Deceptive potassium and magnesium measurements

**Abstract:** Potassium and magnesium are important circulating cations and are predominantly intracellular elements. Only a small fraction of these elements is present in extracellular fluids including blood (~1%). Measurement of the concentration of such small fractions in blood is commonly used to assess and reflect their body content levels. However, some of these measurements can be flawed and a failure to recognize the limitations of these tests may result in misdiagnosis and/or unnecessary follow-up investigations and/or expensive hospital admissions. The focus of this note is three-fold (a) to highlight and discuss separately the less appreciated pitfalls of potassium and magnesium measurements per se, (b) suggestions to identify and rectify these snags and to improve their clinical interpretation, and finally (c) to discuss briefly the clinical inter-relationship between these two predominantly most abundant intracellular cations without dwelling on details which are outside the scope of this note.

**Keywords:** erroneous potassium results; hypermagnesaemia; magnesium deficiency; pseudohyperkalaemia; pseudonormokalaemia.

DOI 10.1515/dx-2014-0037
Received June 13, 2014; accepted July 25, 2014; previously published online September 6, 2014

Pseudonormokalaemia’ masking true hypokalaemia

The causes of pseudohyperkalaemia are generally known, e.g. “mechanical” leading to rupture of RBC membranes causing haemolysis, thrombocytosis/leuocytosis, incorrect order of blood draw causing carryover and/or back flow of K₂EDTA (potassium ethylenediaminetetraacetic) used as anticoagulant for haematology complete blood count (CBC)/blood film contaminating a subsequent sample taken for potassium analysis, leaving the tourniquet for long/fist clenching and old sample [1, 2]. Less known, however, is that delayed separation of serum/plasma from cells in blood samples stored for periods of only few hours and/or at extreme temperature [3–7] can be a significant source of error in potassium measurements.

In vivo and in vitro, the concentration of potassium in blood is maintained by an active transport system, the efficacy of which is dependent on intracellular energy production, utilizing one-third of a cell’s energy expenditure and being contingent on nearly optimum body temperature. For example, whole blood samples kept for 2–4 h at temperatures between 4 and 7°C (e.g., ambient or refrigerated) caused potassium concentrations in plasma/serum to increase [1, 3] albeit at vastly variable rates in different samples, ranging from 0.1 to >1.2 mmol/L [1, 3] or even more [4]. Timely separation (~1 h or less) of serum from cells is necessary to secure accurate potassium measurement. When potassium leaks out of the cell without haemoglobin, it has the potential to masquerade as normokalaemia in patients who are in fact hypokalaemic [1, 3] or albeit at vastly variable rates in different samples, ranging from 0.1 to >1.2 mmol/L [1, 3] or even more [4]. Timely separation (~1 h or less) of serum from cells is necessary to secure accurate potassium measurement. When potassium leaks out of the cell without haemoglobin, it has the potential to masquerade as normokalaemia in patients who are in fact hypokalaemic [1, 3] or produce a reading of pseudohyperkalaemia in patients with normal potassium concentrations [1, 5]. Abnormal results including pseudohyperkalaemia are usually followed-up [1, 5]. However, ‘pseudo-normokalaemia’ may be accepted at face value, thus denying patients’ the appropriate treatment. High ambient temperatures also produce spurious hypokalaemia or pseudonormokalaemia readings in patients on angiotensin converting enzyme inhibitors with true hyperkalaemia [6, 7].

In summary, pseudonormokalaemia is potentially dangerous and is an underappreciated factor in potassium measurement.
In vitro haemolysis is common but in vivo haemolysis can be overlooked

In haemolysed samples, potassium concentration increase, roughly in proportion to the degree of haemolysis [8–10]. The World Health Organization recommends that laboratories do not report potassium concentrations for haemolysed samples because of this [11]. However, this may wrongly imply to the clinical team that potassium concentration cannot be measured analytically. A fatal case of systemic lupus erythematosus with in vivo haemolysis secondary to haemolytic uraemic syndrome highlighted this problem [12]. In this case, serum potassium concentrations were denied to the clinical team despite three repeats because of the laboratory policy of not reporting potassium measurements on all haemolysed samples [12].

Comments on deceptive potassium measurements

Many laboratories do not report potassium concentrations in haemolysed samples while others may issue a proviso such as “sample haemolysed suggest repeat” [12]. Such a policy may be considered prudent, because haemolysis in most cases is in vitro. Three repeats in the case described provided no additional information. Some clinicians may be unaware that potassium concentration can be measured with identical analytical accuracy in haemolysed samples, as in unhaemolysed samples. Results from in vivo haemolysis, however, may be treated in the same way as in vitro results and therefore be suppressed by the laboratory analyser or computer.

In 131,364 unseparated blood samples taken at Primary Care clinics, marked hyperkalaemia >6.0 mmol/L was found in 2244 (1.7%) and moderate hyperkalaemia (5.3–6.0 mmol/L) in 7202 (5.5%) necessitating repeat analyses and in some cases inappropriate hospital admission [5]. However, timely separation of serum from cells at source reduced the number of samples with marked hyperkalaemia by some 77% and moderate hyperkalaemia by 54%. In a separate small series of 40 patients on diuretics, two had pseudonormokalaemia caused by delayed separation of serum from cells [3]. The financial cost of repeat analyses and/or inappropriate hospital admission is not insignificant; but more serious is the failure to identify and treat those with existing hypokalaemia (or hyperkalaemia) presented as pseudonormokalaemia.

A formal liaison policy between clinicians and laboratory staff is of paramount importance if these less appreciated pitfalls are to be avoided and the accuracy of potassium measurements enhanced.

Magnesium; the least appreciated electrolyte

Magnesium is the fourth most abundant cation (after calcium, potassium and sodium) and the second most abundant intracellular cation after potassium, but the physiological and pathological roles of magnesium are the least appreciated. Furthermore, the most common method of assessing magnesium status, namely plasma/serum measurement can be flawed and misleading (see ref. [13] for more details).

Errors in assessing magnesium status falls under two categories namely the overuse of plasma/serum magnesium in identifying deficiency and its underuse in identifying potential hypermagnesaemia. Needless to say that the most common method of assessing magnesium status, namely plasma/serum measurement can be flawed and misleading [13–18]. Furthermore, less consideration is usually given to patient’s history which can provide helpful information regarding potential magnesium deficiency (see Table 1) or excess.

The value of “Modus Vivendi” in highlighting potential magnesium deficiency

Magnesium is dependent on the balance between daily intake and renal loss. The commonly recommended daily intake for adults is 320–400 mg/day (or 6 mg/kg/body

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Table 1  Factors contributing to chronic/latent magnesium deficiency.

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<th>Factor</th>
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<td>Age; elderly absorb less and lose more magnesium</td>
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<td>Daily diet low in magnesium</td>
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<td>Soft drinking water, bottle or hard water low in magnesium</td>
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<tr>
<td>Regular alcohol intake esp. spirits</td>
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<tr>
<td>Refined salt for cooking and in food</td>
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<tr>
<td>Renal tubular disorders with magnesium wasting</td>
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<tr>
<td>Pregnancy, lactation and regular strenuous exercise</td>
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<td>Malabsorption (also short bowel syndrome/intestinal surgery)</td>
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<td>Drugs such as diuretics (loop and thiazide), proton pump inhibitors,</td>
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<tr>
<td>omeprazole, tacrolimus, chemotherapeutic agents such as cisplatin,</td>
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<td>ciclosporin, cetuximab and some phosphate-based drugs</td>
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weight for both genders). An average healthy daily diet supplies ~250 mg of magnesium (120 mg per 1000 calories) with green vegetables, cereals, fish and nuts being a rich source [13]. Refined grains and white flour are generally low in magnesium. Unrefined sea salt is very rich in magnesium at ~12% of sodium mass, however because this makes raw sea-salt bitter, magnesium (and calcium) are removed making purified table salt essentially ~99% sodium chloride [13, 14].

Another important source is water, with some (but not all) hard tap water containing more magnesium than soft water. The bioavailability of magnesium in water is generally good at ~60%; however absorption from water declines significantly with age [15].

Hard water is a general term which encompasses wide ratios of calcium to magnesium [13]. The magnesium content in most hard water (but not all) is 5–20 times higher than in soft water and can potentially provide up to 30% of daily requirement. The term soft water is used to describe water that contains few calcium or magnesium ions. The average magnesium content in soft drinking water is ~6 mg/L. The content of magnesium in bottled water also varies, from 0 to 126 mg/L [16], while carbonated tonic and soda waters contains little or no magnesium.

Significant magnesium deficiency has been reported in both elderly self-caring subjects in the community as well as in hospitalized Norwegians. In a survey involving 37,000 Americans, 39% were found to ingest <70% of the recommended daily magnesium intake and 10% of women over the age of 70 years consumed <42% of the recommended dietary requirement.

Excessive renal loss is a common cause of negative magnesium stores. Alcohol, even in moderate amounts is known to cause magnesium diuresis. Alcohol increases urinary magnesium loss above the baseline by an average of 167% (range 90–357%) and occurs even in individuals with already impoverished/depleted magnesium stores [13]. Spirits such as gin, rum, brandy, cognac, vodka and whisky contain little or no magnesium; fermented apple ciders have 10–50 mg/L of magnesium while beer and wine have levels ranging from ~30–250 mg/L. Although drinks such as some ciders, beer and wine may be considered “magnesium-rich”, they cannot be recommended as a reliable source. In addition, large consumption of magnesium rich beer and wine can have a laxative or even diarrheatic effect, potentially impeding bioavailability and absorption.

It appears reasonable therefore to suggest that a lifestyle associated with low dietary magnesium intake in food and drinking water, the use of purified table salt for cooking and in food, coupled with moderate and regular consumption of alcoholic drinks which cause a net renal magnesium loss can additively lead to impoverished/depleted magnesium stores over time.

Magnesium deficiency can be further compounded with malabsorption and those receiving medications such as diuretics (loop and thiazide), proton pump inhibitors, omeprazole, tacrolimus, chemotherapeutic agents such as cisplatin, ciclosporin, cetuximab and some phosphate-based drugs [13].

In summary, “Modus Vivendi” when carefully examined can highlight the potential causes of latent magnesium deficiency (see Table 1). It is however a common practice for clinicians to rely more on laboratory tests in the diagnosis of magnesium deficiency.

### Plasma/serum magnesium

Magnesium deficiency has been implicated in a wide range of clinical conditions [13] shown in Table 2. Plasma/serum magnesium is a commonly requested test and is informative when magnesium is reduced, indicating

<table>
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<tr>
<th>Electrolytes</th>
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<td>Hypokalaemia</td>
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<td>CVS</td>
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| Ventricular arrhythmias esp. Torsades de Pointes, Cardiac conduction abnormalities- SVTs, Abnormal vascular tone, Congestive cardiac failure Ischaemic heart disease/myocardial infarction Hypertension Pre-eclampsia/eclampsia, primary hypertension Endocrine Type II diabetes mellitus Metabolic The metabolic syndrome Bone Bone-mineral-density (BMD) and osteoporosis Muscular Muscle weakness, fatigue, numbness, tingling, spasms/cramps/tetany, fibromyalgia Neurological Irritability, depression, migraines, increased deep tendon reflexes, vertical and horizontal nystagmus Cancer Colorectal Alcoholics Exhibiting any of the above manifestations Respiratory Asthma
hypomagnesaemia, which warrants supplementation. However, normal plasma/serum magnesium (commonly reported as 0.75 to 1.2 mmol/L) remains problematical because in patients with suspected magnesium deficiency, serum concentrations can be normal despite whole body deficiency [13, 14, 17, 18]. For this reason, the practicable, inexpensive and commonly used plasma/serum magnesium must be regarded as potentially flawed test, capable of identifying magnesium deficiency in some but not all patients with deficiency and negative body stores.

A limited fraction of bone magnesium appears to be present either within the hydration shell or else on the crystal lattice. Based largely on animal studies, it has been speculated that this form of bone surface magnesium may represent a limited buffering capacity [19, 20].

**Magnesium loading test**

So, to exclude with confidence latent/chronic magnesium deficiency in cases with high index of suspicion, but normal plasma/serum magnesium, a dynamic study namely the magnesium loading test is required if renal function is normal. This procedure is probably the best physiological “gold standard test”, which is within the capability of all routine hospital’s laboratories.

It involves the administration of elemental magnesium load (as sulphate or chloride) intravenously followed by assessment of the amount of elemental magnesium excreted in the urine in the following 24 h. A large fraction of the given magnesium load is retained and a smaller amount of the given dose appears in the urine in patients with latent magnesium deficiency.

The loading test measures the body’s retention of magnesium and therefore reflects the degree of deficiency. Attention to details is however paramount for valid interpretation of the data. Patient should empty their bladder immediately before the test. The test involves intravenous administration of 30 mmol of elemental magnesium (1 mmol=24 mg) in 500 mL 5% dextrose over a period of 8–12 h. A slow rate infusion is important because plasma magnesium concentration affects the renal reabsorption threshold and abrupt elevation of plasma concentration above the normal range reduces magnesium retention and increases urinary excretion with its potential misinterpretation. Urine collection begins with the onset of the magnesium infusion and continues over the next 24 h period, including a last void at end of this period.

Patients with adequate body magnesium stores retain <10% of the infused elemental magnesium load. Latent magnesium deficiency is considered to be present if <25 mmol of elemental magnesium are excreted in the 24 h collection. Magnesium body stores are considered repleted when >90% of the elemental magnesium load is excreted in the 24 h urine.

A magnesium loading test is contraindicated in patients with renal impairment, salt losing nephropathy, respiratory failure and medications which affect renal tubular function such as diuretics, Cisplatin, Ciclosporin etc. [13].

**Hypermagnesaemia and magnesium toxicity**

Signs and symptoms of hypermagnesaemia per se may be difficult to diagnose clinically. For example, in a large survey involving more than 1000 hospitalized patients in whom plasma/serum magnesium was elevated; only 13% were suspected on clinical grounds [21]. Furthermore, hypermagnesaemia can mimic signs and symptoms of many other CVS or neurological illnesses, even masquerading in severe cases as pseudo-coma and brain-stem stroke [13, 22–25].

Plasma/serum magnesium measurement can be important in differential diagnosis, because it can accurately establish hypermagnesaemia, if present. The high morbidity of hypermagnesaemia as well as its reversibility makes it important to identify these cases regardless of the normality of renal function. It may be therefore prudent to consider magnesium as an additional test to the commonly requested urea and electrolytes (U&E) profile which would marginally increase the actual cost of automated analysis. Unlike magnesium deficiency which can be associated with normal serum concentration, magnesium excess and toxicity is manifested as identifiable hypermagnesaemia in serum (concentration >1.2 mmol/L).

Iatrogenic overload from over the counter (OTC) magnesium-rich medications [13, 22] is a less appreciated cause of hypermagnesaemia which may be clinically overlooked, because of lack of awareness of their chemical formulation and patients’ perception of them as innocuous e.g., antacids, laxative, analgesic (magnesium salicylate), cathartics containing magnesium and repeated use of Epsom salts as a gargle for halitosis. When OTC medications are taken by elderly patients with intestinal hypomotility from any cause such as narcotics, anticholinergic drugs or obstruction [13], magnesium absorption can be significantly increased causing profound hypermagnesaemia [13, 22] regardless of renal function. Some 310 cases of adverse events were associated with administration
of OTC magnesium containing products in the USA and reported to the FDA between 1968 and 1994. Of these, 45 were classified as serious including 14 deaths.

Comments on deceptive magnesium measurements

Both significant magnesium deficiency and magnesium excess are conditions associated with consequential morbidity and mortality especially in patients with other comorbidities. Both conditions are reversible once identified.

Magnesium deficiency is an under-valued multifactorial disorder, common particularly in the elderly. Plasma/serum magnesium is a useful test because low serum concentration indicates significant deficiency warranting replacement. However, normal magnesium concentration must not be used to exclude negative body stores. “Modus Vivendi” has an important role in identifying at risk patients, such as adults living in areas with soft drinking water or hard water with low magnesium contents, dietary deficiencies and use of diuretics.

Clinical diagnosis of hypermagnesaemia is generally poor and symptoms can mimic neurological/CVS disorders of various severity. Plasma/serum magnesium measurement is pragmatic, inexpensive and a satisfactory test in identifying patients with hypermagnesaemia and if added to urea and electrolytes would marginally increase the cost.

Discussion and conclusions

In this note, some less appreciated and deceptive causes of potentially misleading potassium and magnesium measurements are highlighted.

For potassium measurement, inaccuracy can be minimized by (a) avoiding delayed separation of serum/plasma from cells and/or (b) avoiding storage/keeping of blood samples at extreme temperatures. If timely separation of plasma/serum from cells within approximately 1 h or so is unachievable, an option is to use tubes containing gel barriers to separate and store serum/plasma at source, using inexpensive basic centrifuges [26]. Once separated, re-centrifugation should be avoided [27]. When used, analytes including potassium were stable and unaffected by storage time, temperature or delays in transport. Analytically, potassium is measured with good accuracy of ±0.1 mmol/L, and this can be sustained by eliminating pre-analytical errors [28].

Computer generated comments on haemolysed samples must be explicit, informative and unambiguous, highlighting that the comment applies only if haemolysis is in vitro. Requesting repeat analysis would be prudent, because if the repeat sample is not haemolysed, it would confirm that haemolysis was indeed in vitro. On the other hand, persistent haemolysis on more repeat(s) should raise the possibility of in vivo haemolysis or confirm its presence/magnitude if the patient is known to have a haemolytic disorder. In such cases, results must not be suppressed and potassium concentration must be reported. Clinicians must be encouraged to contact the laboratory and ask for potassium measurement despite haemolysis.

It may be important to briefly reiterate/emphasize relevant aspects of pathophysiological relationship between magnesium and potassium, the two most predominant intracellular elements. Magnesium deficiency is frequently associated with hypokalaemia [13, 17, 29] and in severe cases render hypokalaemia refractory to treatment by potassium alone, making magnesium replacement essential for restitution. More than 50% of clinically significant hypokalaemia has concomitant magnesium deficiency (other causes of hypokalaemia such as re-distribution of potassium between the extra- and intracellular spaces does not involve magnesium per se). Clinically, concomitant potassium and magnesium deficiency is commonly encountered in individuals receiving diuretic therapy (loop or thiazide); other causes include diarrhoea; alcoholism and tubular injuries from nephrotoxic drugs. It is important to point out that magnesium deficiency may not only exacerbate intracellular potassium deficiency and renal wasting but also aggravate its pathological effects on target tissues [30].

An increase in intracellular magnesium profoundly blocks several cardiac potassium channels which can impair cardiovascular function. Hypermagnesaemia is also associated with neuromuscular toxicity. Assessing the rate of rise in plasma/serum magnesium levels is paramount because a rapid increase in plasma/serum magnesium is clinically more detrimental than a slower progressive elevation in blood levels. For this reason, the severity of symptoms of hypermagnesaemia per se does not always correlate with serum concentrations.

Take home message

Because only ~1% of body content of potassium and magnesium are present in blood, comprehensive clinical
history, accurate measurements of this small fraction and proper interpretation of their concentrations are imperative in recognizing deficiency and excess and their inter-related pathophysiology. Attention to such details would not only be consonant with good clinical and laboratory practices but enhance diagnostic efficacy and patients' care.

Acknowledgments: We are grateful for Dr Shirley Firn, a retired consultant in anaesthesia and intensive care for making a number of valuable comments.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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