Hypercalcemia in the Emergency Department: Prevalence, Etiology, and Mortality Rate

Acil Serviste Hiperkalsemi; Prevelans, Etiyoloji ve Mortalite Oranı

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ABSTRACT

Objective: The aim of the study was to describe the prevalence, clinical characteristics of hypercalcemia and the impacts on renal function and survival in emergency department (ED) patients.
Method: We conducted a retrospective cross sectional descriptive study, all patient admitted between January 1, 2017, and January 1, 2018 to the ED of University of Health Sciences Bakirkoy TAR, were screened for the presence of hypercalcemia, defined as a serum calcium level greater than 10.3 mg/dL. Demographic, laboratory and outcome data were collected.
Results: During the study period, 1.246 of 318.527 patients (120.418 patients received a measurement of serum calcium) (0.01%) were found to have hypercalcemia (Serum calcium 11.0±0.8 mg/dL) Mild hypercalcemia seen more frequently (calcium level <12 mg/dL, 94.3%). Renal fuction was normal in 995 (79.8%) of all patients with hypercalcemia. The total mortality rate was 0.01%, and death was associated with higher age, higher calcium level, lower albumin, lower hemoglobin, higher creatinine and higher white blood cells (all p<0.05).
Conclusions: Although hypercalcemia is common in ED, severe hypercalcemia is rare and fatal. Therefore we recommend measuring the serum calcium level in at-risk patients in the ED and treatment should be initiated to detected underlying disease.

Keywords: hypecalcemia, electrolyte disturbance, emergency department

ÖZ

Amaç: Bu çalışmayla acil servise başvuran hastalarda hiperkalsemi prevelansını, klinik özelliklerini, böbrek fonksiyonu üzerine etkilerini ve mortalite oranını belirlemeyi amaçladık.
Yöntem: Retrospektif kesitsel tanımlayıcı olarak 1 Ocak 2017 ve 1 Ocak 2018 tarihleri arasında Sağlık Bilimleri Üniversitesi Bakırköy Dr. Sadi Konuk Eğitim ve Araştırma Hastanesi Acil Servisine başvuran hastalarda, kalsiyum seviyesi 10,3 mg/dL'den daha yüksek olanlar belirlendi. Bu hastaların demografik, laboratuvar ve klinik verileri toplandı.
Bulgular: Bir yıllık süreçte başvuran 318.527 hasta içinden 120.418 hastada kalsiyum seviyesi tetkik edildi ve hastaların 1.246'sında (%0,01) hiperkalsemi saptandı. (Serum kalsiyum 11,0±0,8 mg/dL). Hastaların %94,3'ünde hafif hiperkalsemi vardı (kalsiyum seviyesi <12 mg/dL, %94,3). Hastaların %79,8'inde renal fonksiyonları normaldi. Mortalite oranı %0,01 idi. İleri yaş, ağır hiperkalsemi, kreatinin yüksekliği ve lökositoz durumları mortalite ile ilişkili saptandı (p<0,05). Ek olarak albumin ve hemoglobin değerleri daha düşük olan hastalarda mortalite oranının arttığı görüldü (p<0,05).
Sonuç: Şiddetli hiperkalsemi nadir görülmesine rağmen ölümcül olabilmektedir. Bu nedenle acil servise başvuran risk altındaki hastalarda serum kalsiyum düzeyini ölçmeyi ve zaman kaybetmeden altta yatan hastalığı tedavi etmeyi öneriyoruz.

Anahtar kelimeler: hiperkalsemi, elektrolit bozuklukları, acil servis

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INTRODUCTION

Electrolyte disorders are commonly observed in the ED. Deterioration of calcium levels is very important issue. The clinical range of hypocalcemia and hypercalcemia is wide and can cause death. Although many patients are diagnosed as asymptomatic in practice, it is common in patients applying for ED with different symptoms. There was a few studies on electrolyte disorders in ED. Two of them retrospective study on the epidemiology of hypercalcemia in the ED has been published [1,2]. Also a study on hospitalized patients from Hong Kong confirmed hypercalcemia. (Incidence 1%) [3]. A <5% incidence was found in hospital admission patients and less than 1.0% in outpatients [4,5]. The clinical range of hypercalcemia is wide. It also cause neurologic symptoms such as weakness, lethargy, and even coma. On the other hand, it causes gastrointestinal signs such as vomiting, nausea [6].

Most patients with hypercalcemia are asymptomatic; but symtoms of hypercalcemia usually proportional to calcium elevation. Symptoms may be rapid onset because of calcium serum level variability and the underlying disease. When serum calcium level exceeds 14.0 mg/dL, hypercalcemia crisis occurs. This is associated with mortality. In this case severe complications may occur. Therefore, it is necessary to measure the serum calcium level in patients admitted to ED. In addition, Hypercalcemia can be seen in conjunction with other electrolyte should be noted. Especially magnesium and sodium homeostasis should be looked at when evaluating patients [7].

We evaluated patients who admitted to the ED with symptoms of hypercalcemia. We investigate the prevalence of hypercalcemia, survival of ED patients and hypercalcemia association with renal failure.

MATERIAL AND METHODS

In this retrospective descriptive study , the database of the central laboratory of University of Health Sciences Bakirkoy TAR was scanned for elevated serum calcium levels from the Department of ED. All patients admitted between January 1, 2017, and January 1, 2018. In our hospital, the level of serum calcium is 8.6 to 10.3 mg/dL is normal range. We defined hypercalcemia was serum total calcium concentration greater than 10.3 mg/dL. In addition; serum albumin level affects serum calcium level. Therefore, we perform a correction formula was used to calculate exact calcium level: [1] Corrected total serum calcium level (mg/dL) = measured total calcium level (mg/dL) + 0.8 × [4.0 - albumin concentration (g/dL)].

Patients were divided into three parts depending on serum calcium levels. Mild hypercalcemia (10.3-11.9 mg/dL), moderate hypercalcemia (12.0-14.0 mg/dL), and severe hypercalcemia (>14.0 mg/dL). Demographic data (all identified patientes, namely, age and gender) were recorded. Biochemical data including sodium, magnesium, creatine, albumin concentration, renal function test results and hemogram results were also recorded. All patients followed from the duration of in-hospital to until his or her discharge and in-hospital mortality.

Statistical analysis was performed by use of SPSS 19.0. Data are presented as mean±SD. Student's t-test, Mann Whitney U test was used to compare demographic and biochemical data between survivor and nonsurvivor groups. X^2 test used for the statistical significance of the effect of various degrees of hypercalcemia on mortality rate, renal failure, and other variables. In additon, independent variables was selected on factors that showed significant changes between survivors and nonsurvivors. A P-value less than 0.05 was statistically significant.

RESULTS

During in this study, 318527 patients (all admitted patients) were admitted to our ED, of which 120418 (37%) received a measurement of serum calcium levels. Among them, 1246 patients (0.01%) presented with hypercalcemia. 635 (51%) patients were female and 611 (49%) patients were male. Median serum calcium was 10.77 mg/dL, with 21 mg/dL being the highest serum calcium value observed. Reference calcium level was 8.6-10.3 mg/dL. Mild hypercalcemia was defined as serum calcium level 10.3-11.9 mg/dL, moderate hypercalcemia was defined as 12-14 mg/dL and severe hypercalcemia was defined as 14 mg/dL. Most of patients had mild hypercalcemia (calcium level 10.3-12 mg/dL, 94.37%)

The level of hypercalcemia in respect to the age distribution of the patients participated in our study which was split into 7 groups (20 years, 20-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years,70 years) is investigated. Mild hypercalcemia found to be significantly (p=0.003) in 20-29 years (17.14%) and 50-59 years (17.32%) among all the other age groups. Moderate hypercalcemia found to be significantly (p=0.000) in 50-59 years (25.0%), 60-69 years (25.0%) and 70 years (38.46%). There was no significant difference in the age distribution of groups with severe hypercalcemia (p=0.198) (Table 2).

In order to track seasonal variation of serum calcium levels, the serum calcium levels of the study samples in respect to each month were investigated. Mild hypercalcemia, the case numbers were significantly (p=0.000) elevated in September (24.02%) and

October (23.66%). Moderate/severe hypercalcemia wasn't found to be significantly in respect to each months. Overall, the cases of mild hypercalcemia found to be significantly (p=0.0001) elevated among all the other hypercalcemia groups screened during the whole year.

The major determinants of renal failure are serum urea and creatinine values in respect to plasma calcium levels were investigated. As compared to mild hypercalcemia, serum creatinine levels were significantly (p=0.000) elevated in severe hypercalcemia. With increasing calcium level, the incidence of concurrent renal failure also increased after the uremic group is excluded. Also, urea levels found to be decreased in mild hypercalcemia as compared to severe hypercalcemia.

Since anemia is common in advanced renal failure, hemoglobin levels were also investigated in respect to plasma calcium levels. As compared to severe or moderate hypercalcemia serum hemoglobin is ele-

Table 1. Characteristics of Hypercalcemic Patients.

Female gender, n (%)	635 (50.96)
Male gender, n (%)	611 (49.04)

Table 2. The level of hypercalcemia in respect to the age distribution of the patients.

	Mild (10.3-11.9 mg/dL)	Moderate (11.9-14.0 mg/dL)	Severe (Camg/dL)	P value*
Patients, n (%)	1174 (94.37)	52 (4.18)	18 (1.45)	
Age Groups				
20 years	148 (99.33)	1 (0.67)	0 (0.00)	0.000
20-29 years	197 (98.99)	2 (1.01)	0 (0.00)	0.000
30-39 years	152 (99.35)	1 (0.65)	0 (0.00)	0.000
40-49 years	155 (98.1)	2 (1.27)	1 (0.63)	0.000
50-59 years	200 (92.17)	13 (5.99)	4 (1.84)	0.000
60-69 years	155 (88.57)	13 (7.43)	7 (4.00)	0.000
70 years	167 (89.53)	20 (10.36)	6 (3.11)	0.000
P value	0.003	0.000	0.198	

Table 3. Serum calcium levels stratified for the laboratory finding.

	Mild hypercalcemia Mean+SD Med. (Min.-Max.)	Moderate hypercalcemia Mean+SD Med. (Min.-Max.)	Severe hypercalcemia Mean+SD Med. (Min.-Max.)	p
Calcium	10.84±0.29 10.75- (10.3-11.94)	12.72±0.59 12.58- (12-13.94)	15.65±1.33 15.32- (14.01-19.35)	0.000
Creatinine	1.09±1.16 0.86- (0.21-19.04)	1.77±1.79 0.95- (0.52-8.18)	2.95±2.14 2.98- (0.53-9.13)	0.000
Urea	40.02±28.96 32- (10-276)	74.46±55.71 58.5- (17-264)	118.88±63.42 100- (24-223)	0.000
Albumin	4.82±0.63 4.9- (0.1-6.8)	3.54±0.86 3.6- (2-5.2)	3.29±0.61 3.5- (2.2-4.1)	0.000
WBC	10.89±4.28 9.93- (0-38.5)	14.53±8.49 11- (4.23-37.39)	19.53±10.56 15.69- (7.29-42.1)	0.000
Hemoglobin	13.88±2.19 14- (0-20.9)	11.26±2.61 11.54- (6.63-15.3)	10.38±2.82 10.3- (5.02-14.7)	0.000
Trombocyte	298.44±110.63 289- (1.52-2166)	287.78±165.69 251- (26.7-744)	222.27±95.6 236.5- (55.09-353)	0.005

vated in mild hypercalcemia. Serum albumin level found to be significantly (p=0.000) elevated in mild hypercalcemia compared to moderate or severe hypercalcemia. Also compared to mild hypercalcemia white blood count is elevated in severe hypercalcemia (p=0.001). Hemoglobin levels found to be significantly higher in mild hypercalcemia rather than moderate or severe hypercalcemia (Table 3).

Survival among the study samples is significantly (P=0.002) higher in 20 years 20-29 years of age. Mortality is significantly (P=0.005) higher in70 years

Table 4. Comparison between hypercalcemic patients who survived and those who died.

	Survivors Mean+SD Med. (Min.-Max.)	Non-survivors Mean+SD Med. (Min.-Max.)	p
Calcium	10.93±0.8 10.75- (7.92-19.35)	12.13±1.76 11.75- (8.57-15.76)	0.001
Creatinine	1.13±1.21 0.87- (0.21-19.04)	2.92±2.19 2.28- (0.92-9.13)	0.000
Urea	42.6±32.39 33- (10-262)	110.24±80.24 93- (24-276)	0.000
Albumin	4.74±0.71 4.9- (0.1-6.8)	3.76±0.87 3.6- (2.1-5.5)	0.000
WBC	11.18±4.79 10.06- (0-48.41)	18.11±10.59 13.5- (3.61-42.1)	0.001
Hemoglobin	13.74±2.29 13.9- (0-20.9)	12.41±2.99 12.94- (6.76-16.5)	0.093
Trombocyte	296.08±112.14 288- (1.52-2166)	269.84±160.31 283- (51-536.2)	0.606

* Mann Whitney U test

Table 5. Comparison between level of hypercalcemia in patients who survived and those who died.

	Survivors N (%)	Non survivors N (%)
Mild hypercalcemia	1160 (98.80)	14 (1.20)
Moderate hypercalcemia	51 (98.08)	1 (1.92)
Severe hypercalcemia	16 (88.89)	2 (11.11)*
p		0.002*

*x^2 test

Table 6. Genders of hypercalcemic patients who survived and those who died.

	Survivors N (%)	Non survivors N (%)
Female	625 (98.58)	9 (1.42)
Male	603 (98.69)	8 (1.31)
p	0.530	0.808

* x^2 test

of age. The mortality rate increased significantly as the hypercalcemia progressed. Patients with severe hypercalcemia had the highest mortality rate (11,1% p=0.002) (Table 5). Patients who died had significantly higher calcium, higher white blood count, and lower albumin levels, whereas gender, hemoglobin levels and platelet counts were similar in both survivors and non-survivors (Table 4).

DISCUSSION

We have presented although hypercalcemia was common electrolyte disturbance in patients in the ED but severe hypercalcemia was rare and fatal. The incidence was much lower in our study than in other studies [4,5]. In one of the other studies, the incidence of hypercalcemia was detected 7.5% [1]. Some studies similar to our study, the prevalence of hypercalcemia is low [2]. Also the low prevalence of hypercalcemia was detected in hospitalized patients in some studies [12,13].

In our study on more than 120 000 ED patients, 0.01% were identified to have hypercalcemia defined as a serum calcium exceeding 10.3 mg/dL after correction for serum albumin. Hypercalcemia can be seen in conjunction with other electrolyte should be noted. Especially magnesium and sodium homeostasis should be looked at when evaluating patients [7]. The vast majority of our patients had previously been diagnosed with hyperparathyroidism and malignancy. Hyperparathyroidism and malignancy most common cause of hypercalcemia. Similar results have been shown in the etiology of hypercalcemia in many previous studies [4,5,8,9]. High incidence of hypercalcemia in patients diagnosed with malignancy is explained by several different mechanisms. These mechanisms depend on type and degree of malignancy. Hypercalcemia is common, especially in cases of advanced cancer or terminal stage. These conditions are considered bad prognosis. The average survival expectancy is usually very short in these patients.

Increased bone resorption, calcium absorption from the intestine and reduction of renal tubular reabsorbion are some of the mechanisms of hypercalcemia in the head. Hypercalcemia is also seen in cases such

as severe systemic infections, increased cytokine release, diabetic ketoacidosis, liver abscess [1]. In some studies, uremia has also shown that hypercalcemia is a common cause. Reduction of renal tubular reabsorbion of calcium, reduced glomerular filtration, hypovolemia, nephrotoxic agents are also effected renal failure. Therefore, hypercalcemia can often occur with acute renal failure due to all these mechanisms. This may explain the high incidence of acute renal failure with hypercalcemia. In other studies, acute renal failure with hypercalcemia is commonly reported [1,10,11].

The clinical range of hypercalcemia is very wide. While not symptoms in the asymptomatic period, symptoms become noticeable as serum calcium levels rise [1,2,14]. Depending on the underlying diseases and complications, the increase in serum calcium levels may vary. Therefore, serum calcium levels are very important in patients at risk. Patients with severe hypercalcemia had the highest mortality rate in our study. Patients who died had significantly higher calcium and lower albumin levels, whereas hemoglobin levels, white blood count and platelet counts were similar in both survivors and non-survivors. Similar results to our study have been shown in previous studies [1,2,4].

Our study is limited due to its retrospective. Restrictions such as not documenting all symptoms and symptoms in patients with hypercalcemia, not working with each patient of important data such as Vitamin PTH and Vitamin D, and giving ambulatuar treatment without detecting the underlying disease are in the missing aspects of the study.

Consequently, hypercalcemia is seldom electrolyte disorder in the ED but severe hypercalcemia is rare and harmful. In our study, we found that the mortality rate was higher as hypercalcemia was more severe. Also our results show that in patients with higher hypercalcemia, lower albumin levels, higher age had the highest mortality. Therefore we recommend measuring the serum calcium level in all patients diagnosed with malignancy, both gastrointestinal and neurological symptoms and in at-risk patients in the ED. In at-risk patients, it is important to find the underlying disease starting early in treatment.

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