The Journal of Nutrition, Health & Aging©
Volume 14, Number 10, 2010

CHANGES IN SERUM MAGNESIUM AND PHOSPHATE IN OLDER HOSPITALISED PATIENTS – CORRELATION WITH MUSCLE STRENGTH AND RISK FACTORS FOR REFEEDING SYNDROME

S. HENDERSON[1], F. BOYCE[2], D. SUMUKADAS[3], M.D WITHAM[3,4]

1. Dept of Medicine for the Elderly, Royal Victoria Hospital, Edinburgh; 2. Dept of Medicine for the Elderly, Royal Victoria Hospital, Dundee; 3. Section of Ageing and Health, University of Dundee; 4. Corresponding author: Contact details: Dept of Ageing and Health, Division of Medicine, Mailbox 1, Ninewells Hospital, Dundee DD1 9SY, UK, Tel: +44 1382 632436. Fax: +44 1382 660675. Email: m.witham@dundee.ac.uk

Abstract: *Objectives:* To evaluate changes in serum magnesium and phosphate over time in hospitalised older patients, examine whether such changes were associated with changes in muscle strength, and assess whether risk factors for refeeding syndrome were associated with falls in serum magnesium and phosphate. *Design and Setting:* Community dwelling patients aged 70 and over, admitted to a specialist Medicine for the Elderly assessment unit were included in a prospective study. *Measurements:* Weight, height, triceps skinfold thickness and mid arm circumference were recorded at baseline. Serum magnesium and phosphate was measured on admission, and at days 1, 2, 3, 5, 7, 10, 14, 21, 28 after admission, along with handgrip and quadriceps strength measured in the non-dominant limbs using a portable dynamometer. *Results:* 43 patients were recruited with a mean age of 83.8 years (SD 7.5). 58% were female. Mean baseline serum magnesium and phosphate levels were 0.89mmol/L and 1.07mmol/L respectively. 10/43 patients had a fall in serum magnesium of at least 0.2mmol/l from baseline and 20/43 had a similar fall in phosphate. No correlation was shown between these changes in electrolytes and muscle strength. Regression analyses did not show that risk factors for refeeding syndrome were associated with falls in electrolyte levels. *Conclusion:* Changes in serum magnesium and phosphate levels do not correlate with changes in muscle strength in older hospitalised patients. Risk factors for refeeding syndrome did not predict falls in serum phosphate or magnesium.

Key words: Muscle, older, magnesium, phosphate.

Introduction

Magnesium and phosphate are key intracellular ions that are involved in a wide range of physiological functions, especially around energy generation. Phosphate is necessary for generation of adenosine triphosphate (ATP) and phosphocreatine, and magnesium is a cofactor in the production of ATP. Muscle contractile function is dependent on adequate supplies of ATP, which requires both phosphate and magnesium.

Low serum phosphate and magnesium levels have been reported to be common amongst older hospitalised patients; serum phosphate levels below the normal range occur in 15 to 30% of hospitalised older patients (1, 2). Even when serum magnesium levels are normal, intracellular levels may be low, as is commonly seen in older patients with alcoholism, heart failure and those taking diuretic therapy (3-5). A significant overlap exists between risk factors for hypomagnesemia and hypophosphatemia and those for refeeding syndrome, suggesting that refeeding syndrome may be a common cause of these depressed electrolyte states in older people. Refeeding syndrome is known to cause muscle weakness, delirium, heart failure, arrhythmias and increases susceptibility to infection (6) – all of which are common problems in hospitalised older people.

Cross-sectional data suggests that a significant correlation exists between serum magnesium levels and muscle strength (7). Although data on such an association involving serum phosphate levels are lacking, even mildly depressed serum phosphate levels are associated with a markedly increased risk of death in older hospitalised patients (1, 2).

If low serum magnesium and phosphate are due to refeeding syndrome, it would be expected that levels would fall at some point during hospital admission. This fall is seen early in other settings (e.g. critical care) (8) when refeeding occurs, but has not been studied in older hospitalised patients. Patients with geriatric syndromes, e.g. poor mobility or falls, may start to eat relatively early after admission, although increased intake may be delayed in patients with an acute intercurrent illness on admission. It is also unclear whether low phosphate and magnesium are causative in explaining low muscle strength and higher death rates, respectively, or whether these observed associations are due to impaired homeostasis in frail, unwell individuals.

The aim of this study was therefore to examine the time course of changes in serum magnesium and phosphate in older hospitalised patients, to test whether risk factors for refeeding syndrome predicted reductions in serum phosphate and magnesium, and to examine the correlation between changes in these ions and changes in muscle strength.

Received January 7, 2010
Accepted for publication March 5, 2010

Methods

Patients

We performed a prospective, longitudinal cohort study on patients admitted to the Medicine for the Elderly service in Dundee. Patients aged 70 years or over admitted from the community to the Medicine for the Elderly service were eligible for inclusion. Patients were excluded if they were receiving parenteral nutrition, or enteral nutrition via nasogastric tube or gastrostomy. Patients were also excluded if they were unable to give written informed consent or had been enrolled into the study during a previous hospital admission.

Written informed consent was obtained from all participants; enrollment took place 24 hours after hospital admission to allow sufficient time for perusal of the study information. Approval was obtained from Tayside Research Ethics Committee (ref no 07/S1402/78). The study conformed to the principals enshrined in the Declaration of Helsinki.

Outcome measures

Serum biochemistry (sodium, potassium, urea, creatinine, calcium, phosphate, magnesium, albumin, C-reactive protein) was obtained on admission, and at 1, 2, 3, 5, 7, 10, 14, 21 and 28 days after admission. Analyses were performed by the Department of Biochemical Medicine, NHS Tayside, Dundee, using a Roche P800 multichannel analyser (Roche Diagnostics, Lewes, UK). Handgrip dynamometry was performed each timepoint using a hand-held dynamometer (Takei, Japan), using the non-dominant hand. Grip strength is an important marker of frailty in older people (9). Hand held devices have good correlation with the gold standard Biodex dynamometry in older people (10). Leg dynamometry was performed using the Lafayette model 01163 dynamometer (Lafayette Instrument Company, Lafayette, USA) at each timepoint. This is a simple measure of quadriceps strength in older people that has a good inter rater reliability (11). Leg dynamometry was performed with the patient sitting in a chair, with the knee joint in 90 degrees of flexion. The dynamometer was placed above the ankle of the non-dominant leg. Patients were instructed to extend their leg against the dynamometer as hard as possible using constant pressure. The highest of three readings was recorded.

Weight, body mass index, triceps skinfold thickness and mid-arm circumference were performed at 1, 14 and 28 days after admission. All patients received usual multidisciplinary geriatric medical care, including care by a clinical dietitian not associated with the study. The Malnutrition Universal Screening Tool (MUST) score was derived from patient charts (12), and past medical history was used to calculate the Charlson comorbidity score (13). Cognitive impairment was defined as an abbreviated mental test score of <8/10, or a Folstein mini-mental state examination (MMSE) of <24/30 (14). Renal impairment on admission was defined as an estimated glomerular filtration rate of <30ml/min by the MDRD4 equation (15). Alcohol excess was defined as >14 standard units of alcohol per week.

Statistical analysis

Statistical analyses were performed using SPSS version 15 (SPSS, Chicago, USA). The primary outcome measure was the change in serum magnesium and phosphate levels during hospitalisation. Secondary outcomes were the change in hand grip strength and quadriceps strength and their correlation to the changes in serum magnesium and phosphate levels during hospitalisation. As this was a pilot study, no *a priori* sample size calculation was performed. Univariate linear regression was used to derive regression coefficients (B); baseline factors associating with a significance of $p<0.1$ were entered into a stepwise multivariate linear regression to ascertain which factors were independently associated with low baseline electrolyte levels or with a fall in electrolyte levels.

Results

43 patients were enrolled between February 2008 and December 2008. Baseline details are given in Table 1. At baseline, no patient had a serum phosphate level below the normal range (0.8 mmol/L), and 1/43 (2%) of patients had a serum magnesium level below the normal range (0.7 mmol/L). During the study period, phosphate levels fell to <0.8 mmol/L in 14/43 (33%) of patients; a total of 3/43 (7%) of patients returned at least one magnesium measurement below 0.7 mmol/L. 20/43 (47%) experienced a fall in serum phosphate of at least 0.2 mmol/L from baseline; 10/43 experienced a fall in serum magnesium of at least 0.2 mmol/L from baseline.

Table 1
Baseline characteristics

Mean age (years) (SD)	83.8 (7.5)
Female sex	25/43 (58%)
Weight loss in past 6 months (3Kg or more)	16/43 (37%)
Vomiting	6/43 (14%)
Diarrhoea	3/43 (7%)
Diabetes mellitus	9/43 (21%)
Chronic heart failure	10/43 (23%)
Active cancer	5/43 (12%)
Alcohol excess	2/43 (5%)
On proton pump inhibitor	22/43 (51%)
Received intravenous fluids during admission	11/43 (26%)
Laxatives	10/43 (23%)
Diuretics	26/43 (60%)
Calcium and vitamin D	9/43 (21%)
Beta 2 agonists	11/43 (26%)
Theophylline	1/43 (2%)
MUST score on admission: 0	25/43 (58%)
1	3/43 (7%)
2 or more	15/43 (35%)
Body mass index (Kg/m^2)(SD)	23.8 (5.6)
Triceps skinfold thickness (mm) (SD)	10.5 (6.3)
Mid-arm circumference (cm) (SD)	26.7 (5.4)
Handgrip (Kg) (SD)	12.3 (6.1)
Leg dynamometry (Kg) (SD)	3.6 (1.5)

Na (mmol/L)	138.5 (3.9)
K (mmol/L)	4.25 (0.67)
Mg (mmol/L)	0.89 (0.17)
Phosphate (mmol/L)	1.07 (0.10)
eGFR<30 ml/min	8/43 (19%)
Mean number of medications (SD)	8.2 (2.8)
Mean Charlson score (SD)	2.3 (1.7)
Cognitive impairment	22/43 (51%)

MUST: Malnutrition Universal Screening Tool. eGFR: Estimated glomerular filtration rate

Relationship between baseline electrolyte levels and muscle strength

There was no correlation between baseline phosphate levels and muscle strength. Baseline magnesium showed modest, but still non-significant correlation with leg strength but not handgrip (Table 2).

Table 2

Correlation between muscle strength, baseline electrolyte values and changes in electrolyte values

	Handgrip		Leg strength	
	r	p	r	p
Baseline magnesium vs baseline muscle strength	0.15	0.36	0.32	0.06
Baseline phosphate vs baseline muscle strength	-0.02	0.89	0.07	0.68
Change in magnesium vs change in muscle strength	-0.03	0.76	-0.01	0.94
Change in phosphate vs change in muscle strength	0.13	0.18	0.10	0.31

r=Pearson's correlation coefficient

Changes in electrolytes and muscle strength during admission

No correlation was observed between changes in electrolytes from baseline compared to changes in muscle strength from baseline (Table 2).

Baseline factors predicting a fall in serum magnesium or phosphate during admission

Univariate regression using each baseline variable in turn (Table 3) showed that lower baseline phosphate was associated with lower BMI, lower mid arm circumference, lower triceps skinfold thickness, recent weight loss of >3Kg, lower number of medications and laxative use (all $p<0.1$). Renal impairment was associated with higher baseline phosphate levels. Similarly, increasing age, recent weight loss, low BMI and higher numbers of medications on admission were associated with a lower nadir in phosphate. Greater falls in phosphate were very highly correlated with higher baseline phosphate ($r=0.79$, $p<0.001$), suggesting regression to the mean. Linear regression incorporating the above baseline variables showed that only BMI independently predicted baseline phosphate ($p=0.004$) and BMI plus an history of weight loss independently predicted the nadir in phosphate ($p=0.005$).

For magnesium, lower admission values were correlated with younger age only, although patients with lower admission magnesium levels were more likely to receive intravenous fluids during admission. Univariate analysis suggested that a history of vomiting, female sex and the presence of heart failure were associated with a lower nadir magnesium level

Table 3

Univariate associates of baseline and nadir phosphate and magnesium levels.

Factor	Baseline phosphate		Baseline magnesium		Nadir phosphate		Nadir magnesium	
	B	p	B	p	B	p	B	p
Age	-0.003	0.45	0.006	0.06	0.006	0.06	0.00	0.95
Sex	0.036	0.55	-0.049	0.30	0.052	0.28	-0.081	0.001
Weight loss	-0.11	0.07	0.00	0.99	-0.10	0.03	0.018	0.51
Vomiting	0.064	0.46	0.054	0.43	-0.034	0.64	0.11	0.003
Diarrhoea	-0.09	0.44	-0.094	0.30	-0.070	0.45	0.006	0.90
Diabetes mellitus	-0.026	0.73	-0.018	0.76	-0.039	0.50	-0.006	0.85
Chronic heart failure	-0.009	0.90	-0.013	0.82	-0.067	0.23	-0.062	0.03
Active cancer	0.049	0.60	-0.019	0.80	0.039	0.60	-0.036	0.35
Alcohol excess	-0.13	0.35	0.088	0.42	0.018	0.87	0.050	0.39
Proton pump inhibitor use	0.031	0.60	-0.032	0.50	-0.049	0.31	-0.004	0.87
Intravenous fluids	0.073	0.27	0.13	0.01	0.005	0.92	-0.004	0.88
Laxatives	0.14	0.04	0.057	0.30	-0.021	0.70	-0.001	0.97
Diuretics	0.081	0.19	-0.009	0.85	-0.033	0.51	-0.024	0.36
Calcium and vitamin D	-0.10	0.16	-0.025	0.66	0.010	0.87	0.017	0.60
Beta 2 agonists	0.076	0.27	-0.051	0.34	-0.051	0.35	0.001	0.98
Theophylline	-0.16	0.42	0.25	0.11	-0.14	0.36	0.054	0.51
MUST score	-0.035	0.21	0.016	0.44	0.008	0.71	0.001	0.94
Body mass index	0.019	0.003	-0.005	0.33	-0.009	0.10	-0.003	0.28
Triceps skinfold thickness	0.009	0.07	-0.003	0.44	-0.005	0.19	-0.003	0.13
Mid arm circumference	0.016	0.005	-0.004	0.37	-0.004	0.44	-0.001	0.67
eGFR<30ml/min	0.20	0.007	0.090	0.13	-0.002	0.98	-0.016	0.63
Number of medications	0.025	0.017	-0.013	0.12	-0.019	0.02	-0.007	0.12
Charlson score	0.00	1.0	-0.012	0.40	-0.005	0.72	-0.004	0.57
Cognitive impairment	0.018	0.77	-0.002	0.96	0.024	0.62	0.020	0.44

MUST: Malnutrition Universal Screening Tool. eGFR: Estimated glomerular filtration rate

(p<0.1); once again, the degree of fall in magnesium was very strongly correlated (r=0.85, p<0.001) with higher baseline magnesium, suggesting regression to the mean. It is noteworthy that use of proton pump inhibitors and diuretics was not associated with lower magnesium, despite this being a known side-effect of these medication classes (16). Linear regression incorporating the above baseline variables showed that age and future intravenous fluid use were independently associated with baseline magnesium (p=0.005); gender and vomiting were independently associated with the nadir in magnesium (p<0.001)

Relationship between changes in electrolytes and changes in muscle strength during admission

The median time to the lowest phosphate level was 3 days (interquartile range 8 days), whereas the median time to lowest leg strength was 2 days (IQR 5 days). Subtracting the time to lowest leg strength from time to lowest phosphate level for each individual revealed that the mean difference was -2.9 days (95%CI -6.0 to 0.3, p=0.07), suggesting that for most patients, leg strength fell several days before the greatest fall in phosphate. Similar results were found for magnesium (data not shown).

Discussion

Our results confirm that mild degrees of hypophosphataemia and hypomagnesaemia are not uncommon in older hospitalised patients. However, we failed to establish a strong correlation between muscle strength and either magnesium or phosphate levels. In particular, intra-individual changes in magnesium and phosphate levels were not paralleled by changes in muscle strength, and changes in muscle strength tended to precede changes in electrolyte levels, suggesting that changing serum electrolyte levels did not have a causal role.

Previous cross-sectional studies have suggested that serum magnesium correlates weakly with muscle strength (7), and that such associations persist after adjusting for several baseline factors associated with low serum magnesium levels. Our inability to duplicate these findings may be because the participants we recruited were acutely unwell. It is also possible that the range of muscle strength was not wide enough to show correlations with magnesium levels. Previous cross-sectional studies have shown only weak associations between serum magnesium levels and muscle strength, and it is possible that similar weak correlations could have been missed due to our small study size.

Although cross-sectional studies have suggested that risk factors for refeeding syndrome are associated with hypophosphataemia, we did not find that these risk factors were able to predict the occurrence of falls in magnesium or phosphate in this longitudinal study, although low anthropometric indices at baseline did correlate with lower serum phosphate at baseline. Our findings argue against refeeding syndrome being responsible for many of the cases of hypomagnesaemia or hypophosphataemia that we detected in this study.

Strengths of our study include prospective design and longitudinal data, which so far have been lacking in studies of low magnesium and phosphate in old, frail patients. The inclusion of a wide range of baseline data, including anthropometric data is a further strength, as is the inclusion of very old patients with significant comorbid disease including cognitive impairment.

Our study sample is however small, and we have focused on muscle strength as a clinical marker of the effects of electrolyte disturbance. Our study was too small to determine whether other clinical syndromes associated with hypomagnesaemia and hypophosphataemia (e.g. arrhythmias, infection, delirium, heart failure exacerbation) could be more prevalent in patients with mild degrees of hypomagnesaemia and hypophosphataemia. It is likely that only intervention studies will be able to fully settle these questions, but there is evidence to suggest that reduced grip strength is a surrogate marker for a wide range of adverse outcomes in older people, including longer length of stay and increased postoperative complications, as well as disability and death (17).

The very frail and very ill are likely to be underrepresented in our study, as we required participants to give informed consent. Furthermore, the need for participants to reflect on the study for 24 hours prior to consenting meant that we were unable to chart changes in muscle strength over the first day of admission. It is also important to remember that serum magnesium and phosphate levels do not necessarily represent the levels of these ions within cells (18). It is possible that a larger proportion of older people are magnesium and phosphate deplete than we detected using serum electrolyte levels; this is certainly known to be the case in patients with heart failure (3). However intracellular magnesium and phosphate levels are impractical to measure in clinical practice and thus do not provide a useful way of detecting depletion in the clinical setting.

In conclusion, changes in serum magnesium and phosphate levels in older hospitalised people do not correlate with changes in muscle strength. Further work may still be merited to test whether supplementation of magnesium and phosphate can improve other clinical parameters known to be affected by deficiency of these electrolytes.

Acknowledgements: With thanks to the staff and patients of Royal Victoria Hospital, Dundee, UK.

Conflicts of interest: None to declare: Funding: Dr Witham is funded by a Scottish Government NES/CSO Clinician Scientist award.

Financial disclosure: None of the authors had any financial interest or support for this paper.

References

1. Sumukadas D, Jenkinson F, Witham MD. Associations and consequences of hypophosphataemia in older hospitalised women. Age Ageing 2009;38:112-5.
2. Kagansky N, Levy S, Koren-Morag N, Berger D, Knobler H. Hypophosphataemia in

old patients is associated with the refeeding syndrome and reduced survival. J Intern Med 2005;257:461-8.
3. Ralston MA, Murnane MR, Kelley RE, Altschud RA, Unverferth DV, Leier CV. Magnesium content of serum, circulating mononuclear cells, skeletal muscle, and myocardium in congestive heart failure. Circulation 1989;80:573-80.
4. Dorup I, Skajaa K, Clausen T, Kjeldsen K. Reduced concentrations of potassium, magnesium, and sodium-potassium pumps in human skeletal muscle during treatment with diuretics. BMJ 1988;296:455-8.
5. Aagaard NK, Andersen H, Vilstrup H, Clausen T, Jakobsen J, Dorup I. Decreased muscle strength and contents of Mg and Na,K-pumps in chronic alcoholics occur independently of liver cirrhosis. J Intern Med 2003;253:359-66.
6. Crook MA, Hally V, Panteli JV. The importance of the refeeding syndrome. Nutrition 2001;17:632-7.
7. Dominguez LJ, Barbagallo M, Lauretani F, et al. Magnesium and muscle performance in older persons: the InCHIANTI study. Am J Clin Nutr 2006;84:419-26.
8. Zazzo JF, Troche G, Ruel P, Maintenant J. High incidence of hypophosphatemia in surgical intensive care patients: efficacy of phosphorus therapy on myocardial function. Intensive Care Med 1995;21:826-31.
9. Syddall H, Cooper C, Martin F, Briggs R, Aihie SA. Is grip strength a useful single marker of frailty? Age Ageing 2003;32:650-6.
10. Martin HJ, Yule V, Syddall HE, Dennison EM, Cooper C, Aihie SA. Is hand-held dynamometry useful for the measurement of quadriceps strength in older people? A comparison with the gold standard Biodex dynamometry. Gerontology 2006;52:154-9
11. Wang CY, Olson SL, Protas EJ. Test-retest strength reliability: hand-held dynamometry in community-dwelling elderly fallers. Arch Phys Med Rehabil 2002;83:811-5.
12. Elia M: Screening for Malnutrition: A Multidisciplinary Responsibility. Development and Use of the Malnutrition Universal Screening Tool (MUST) for Adults. Malnutrition Advisory Group (MAG), a Standing Committee of BAPEN. Redditch, Worcs.: BAPEN. 2003
13. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83
14. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.
15. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461-70.
16. Cundy T, Dissanayake A. Severe hypomagnesaemia in long-term users of proton-pump inhibitors. Clin Endocrinol 2008;69:338-41.
17. Bohannon RW. Hand-grip dynamometry predicts future outcomes in aging adults. J Geriatr Phys Ther 2008;31:3-10.
18. Amanzadeh J, Reilly RF. Hypophosphatemia: an evidence-based approach to its clinical consequences and management. Nat Clin Pract Nephrol 2006;2:136-48.