present study are in line with our previous findings [11].

The present study has several limitations: due to its retrospective design, we cannot exclude that information, which was not documented in the electronic patient charts resulted in missing data. Moreover, the determination of serum calcium occurred at the discretion of the emergency department physician in charge, thus the true prevalence might vary – however, due to the large sample size and the comparability of our results, we consider this effect negligible. Finally, external validity is limited due to the single center design of the current analysis.

In conclusion, hypercalcemia is frequently encountered in the emergency department. Especially in patients with underlying malignancy as well as a combination of provoking

Table 4:
Treatment of hypercalcemia on admission.

		N (%)	Mean dose (SD)
Intravenous hydration	Balanced crystalloid	118 (73%)	1406 ml (1480)
	Saline 0.9%	24 (15%)	1611 ml (1453)
	Sodium bicarbonate 1.4%	2 (1%)	2250 ml (915)
	Balanced crystalloid + Sodium bicarbonate 1.4%	2 (1%)	2250 ml (827)
Bisphosphonate		26 (16%)	4 mg (0) for zoledronate, 3 mg (0) ibandronate
Loop diuretics		25 (16%)	37 mg (19)
Calcitonin		17 (11%)	331 U (210)
Glucocorticoids		9 (6%)	45 mg (44)
Denosumab		2 (1%)	90 mg (42)
Cinacalcet		2 (1%)	30 mg (0)

factors such as calcium substitution and for example, thiazide diuretics, the level of suspicion for hypercalcemia should be high in presence of unspecific and otherwise unexplained symptoms. Bisphosphonates proved to be a relevant treatment option for the correction of hypercalcemia in hospitalised patients without side effects.

Data availability

Datasets analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Author contributions

SR: conception of the study, database design, analysis and interpretation, manuscript draft. AL: data gathering, manuscript draft. AE: manuscript draft. MH: manuscript draft. GL: conception of the study, database design, analysis and interpretation, manuscript draft.

Potential competing interests

All authors have completed and submitted the International Committee of Medical Journal Editors form for disclosure of potential conflicts of interest. No potential conflict of interest was disclosed.

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