Risk variables associated with abnormal calcium, magnesium and phosphate levels among emergency department patients

(abnormal calcium, magnesium and phosphate levels)

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PD and DT developed the protocol for the project that this research was drawn from. DT obtained ethics committee approval. PD, JS, WS, EdeT and MY assisted with collection. AU and DT undertook the data analysis. All authors contributed to results interpretation. All authors contributed to drafting and critical revision of the manuscript. DT supervised the project overall. All authors take responsibility for the manuscript.

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(Running title: calcium, magnesium and phosphate)

ABSTRACT

Background

The utility of calcium, magnesium and phosphate measurement in the emergency department (ED) is limited. We aimed to determine clinical risk variables for abnormal levels of these electrolytes in order to inform the development of an ordering guideline.

Methods

We performed a retrospective, observational study of patients who presented to a tertiary referral ED between January and June 2017. Adult patients who had serum calcium, magnesium or phosphate tests completed during their ED stay were included. Presenting symptoms and signs, co-morbidities, medication use and laboratory values were extracted from the medical record. Patients with missing data items were excluded. Logistic regression models determined clinical risk variables associated with low and high levels of each electrolyte.

Results

33,120 adults presented during the study period. Of the 1,679 calcium, 1,576 magnesium and 1,511 phosphate tests, 228 (13.6%), 158 (10.0%) and 387 (25.6%) were abnormal, respectively. Significant risk variables ($p < 0.05$) for abnormal levels were: hypocalcemia - vomiting, perioral numbness, hand/foot spasm, calcium and phosphate supplements and chemotherapy (OR range 5.9-17.3); hypercalcemia - female sex, vomiting, polyuria, confusion, hyperparathyroidism, cancer and type 1 diabetes (OR range 2.3-9.7); hypomagnesemia - female sex, proton pump inhibitor use, tacrolimus use, alcohol abuse and type 2 diabetes (OR range 2.2-13.1); hypermagnesemia - lethargy, thiazide use, and chronic kidney disease (OR range 4.3-4.5); hypophosphatemia - nausea, seizure and glucocorticoid use (OR range 1.7-2.1); and hyperphosphatemia - polyuria, diuretics and chronic kidney disease (OR range 1.9-5.0).

Conclusion

A range of demographic, co-morbid, medication and clinical variables are associated with abnormal calcium, magnesium and phosphate levels. These findings will inform the development of clinical guidelines to rationalise calcium, magnesium and phosphate testing. Justification may be required for testing patients with no risk variables.

Keywords: Calcium, Magnesium, Phosphate, Utility, Emergency Health Service, Choosing Wisely

INTRODUCTION

The Choosing Wisely initiative was introduced in 2012 in order to reduce unnecessary or harmful laboratory and imaging investigations. Its ultimate purpose was to improve patient care and minimise spending on tests and treatments that provide minimal or no patient benefit.^{1,2} Specific focus has been on, amongst other things, the testing of coagulation, blood cultures and prostate specific antigen where not indicated by scientific evidence.^{3,4}

In line with the Choosing Wisely initiative, we undertook an emergency department (ED) research project that aimed to determine how frequently calcium (Ca), magnesium (Mg) and phosphate (PO₄) tests are ordered and how frequently the test results change patient management.⁵ We found that 1,716 (5.2%) of 33,120 patients had at least one Ca, Mg or PO₄ test completed in the ED. 776 (16.2%) tests were abnormal although only 56 (1.2%) changed ED management. So, although testing is

common, the yield of abnormal results is low and patient management is rarely changed. These findings support those of earlier research.⁶

There is a need, therefore, for better targeting of patients most likely to benefit from testing of these electrolytes. The medical literature has numerous reports of a wide range of clinical signs, symptoms, comorbidities and medications that are associated with abnormalities in these electrolytes. However, these reports derive from settings other than the ED. We aimed to determine the variables associated with abnormal Ca, Mg and PO₄ levels within a large cohort of ED patients. The findings will inform the development of guidelines and decision support tools to minimise unnecessary testing of these electrolytes.

METHODS

Study Design and Setting

We undertook a retrospective medical record review of adult patients who had at least one Ca, Mg or PO₄ test in the ED of a tertiary referral hospital in metropolitan <city>, <country>. The ED has a mixed (paediatric and adult) annual census of approximately 90,000 patients. The study was approved by the institution's Human Research Ethics Committee.

Study Population

Adult patients (aged ≥ 18 years) presenting to the ED between January 1 and June 30 2017 (inclusive) were included if they had at least one Ca, Mg and/or PO₄ test ordered and completed (results available to the ED staff) during their time in the ED. Patients with missing data were excluded. The patient population for this study was the same as that analysed in our descriptive study.⁵

Study Protocol

Patients were identified electronically using the ED electronic medical record system, Cerner FirstNet® (version 2015.01.17, Cerner Corporation, North Kansas City, Missouri, USA). The system allows for screening and identification of patients who underwent a range of ED investigations.

An Excel[®] spreadsheet was designed, trialled and revised specifically for the project. Electronic data were downloaded and entered directly into the study spreadsheet: name, age, gender, presentation date, triage category and pain scores, presenting complaint (coded and descriptive), corrected Ca, Mg and/or PO₄ levels, and discharge destination. ED discharge summaries were then accessed to extract presenting symptoms and signs, co-morbidities, current medications and changes to ED management. Scanned electronic records were also accessed to clarify patient presenting symptoms and/or past medical history. Interrogation was particularly detailed in order to identify predetermined symptoms and signs, co-morbidities and medications known to be associated with abnormalities in Ca, Mg and PO₄ levels (see Appendix).

Reference ranges for pathology tests were obtained from the institution's pathology department. The reference ranges for corrected Ca, Mg and PO₄ levels were 2.15-2.55 mmol/L, 0.66-1.07 mmol/L and 0.87-1.45 mmol/L, respectively. Values outside of these ranges were deemed to be abnormal. Unique time-stamps for pathology tests were compared with the most accurate time-of-discharge reported for each patient who was transferred to the ward from ED. Patients who were discharged home or to the short stay unit (SSU) were assumed to have had their test completed in the ED prior to transfer.

All medical record reviews were then undertaken by the principal investigator (PD).

Following data collection, 85 (5%) patients were randomly selected and their data re-checked for accuracy of data extract and entry. No systemic data extraction errors were identified.

Key Outcome Measures

The primary study outcome was clinical variables associated with abnormal (high or low) Ca, Mg and/or PO₄ levels.

Data Analysis

In our descriptive study⁵, 1716 patients who had a Ca, Mg or PO₄ test completed in the ED were enrolled. We used the same patient population for this study. When comparing two patient subgroups (e.g. with/without a potential risk factor for an electrolyte abnormality), a clinically significant difference in the proportions of patients observed to have the outcome of interest (e.g. electrolyte abnormality) was deemed to be 5% (e.g. 6% versus 1%). Given these proportions and a patient ratio of 1:10 (with/without a risk factor), the study had a power of 0.91 to demonstrate a difference between the two subgroups (alpha 0.05, 2-sided).

Patients were separated into nine subgroups: normal/low/high for Ca/Mg/PO₄. For each electrolyte, patients in the low and high level subgroups were compared with

patients in the normal/high and normal/low level subgroups, respectively, using univariate analyses (Odds Ratio [OR], 95% confidence intervals [95%CI]). The subgroups were compared across a range of variables including those previously reported as risk factors for high/low Ca, Mg or PO₄ levels: demographics, signs and symptoms, co-morbidities and usual medication use (see Appendix).

The range of potential risk factors was extensive (n=66) and identical for the univariate analysis of each electrolyte, despite some variables not known to have an association with certain electrolyte abnormalities. Hence, only those variables found to have some association with an abnormal electrolyte level ($p < 0.10$) were entered into the logistic regression models to further analyse the associations. Intercooled Stata 6.0 for Windows 98/95/NT (Stata Corporation, College Station, Texas, USA) was used for all analyses. The level of significance was $p < 0.05$.

The study was unfunded.

RESULTS

Over the study period, 33,120 adult patients presented to the ED. Of these, 1,716 (5.2%) patients met the study entrance criteria. These patients had a mean (standard deviation) age of 64 (20.1) years and 810 (47.2%) were male.

There were a total of 4,776 individual electrolyte tests completed while the patients were in the ED (1,683 Ca, 1,579 Mg and 1,514 PO₄ tests). Small numbers of patients (4, 3 and 3, respectively) were not included in the regression models due to a missing data item. Hence, 1,679 Ca, 1,576 Mg and 1,511 PO₄ tests were analysed. Of these, 25 (1.5%) and 203 (12.1%) Ca levels were low and high, respectively; 128 (8.1%) and 30 (1.9%) Mg levels were low and high, respectively; 224 (14.8%) and 163 (10.8%) PO₄ levels were low and high, respectively.

Variables associated with low and high Ca levels are reported in Tables 1 and 2, respectively. Low levels were associated with vomiting, perioral numbness, hand or foot spasm, Ca and PO₄ supplement use, and chemotherapy ($p < 0.05$). High levels were associated with female sex, vomiting, polyuria, confusion, hyperparathyroidism, cancer and type 1 diabetes ($p < 0.05$). Hypothyroidism was a significant protective factor against high levels.

Variables associated with low and high Mg levels are reported in Tables 3 and 4, respectively. Low levels were associated with female sex, proton pump inhibitor use, tacrolimus use, alcohol abuse and type 2 diabetes ($p<0.05$). High levels were associated with lethargy, thiazide use, and chronic kidney disease ($p<0.05$). Female sex was a significant protective factor against high levels.

Variables associated with low and high PO_4 levels are reported in Tables 5 and 6, respectively. Low levels were associated with nausea, seizure and glucocorticoid use ($p<0.05$). Female sex and diuretics were significant protective factors. High levels were associated with polyuria, diuretics and chronic kidney disease ($p<0.05$). Palpitations was a significant protective factor against high levels.

DISCUSSION

Our findings indicate that Ca, Mg and PO₄ testing is commonly undertaken in the ED and that small proportions of patients have abnormal levels. Moreover, we have reported that, in the same patient population, only 1.2% of all tests resulted in a management change.⁵ Arguably, the reason for testing is to identify patients at risk from electrolyte abnormalities and who need treatment in the ED or soon thereafter. It is clear, therefore, that testing for these electrolytes needs to be rationalised.

This study has determined risk variables associated with abnormal Ca, Mg and PO₄ levels in a large cohort of ED patients. The important risk variables associated with an abnormality are summarised in the Box. These variables will inform the development of clinical guidelines designed to better target patients at risk of a Ca, Mg or PO₄ abnormalities. For any given patient, an absence of these risk variables may require Ca, Mg or PO₄ testing to be otherwise justified.

Some variables found to be associated with an electrolyte abnormality have not been included in the Box. These comprise protective variables and those that are common and that have relatively small effect sizes e.g. females (OR 1.6 and 1.9).

Risk variables for Ca, Mg and PO₄ abnormalities have been investigated in a range of patient populations and in number of settings. To our knowledge, this is the first study

to investigate this issue in the ED. Overall, our findings are consistent with those of other studies. Hypercalcaemia has commonly been reported in malignancy and hyperparathyroidism.⁷⁻¹⁰ Hypocalcaemia is commonly associated with paraesthesias.^{7,8} Vomiting, confusion and lethargy have also been associated with Ca abnormalities.^{7,8,11} Cancer, chronic kidney disease, diabetes, and alcoholism have each been associated with Ca, Mg and PO₄ abnormalities.^{6,9,10,12} Medications, including Vitamin D, proton pump inhibitors and glucocorticoids have been associated with hypercalcaemia, hypomagnesaemia and hypophosphataemia, respectively.^{7,13} Although we did not find a significant association between vitamin D and any electrolyte abnormality, there were trends towards some associations (ORs 1.3, 1.4).

This study's findings provide scope and guidance for future research. Firstly, intervention initiatives are indicated to reduce over-investigation of Ca, Mg and PO₄ levels. In the first instance, this may include ED physician education with regular monitoring and feedback on electrolyte testing. There could also be uncoupling of electronic investigation care sets, where groups of electrolytes are routinely ordered together for specific presenting complaints (e.g. jaundice). Uncoupling would require a specific order for each electrolyte. Secondly, the findings of this study need to be reproduced in a larger, multi-center study, perhaps with the inclusion of additional potential risk variables. This would add external validity and would help refine the important variables that are indications for testing. Thirdly, a clinical guideline is

recommended, based upon the multi-center study findings, to help ED physicians better target their electrolyte testing. Finally, once implemented, this clinical guideline should be evaluated prospectively for a range of important endpoints: numbers of tests done, cost savings and adverse patient outcomes consequent upon fewer tests being undertaken.

LIMITATIONS

This study has several limitations. Selection bias is unlikely as electronic screening was employed to identify all eligible patients, the study period was extensive and very few patients were excluded. However, as a single-centered, observational study, its external validity may be questionable.

We did not examine a number of very uncommon variables previously demonstrated to be associated with Ca, Mg or PO₄ abnormalities e.g. granulomatous disease, immobilisation, inherited renal tube defects and tissue breakdown.¹³⁻¹⁵ Therefore, although this study of risk variables is incomplete, the most commonly reported risks have been included. Furthermore, it is unlikely that future studies would have sufficient power to adequately examine such uncommon conditions.

Data downloaded electronically were likely to be accurate although, in small number of cases, data were incomplete. The existence of risk factors for some patients would not be known if they were not recorded in the medical record by the treating clinician. Hence, the numbers of patients with risk variables may have been under-estimated. During the manual medical record review, some documented data items may have been missed by the data extractor. However, the data quality assurance exercise revealed no irregularities.

We defined a low or high electrolyte level as one being outside of the normal laboratory range. Levels just outside of the range are likely to be of no clinical significance. Examination of the association between risk variables and levels well outside the normal range may have been more robust and clinically useful.

Some risk variables had large and significant effect sizes (ORs). However, the small numbers of patients with some of these risk variables (e.g. paraesthesia and hypocalcaemia) may have biased the findings. This may have led to inaccuracy in the observed association between some risk factors and electrolyte levels.

CONCLUSION

Calcium, Mg and PO₄ testing is commonly undertaken in the ED setting. However, only small proportions of tests reveal abnormalities. A range of demographic, clinical, medication, co-morbid variables are associated with abnormal levels of these electrolytes. The presence of one or more of these variables will flag a patient at potential risk and may inform a decision to investigate. Large multi-center studies are recommended to better define the nature and importance of risk variables. The findings will inform the development of evidence-based clinical guidelines in an endeavour to rationalise testing of these electrolytes. For patients without any risk variables, Ca, Mg and PO₄ testing may need to be otherwise justified.

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Table 1. Logistic regression results: Variables associated with a low calcium level

risk variable		calcium level low (n=1679)		OR	(95%CI)	p
		no	yes			
Vomiting	no	1456	17	1		
	yes	198	8	4.3	(1.7, 10.9)	0.002
Perioral numbness	no	1650	24	1		
	yes	4	1	17.1	(1.3, 217.9)	0.03
Hand or foot spasm	no	1650	23	1		
	yes	4	2	11.7	(1.2, 116.8)	0.04
Paraesthesia	no	1606	21	1		
	yes	48	4	4.1	(0.9, 17.6)	0.06
Calcium supplement	no	1515	18	1		
	yes	139	7	3.0	(1.1, 8.3)	0.03
Phosphate supplement	no	1645	24	1		
	yes	9	1	17.3	(2.0, 153.2)	0.01
Cyclosporine	no	1646	24	1		
	yes	8	1	6.5	(0.4, 96.3)	0.17
Chemotherapy	no	1617	23	1		
	yes	37	2	5.9	(1.2, 27.6)	0.02
Hyperparathyroidism	no	1643	24	1		
	yes	11	1	2.8	(0.2, 43.9)	0.46
Diarrhoea	no	1629	23	1		
	yes	25	2	3.1	(0.5, 18.3)	0.22
Hypothyroidism	no	1629	24	1		
	yes	25	1	2.8	(0.8, 10.7)	0.12

Table 2. Logistic regression results: Variables associated with a high calcium level

risk variable		calcium level high (n=1679)		OR	(95%CI)	p
		no	yes			
Age, years	18-39	230	19	1		
	40-59	359	34	1.1	(0.6, 2.0)	0.83
	60-79	478	86	1.6	(0.9, 2.9)	0.11
	≥80	409	64	1.3	(0.7, 2.3)	0.44
Gender	male	707	82	1		
	female	769	121	1.6	(1.2, 2.3)	<0.01
Vomiting	no	1304	169	1		
	yes	172	34	1.7	(1.1, 2.6)	0.02
Lethargy	no	1300	168	1		
	yes	176	35	1.3	(0.9, 2.0)	0.19
Muscle weakness	no	1368	178	1		
	yes	108	25	1.6	(1.0, 2.7)	0.05
Polyuria	no	1472	199	1		
	yes	4	4	9.7	(2.2, 44.0)	<0.01
Confusion	no	1372	172	1		
	yes	104	31	2.3	(1.4, 3.6)	<0.01
Palpitations	no	1297	190	1		
	yes	179	13	0.8	(0.4, 1.4)	0.44
Paraesthesia	no	1426	201	1		
	yes	50	2	0.3	(0.1, 1.5)	0.16
Proton pump inhibitor	no	992	118	1		
	yes	484	85	1.0	(0.7, 1.4)	0.96
Vitamin D	no	1112	128	1		
	yes	364	75	1.3	(0.9, 1.8)	0.14
Insulin	no	1378	181	1		
	yes	98	22	0.9	(0.5, 1.7)	0.76
Beta agonist	no	1341	172	1		
	yes	135	31	1.5	(1.0, 2.4)	0.06
Phosphate supplements	no	1469	200	1		
	yes	7	3	3.0	(0.7, 12.7)	0.14
Chronic kidney disease	no	1308	164	1		
	yes	168	39	1.3	(0.8, 2.0)	0.24
Hyperparathyroidism	no	1469	198	1		

	yes	7	5	4.3	(1.3, 15.1)	0.02
Cancer	no	1129	128	1		
	yes	347	75	1.7	(1.2, 2.4)	<0.01
Hypothyroidism	no	1396	198	1		
	yes	80	5	0.4	(0.1, 0.95)	0.04
Type 1 diabetes	no	1462	197	1		
	yes	14	6	3.6	(1.1, 11.9)	0.04
Type 2 diabetes	no	1206	148	1		
	yes	270	55	1.4	(0.9, 2.1)	0.09

Table 3. Logistic regression results: Variables associated with a low magnesium level

risk variable		magnesium level low (n=1576)		OR	(95%CI)	p
		no	yes			
Age, years	18-39	230	10	1		
	40-59	350	19	0.9	(0.4, 2.3)	0.88
	60-79	469	59	2.0	(0.9, 4.6)	0.10
	≥80	399	40	1.8	(0.8, 4.4)	0.17
Gender	male	702	49	1		
	female	746	79	1.9	(1.3, 3.0)	<0.01
Nausea	no	1253	99	1		
	yes	195	29	1.5	(0.9, 2.5)	0.15
Vomiting	no	1279	106	1		
	yes	169	22	1.3	(0.7, 2.3)	0.40
Lethargy	no	1281	105	1		
	yes	167	23	1.2	(0.7, 2.1)	0.51
Palpitations	no	1252	120	1		
	yes	196	8	0.9	(0.4, 2.0)	0.83
Diarrhoea	no	1373	110	1		
	yes	75	18	1.8	(0.9, 3.8)	0.10
Diuretics	no	1122	85	1		
	yes	326	43	0.8	(0.5, 1.3)	0.34
Proton pump inhibitor	no	1002	51	1		
	yes	446	77	2.2	(1.4, 3.3)	<0.01
Vitamin D	no	1090	76	1		
	yes	358	52	1.2	(0.8, 2.0)	0.40
ARB	no	1225	100	1		
	yes	223	28	1.2	(0.7, 2.0)	0.58
ACE inhibitor	no	1264	103	1		
	yes	184	25	1.4	(0.8, 2.4)	0.23

Beta agonist	no	1315	106	1		
	yes	133	22	1.7	(1.0, 3.0)	0.06
Calcium supplement	no	1332	103	1		
	yes	116	25	1.5	(0.8, 2.7)	0.22
Magnesium supplement	no	1339	110	1		
	yes	109	18	0.7	(0.3, 1.3)	0.24
Glucocorticoid	no	1324	109	1		
	yes	124	19	0.9	(0.4, 1.7)	0.71
Digoxin	no	1415	120	1		
	yes	33	8	1.7	(0.7, 4.4)	0.23
Tacrolimus	no	1434	118	1		
	yes	14	10	13.1	(4.1, 41.3)	<0.01
Chemotherapy	no	1420	122	1		
	yes	28	6	2.0	(0.7, 5.9)	0.19
Chronic kidney disease	no	1277	106	1		
	yes	171	22	0.6	(0.4, 1.1)	0.13
Cancer	no	1114	88	1		
	yes	334	40	1.6	(1.0, 2.6)	0.05
Pancreatitis	no	1436	123	1		
	yes	12	5	0.9	(0.2, 3.8)	0.84
Pancreatic insufficiency	no	1443	125	1		
	yes	5	3	4.4	(0.7, 25.6)	0.10
Diarrhoea	no	1427	121	1		
	yes	21	7	3.1	(1.0, 10.0)	0.05
Chronic liver disease	no	1415	118	1		
	yes	33	10	0.9	(0.3, 2.6)	0.92
Alcohol abuse	no	1388	105	1		
	yes	60	23	9.3	(4.6, 19.1)	<0.01
Type 2 diabetes	no	1193	76	1		
	yes	255	52	2.9	(1.9, 4.7)	<0.01

Table 4. Logistic regression results: Variables associated with a high magnesium level

risk variable		magnesium level high (n=1576)		OR	(95%CI)	p
		no	yes			
Gender	male	729	22	1		
	female	817	8	0.4	(0.2, 1.0)	0.04
Lethargy	no	1366	20	1		
	yes	180	10	4.3	(1.7, 10.7)	<0.01
Diuretics	no	1192	15	1		
	yes	354	15	1.3	(0.5, 3.7)	0.56
Furosemide	no	1420	23	1		
	yes	126	7	1.6	(0.5, 5.3)	0.40
Thiazide	no	1510	26	1		
	yes	36	4	4.5	(1.1, 18.4)	0.03
Vitamin D	no	1151	15	1		
	yes	395	15	1.4	(0.6, 3.5)	0.48
Insulin	no	1436	24	1		
	yes	110	6	1.0	(0.3, 3.5)	0.94

Calcium supplement	no	1411	24	1		
	yes	135	6	1.3	(0.4, 4.3)	0.69
Lithium	no	1540	29	1		
	yes	6	1	7.9	(0.4, 160.0)	0.18
Bisphosphonate	no	1501	27	1		
	yes	45	3	2.0	(0.4, 8.8)	0.37
Phosphate binders	no	1533	27	1		
	yes	13	3	3.5	(0.6, 20.3)	0.16
Chronic kidney disease	no	1367	16	1		
	yes	179	14	4.5	(1.7, 12.1)	<0.01
Diabetes type 2	no	1251	18	1		
	yes	295	12	1.3	(0.5, 3.6)	0.55

Table 5. Logistic regression results: Variables associated with a low phosphate level

risk variable		phosphate level low (n=1511)		OR	(95%CI)	p
		no	yes			
Gender	male	600	121	1		
	female	687	103	0.7	(0.5, 0.9)	0.02
Nausea	no	1115	177	1		
	yes	172	47	1.7	(1.1, 2.6)	<0.01
Vomiting	no	1140	186	1		
	yes	147	38	1.3	(0.9, 2.1)	0.18
Confusion	no	1196	200	1		
	yes	91	24	1.6	(1.0, 2.6)	0.06

Seizure	no	1236	206	1		
	yes	51	69	2.1	(1.2, 3.8)	0.01
Diuretics	no	965	186	1		
	yes	322	38	0.6	(0.4, 0.9)	0.01
Phosphate supplements	no	1282	221	1		
	yes	5	3	2.5	(0.5, 11.9)	0.26
Antacids	no	1275	218	1		
	yes	12	6	2.3	(0.8, 6.6)	0.12
Glucocorticoids	no	1182	189	1		
	yes	105	35	1.7	(1.1, 2.7)	0.02
Tacrolimus	no	1272	215	1		
	yes	15	9	2.4	(1.0, 6.2)	0.06
Chronic kidney disease	no	1125	198	1		
	yes	162	26	1.6	(0.8, 3.4)	0.21

Table 6. Logistic regression results: Variables associated with a high phosphate level

		phosphate level high (n=1511)		OR	(95%CI)	p
		no	yes			
Polyuria	no	1343	160	1		
	yes	5	3	5.0	(1.1, 23.6)	0.04

Hand or foot spasm	no	1344	161	1		
	yes	4	2	5.1	(0.8, 32.1)	0.08
Confusion	no	1240	156	1		
	yes	108	7	0.5	(0.2, 1.0)	0.07
Palpitations	no	1171	156	1		
	yes	177	7	0.4	(0.2, 0.9)	0.03
Diuretics	no	1054	97	1		
	yes	294	66	1.9	(1.2, 3.0)	<0.01
Furosemide	no	1241	140	1		
	yes	107	23	0.8	(0.4, 1.5)	0.43
Thiazides	no	1318	155	1		
	yes	30	8	1.6	(0.6, 3.9)	0.34
Vitamin D	no	1019	96	1		
	yes	329	67	1.4	(0.9, 2.2)	0.09
Insulin	no	1257	141	1		
	yes	91	22	0.8	(0.4, 1.7)	0.61
Calcium supplement	no	1236	138	1		
	yes	112	25	1.1	(0.6, 1.9)	0.78
Digoxin	no	1310	162	1		
	yes	38	1	0.1	(0.01, 1.0)	0.06
Cyclosporine	no	1343	159	1		
	yes	5	4	4.1	(1.0, 17.0)	0.06
Phosphate binders	no	1339	157	1		
	yes	9	6	1.8	(0.6, 6.0)	0.32
Chronic kidney disease	no	1213	110	1		
	yes	135	53	3.5	(2.2, 5.4)	<0.001
Hypothyroidism	no	1284	148	1		
	yes	64	15	1.9	(1.0, 3.6)	0.06
Type 1 diabetes	no	1336	156	1		
	yes	12	7	3.5	(1.0, 12.4)	0.06
Type 2 diabetes	no	1094	119	1		
	yes	254	44	1.1	(0.7, 1.7)	0.81

Box. Important risk variables for calcium, magnesium or phosphate abnormalities

calcium	magnesium	phosphate
<i>Medical History</i>		
Ca or PO ₄ supplements	tacrolimus	chronic kidney disease
hyperparathyroidism	alcohol abuse	diuretics
chemotherapy	thiazide diuretics	glucocorticoids
type 1 diabetes	chronic kidney disease	
cancer	type 2 diabetes	
	proton pump inhibitor	
<i>Signs and Symptoms</i>		
perioral numbness	lethargy	polyuria
hand or foot spasm		seizures
polyuria		nausea
vomiting		
confusion		

Ca calcium, PO₄ phosphate

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