

# openheart Subclinical magnesium deficiency: a principal driver of cardiovascular disease and a public health crisis

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## ABSTRACT

Because serum magnesium does not reflect intracellular magnesium, the latter making up more than 99% of total body magnesium, most cases of magnesium deficiency are undiagnosed. Furthermore, because of chronic diseases, medications, decreases in food crop magnesium contents, and the availability of refined and processed foods, the vast majority of people in modern societies are at risk for magnesium deficiency. Certain individuals will need to supplement with magnesium in order to prevent suboptimal magnesium deficiency, especially if trying to obtain an optimal magnesium status to prevent chronic disease. Subclinical magnesium deficiency increases the risk of numerous types of cardiovascular disease, costs nations around the world an incalculable amount of healthcare costs and suffering, and should be considered a public health crisis. That an easy, cost-effective strategy exists to prevent and treat subclinical magnesium deficiency should provide an urgent call to action.

## MAGNESIUM IN HUMAN BIOLOGY

'Magnesium is the seventh most abundant element in the Earth's crust by mass or molarity...In vertebrates, magnesium is extremely abundant and it is the second most common intracellular cation (potassium being the first). Extracellular magnesium accounts for only ~1% of total body magnesium, which is found primarily in serum and red blood cells'.<sup>1</sup>

Magnesium is the fourth most common cation in our body, the second most common intracellular cation and the most common intracellular divalent cation.<sup>2</sup> The human body contains around 25 g of magnesium.<sup>3</sup> Magnesium is necessary for the functioning of over 300 enzymes in human,<sup>4</sup> with 90% of total body magnesium being contained in the muscles and bones (~27% and ~63%, respectively), 90% of which is bound and with only 10% being free.<sup>5</sup> In the serum, 32% of magnesium is bound to albumin, whereas 55% is free.<sup>5</sup>

Some of the main functions of magnesium in human biology include the maintenance of ionic gradients (keeping intracellular sodium and calcium low and potassium high),

cellular and tissue integrity, mitochondrial oxidative phosphorylation (ATP production and activation), and DNA, RNA and protein synthesis and integrity.<sup>3,6</sup>

The elimination of magnesium is mainly controlled by the kidneys, increasing in the urine when there is magnesium surplus and falling to just 1 mEq of magnesium (~12 mg) during deficits.<sup>3</sup> However, despite renal conservation, magnesium can be pulled from the bone (as well as muscles and internal organs) in order to maintain normal serum magnesium levels when intakes are low.<sup>7,8</sup> Thus, a normal serum magnesium level does not rule out magnesium deficiency, which predisposes to osteopaenia, osteoporosis and fractures.

An excess of heavy metals due to soil contamination and a lack of minerals due to soil erosion also may predispose to micronutrient deficits.<sup>9</sup> The importance of the mineral content of soil and water, once greatly appreciated, think low iodine levels in soil and the increased prevalence of goitre, has all but been forgotten.<sup>10</sup> Furthermore, refined foods are depleted of magnesium during their processing.<sup>11</sup> In order to prevent chronic diseases, we need to change our mindset away from exclusively treating acute illness and instead focus more on treating the underlying causes of chronic diseases, such as magnesium deficiency.

There are two types of nutrient deficiencies, frank deficiencies (such as scurvy from ascorbic acid deficiency or goitre from iodine deficiency) and subclinical deficiencies (a clinically silent reduction in physiological, cellular and/or biochemical functions). It is the latter that is most concerning as it is hard to diagnose and predisposes to numerous chronic diseases. And while both result in negative health consequences, the former has obvious symptoms (hence frank deficiency), whereas the latter may have negative or variable health effects that are not so apparent (eg, vascular calcification). The evidence



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in the literature suggests that subclinical magnesium deficiency is rampant and one of the leading causes of chronic diseases including cardiovascular disease and early mortality around the globe, and should be considered a public health crisis.<sup>12–14</sup>

### MAGNESIUM INTAKE

'The homeostatic mechanisms to regulate magnesium balance were developed millions of years ago. Investigations of the macro- and micro-nutrient supply in Paleolithic nutrition of the former hunter/gatherer societies showed a magnesium uptake with the usual diet of about 600 mg magnesium/day, much higher than today'. Our homeostatic mechanisms and genome are still the same as with our ancestors in the Stone Age. This means our metabolism is best adapted to a high magnesium intake.<sup>5</sup>

In developed countries, the average intake of magnesium is slightly over 4 mg/kg/day.<sup>15</sup> More than a quarter of obese and non-obese youth have inadequate intakes of magnesium (27% and 29%, respectively). The authors of a study concluded: 'Even though children may consume an excess of energy, they may not be meeting all of their micronutrient needs'.<sup>16</sup> In other words, children are overfed and undernourished. One expert has argued that a typical Western diet may provide enough magnesium to avoid frank magnesium deficiency, but it is unlikely to maintain high-normal magnesium levels and provide optimal risk reduction from coronary artery disease and osteoporosis. That is, 'Various studies have shown that at least 300 mg magnesium must be supplemented to establish significantly increased serum magnesium concentrations...'.<sup>5</sup> In other words, most people need an additional 300 mg of magnesium per day in order to lower their risk of developing numerous chronic diseases. So while the recommended daily allowance (RDA) for magnesium (between 300 and 420 mg/day for most people) may prevent frank magnesium deficiency, it is unlikely to provide optimal health and longevity, which should be the ultimate goal.

Importantly, much of the population may not even be meeting the RDA for magnesium. For example, the average magnesium intake in men and women in Taiwan is only 250 mg and 216 mg, respectively, or 68%–70% of the recommended dietary reference intake.<sup>17</sup> The authors of the study concluded: 'Taiwanese elderly persons had suboptimal levels of dietary magnesium intake, which although may be sufficient to avoid overt magnesium deficiency, may not be sufficient to reduce the risk of diabetes in the elderly'.<sup>17</sup> The National Nutrition Survey in Japan found that for people 15–49 years old the intake of magnesium was below the Japanese RDA.<sup>18</sup> Moreover, around half (48%) of the US population consumes less than the recommended amount of magnesium from food.<sup>19</sup> The US Department of Agriculture states that the average magnesium intake in women and men is 228 mg/day and 323 mg/day, respectively. Based on these data, one group of authors noted: 'These intake levels suggest

that a substantial number of people may be at risk for Mg deficiency, especially if concomitant disorders and/or medications place the individual at further risk for Mg depletion'.<sup>7</sup> The most recent published review on magnesium concluded: 'Approximately 50% of Americans consume less than the Estimated Average Requirement (EAR) for magnesium, and some age groups consume substantially less'.<sup>20</sup>

Lakshmanan *et al* collected daily food records for 1 year in 34 men and women. They found that the mean magnesium intake was 323 mg/day and 234 mg/day in men and women, respectively (around 4 mg/kg/day). Despite this level of intake, the overall patient population was in negative magnesium balance (–32 and –25 mg/day, respectively).<sup>21</sup> Moreover, 75% of women consumed less than the RDA (300 mg/day) and only one out of the eighteen women were in equilibrium. Considering that the average intake of magnesium in the USA is around 228 mg/day in women and 266 mg/day in men,<sup>12</sup> a large percentage of Americans may be at risk of negative magnesium balance. Indeed, 'Only American diets containing more than 3000 kcal/day may provide 300 mg or more magnesium'.<sup>21</sup> Another long-term study lasting 50 weeks found that somewhere between 180 mg and 320 mg of magnesium/day is required in order to maintain positive magnesium balance.<sup>22</sup> And since many individuals may be consuming below 320 mg/day of magnesium, this poses a major public health threat.

The data are consistent around the world that magnesium intake may be inadequate. Indeed, the intake of magnesium in Germany was determined to be only 200 mg for women and 250 mg for men.<sup>5,23</sup> In Kiev a study on 780 men aged 20–59 found that the overall population consumed insufficient magnesium from food rations (10% less than the recommended value). The authors also found a correlation between the low magnesium consumption in food and the prevalence of risk factors for ischaemic heart disease, such as hyperlipoproteinaemia, arterial hypertension and body weight.<sup>24</sup> In 2004, Durlach concluded: 'About 20% of the population consumes less than two-thirds of the RDA for Mg. Women, particularly, have low intakes. For example, in France, 23% of women and 18% of men have inadequate intakes. Mg deficiency during pregnancy can induce maternal, fetal, and pediatric consequences that might last throughout life'.<sup>25</sup> The median magnesium intake in an elderly population (832 subjects aged 70 years or older) in Southern France was also found to be below the RDA.<sup>26</sup> Another French study on 2373 subjects (4–82 years of age) noted that 71.7% of men and 82.5% of women had an inadequate magnesium intake.<sup>27</sup>

### MAGNESIUM DEFICIENCY

'Hypomagnesemia is a relatively common occurrence in clinical medicine. That it often goes unrecognized is due to the fact that magnesium levels are rarely evaluated since few clinicians are aware of the many clinical

states in which deficiency, or excess, of this ion may occur'.<sup>28</sup>

In developed countries, older data estimated that the prevalence of marginal magnesium deficit is 15%–20% of the population.<sup>15</sup> This corroborates more recent data indicating that around 10%–30% of a given population has subclinical magnesium deficiency based on serum magnesium levels <0.80 mmol/L.<sup>29</sup> The 2006 National Health and Nutrition Survey found low serum concentrations of magnesium in 36.3% and 31% of female and male Mexican adults, respectively.<sup>30</sup> The authors of the study concluded: 'Low serum concentrations of...magnesium are published for the first time and show significant prevalence of deficiencies',<sup>30</sup> and up to 20% of the general population has low serum magnesium levels.<sup>31</sup> A systematic review of 37 articles discovered that magnesium deficiency was a possible public health concern for older adults.<sup>32</sup>

Magnesium deficiency has been found in 84% of postmenopausal women with osteoporosis diagnosed by low magnesium trabecular bone content and Thoren's magnesium load test.<sup>33</sup> Among apparently healthy university students in Brazil, 42% were found to have subnormal magnesium status (based on plasma or erythrocyte magnesium levels).<sup>13</sup> The average magnesium intake was only around 215 mg/day. Magnesium depletion has been found in 75% and 30.8% of patients with poorly controlled type 2 diabetes based on serum and intracellular magnesium status, respectively.<sup>34</sup>

Magnesium deficiency can be present despite normal serum magnesium levels.<sup>6</sup> Approximately 20% of 381 unselected elderly men and women (most of them in their 80s) were found to have low erythrocyte potassium and magnesium levels. The authors of the study concluded: 'This study underlines the large prevalence of magnesium and potassium deficiencies in the elderly'.<sup>35</sup> Another study concluded: 'The commonly designated low limit of the normal range...is below levels that exist in patients with marginal deficiencies that can predispose to development of pathologic findings, so that the prevalence and importance of this disease is insufficiently considered...It is a statistical error to use the confidence limits of the normal population as the exclusion limit for those with abnormal Mg status'.<sup>36</sup> In other words, our normal range of serum magnesium is inaccurate and that serum magnesium levels at the lower end of normal likely suggest marginal magnesium deficiency.<sup>29</sup> Indeed, 'The magnesium content of the plasma is an unreliable guide to body stores: muscle is a more accurate guide to the body content of this intracellular cation'.<sup>37</sup>

Another study highlighting the discrepancy between serum and body magnesium levels concluded: 'Although serum-K and serum-Mg values in patients receiving long-term treatment for hypertension or uncompensated heart disease usually are normal, muscle-Mg and muscle-K contents are reduced in around 50% of these patients...Evaluation of the K and Mg status during diuretic treatment should be preferentially based on

tissue determinations. The muscle biopsy method is rapid, reliable and may reveal conditions of deficiency...oral supplements of Mg have proved to be adequate to restore the normal K/Mg status'.<sup>38</sup>

Among critically ill postoperative patients, 36.5% were found to have magnesium deficiency based on ionised magnesium levels in red blood cells.<sup>39</sup> In one study of patients from a medical intensive care unit (ICU), 65% had hypomagnesaemia. The author concluded: 'The prevalence of normomagnesemic Mg deficiency in critically ill patients may be even higher (than 65%, my insertion) and may contribute to the pathogenesis of hypocalcemia, cardiac arrhythmias and other symptoms of Mg deficiency'.<sup>40</sup> Finally, 6.9%–11% of hospitalised patients have been noted to have hypomagnesaemia on routine exam posing on unrecognised need.<sup>41</sup>

The overall incidence of hypomagnesaemia in one study was noted to be between 5% and 8% of the overall population, and in young women (aged 18–22) the incidence was approximately 20%.<sup>5</sup> One of the largest studies, a cross-sectional study in an unselected population of more than 16000 subjects in Germany, found a prevalence of hypomagnesaemia (magnesium levels below 0.76 mmol/L) of 14.5%.<sup>5</sup> <sup>42</sup> Over 15% of hospitalised elderly patients have been found with low serum magnesium levels.<sup>43</sup> Another study noted: 'At ICU admission 52.5% had total hypomagnesemia and 13.5% total hypermagnesemia; with respect to the Mg(2+) 9.7% showed ionized hypomagnesemia and 23.6% ionized hypermagnesemia. Patients who developed ionized hypermagnesemia had higher mortality than patients without ionized hypermagnesemia development (P=0.04)'.<sup>44</sup> And it has been noted that 'Hypomagnesemia detected at the time of admission of acutely ill medical patients is associated with an increased mortality rate for both ward and medical ICU patients'.<sup>45</sup> Magnesium depletion is present in about half of all ICU patients.<sup>46</sup> More than 50% of those hospitalised with either of the following conditions are likely to be magnesium-deficient based on an intravenous retention >20%: hypertension, coronary artery disease, cerebrovascular event, gastrointestinal issues or alcoholism.<sup>47</sup>

Based on 183 peer-reviewed studies published from 1990 to 2008, one group of authors concluded: 'The perception that 'normal' serum magnesium excludes deficiency is common among clinicians. This perception is probably enforced by the common laboratory practice of highlighting only abnormal results. A health warning is therefore warranted regarding potential misuse of 'normal' serum magnesium because restoration of magnesium stores in deficient patients is simple, tolerable, inexpensive and can be clinically beneficial'.<sup>48</sup>

One study found that 10 out of 11 apparently healthy women were magnesium-deficient based on the oral magnesium load test. The authors concluded: 'The results showed there are more frequent deficiencies of magnesium in organisms than it is generally assumed'.<sup>49</sup> Another study showed that 37.6% of patients with type



2 diabetes and 10.9% of age-matched and sex-matched healthy controls have low plasma magnesium levels.<sup>50</sup>

Of patients with severe chronic airway obstruction, 11.6% have serum magnesium levels less than the lower normal limit. The authors of the study concluded: '...routine serum magnesium determination is recommended in patients with chronic obstructive lung disease taking diuretic drugs or corticosteroids'.<sup>51</sup>

Hypomagnesaemia was identified in 47% of 1033 samples based on both routine magnesium determinations as well as physician-initiated requests for magnesium measurements.<sup>52</sup> Importantly, only 10% of the hypomagnesaemia findings were found by physician-initiated requests, underscoring the fact that low magnesium blood levels are an overlooked issue by medical doctors.

About 80% of patients with hypertension treated for at least 6 months with either hydrochlorothiazide or a single non-diuretic drug have been found to have magnesium depletion based on retention of a parenterally administered magnesium load.<sup>53</sup> More troubling is that despite being magnesium-depleted, patients treated with hydrochlorothiazide had high normal serum magnesium. This study underlines how patients can have normal or even higher magnesium levels in the blood despite magnesium depletion. Another study confirmed these findings that 'thiazides induce a magnesium depletion not detectable by monitoring serum levels'.<sup>54</sup> There is a correlation between low magnesium bone concentrations and increased magnesium retention after an intravenous magnesium load, suggesting that magnesium is retained in the bone after the test.<sup>55</sup>

After several weeks of strenuous physical activity, serum magnesium can increase with no change in erythrocyte magnesium levels despite a reduction in mononuclear cell magnesium levels. The authors of a study concluded that the reduction in mononuclear cell magnesium content 'reflects a reduction in exchangeable magnesium body stores, and the onset of a magnesium deficiency state'.<sup>56</sup> This study also indicates that just 6–12 weeks of strenuous physical activity can lead to magnesium deficiency. Another study concluded: 'Serum and urinary magnesium concentrations decrease during endurance running, consistent with the possibility of magnesium deficiency. This may be related to increased demand in skeletal muscle'.<sup>57</sup>

One study found low levels of erythrocyte magnesium in 119 of 179 (66%) patients admitted consecutively to the ICU.<sup>58</sup> The prevalence of hypomagnesaemia at ICU admission has been estimated at around 51.3%, with a prevalence of ionised hypomagnesaemia at ICU admission ranging between 14.4% and 22%.<sup>44</sup>

While a normal serum magnesium is considered to be 0.7–1 mmol/L, the optimal serum magnesium concentration has been proposed to be >0.80 mmol/L.<sup>59</sup> Chronic latent magnesium deficiency has been defined as '...a serum magnesium concentration of between 0.75 and 0.849 mmol/L (within the reference interval), with a

positive magnesium load test indicating magnesium deficiency'.<sup>14</sup>

### In summary

'Abnormalities of serum Mg may be the most underdiagnosed serum electrolyte abnormality in clinical practice today. The incidence appears to range from 12.5% to 20% on routine determination'.<sup>41</sup>

### 'NORMAL' SERUM MAGNESIUM LEVELS

#### 0.75–0.95 mmol/L<sup>29</sup>

- ▶ A serum magnesium <0.82 mmol/L (2.0 mg/dL) with a 24-hour urinary magnesium excretion of 40–80 mg/day is highly suggestive of magnesium deficiency.<sup>29</sup>
- ▶ One group of experts has recommended magnesium supplementation in subjects experiencing symptoms that reflect magnesium deficiency if the serum level is below 0.9 mmol/L,<sup>36</sup> with levels less than 0.8 mmol/L necessitating magnesium.
- ▶ Serum magnesium levels above 0.95 mmol/L may indicate hypermagnesaemia.

### DIETARY FACTORS AFFECTING MAGNESIUM STATUS

'Although magnesium intakes have been gradually falling since the beginning of the century, there were sharply increased intakes of nutrients that increased its requirements [particularly high vitamin D and phosphorus intakes]...The major source of phosphorus derives from soft drinks that contain phosphoric acid, the consumption of which has been rising markedly in the last quarter of a century'.<sup>60</sup>

Since 1940 there has been a tremendous decline in the micronutrient density of foods. In the UK for example, there has been loss of magnesium in beef (–4 to –8%), bacon (–18%), chicken (–4%), cheddar cheese (–38%), parmesan cheese (–70%), whole milk (–21%) and vegetables (–24%).<sup>61</sup> The loss of magnesium during food refining/processing is significant: white flour (–82%), polished rice (–83%), starch (–97%) and white sugar (–99%).<sup>12</sup> Since 1968 the magnesium content in wheat has dropped almost 20%, which may be due to acidic soil, yield dilution and unbalanced crop fertilisation (high levels of nitrogen, phosphorus and potassium, the latter of which antagonises the absorption of magnesium in plants).<sup>62</sup> One review paper concluded: 'Magnesium deficiency in plants is becoming an increasingly severe problem with the development of industry and agriculture and the increase in human population'.<sup>62</sup> Processed foods, fat, refined flour and sugars are all devoid of magnesium, and thus our Western diet predisposes us to magnesium deficiency. Good dietary sources of magnesium include nuts, dark chocolate and unrefined whole grains.

Increased calcium and phosphorus intake also increases magnesium requirements and may worsen or precipitate magnesium deficiency.<sup>63–65</sup> Dairy, especially cheese, has a very high phosphorus to magnesium (Mg) ratio. For

example, cheddar cheese has a phosphorus:magnesium ratio of ~18 and a calcium:magnesium ratio of ~26,<sup>66</sup> whereas pumpkin seeds have a phosphorus:magnesium ratio of 0.35 and a calcium:magnesium ratio of 0.21.<sup>67</sup> Some have argued that the optimal dietary calcium:magnesium ratio is close to 2:1.<sup>15</sup>

The amount of dietary magnesium required to maintain positive balance depends on numerous factors including the patient population as well as dietary and lifestyle choices. Indeed, magnesium balance decreases when calcium intake is over 10 mg/kg/day.<sup>21</sup> Thus, the minimum required magnesium intake to maintain positive balance is not universal. Indeed, 'Magnesium, like other dietary components, interacts with several nutrients and its requirement is modified not only by their levels but also by their form or type. The American diet is low in calcium and fiber as well as in magnesium, and high in protein and phosphorus'.<sup>21</sup> Excess calcium, phosphorus and vitamin D may also lead to increased magnesium loss increasing magnesium requirements.<sup>60</sup>

The phosphate to calcium ratio in the USA during 1932–1939 was approximately 1.2:1, rising to 4:1 in those who substituted the intake of soda for milk, but other data suggest that the phosphate:calcium ratio is around 1.5:1.<sup>60</sup> Nonetheless, the most dramatic change that has occurred since the early 1900s until now regarding phosphate, calcium and magnesium has been a reduction in magnesium intake, going from around 500 mg/day to an average of 250 mg/day. Thus, the calcium:magnesium ratio has increased from approximately 2:1 to 5:1, and the phosphate:magnesium ratio has increased from 1.2:1 to around 7:1.<sup>60</sup> The increase in dietary phosphate has come from phosphate additives, found in many food items but especially processed meats, as well as from phosphoric acid found in soft drinks.

One group of authors concluded: 'The prevalence and incidence of type 2 diabetes in the United States increased sharply between 1994 and 2001 as the ratio of calcium-to-magnesium intake from food rose from <3.0 to >3.0'.<sup>19</sup> Another group of authors noted a 3.25-fold increased risk of diabetes at plasma magnesium levels <0.863 mmol/L (despite 0.75 mmol/L being considered a 'normal' level).<sup>17</sup> In other words, patients with diabetes appear to be magnesium-deficient and magnesium deficiency likely increases the risk of diabetes.

Dietary aluminium may lead to magnesium deficit by reducing the absorption of magnesium by approximately fivefold, reducing magnesium retention by 41% and causing a reduction of magnesium in the bone.<sup>68</sup> And since aluminium is widely prevalent in modern-day society (such as in aluminium cookware, deodorants, over-the-counter and prescription medications, baking powder, baked goods, and others), this could be a major contributor to magnesium deficiency. In fact, an area near a Skawina aluminium plant in Poland was found to have a lower percentage of people with normal magnesium levels in red blood cells and urine compared with those in Chorzów.<sup>69</sup>

A common misconception is that consuming phytate-rich foods can lead to nutrient deficiencies particularly magnesium depletion via binding by phytic acid. However, urinary magnesium excretion will drop to compensate for a reduction in bioavailable magnesium.<sup>70</sup> And most high-phytate foods are also good sources of magnesium (grains and beans are good examples). Thus, it is unlikely that consuming foods high in phytate will lead to magnesium depletion. However, a vitamin B<sub>6</sub>-deficient diet can lead to a negative magnesium balance via increased magnesium excretion.<sup>71</sup>

## MAGNESIUM BALANCE

A study of 11 postmenopausal women (aged 49–71 years) found that an intake of 107 mg/day of magnesium was inadequate for maintaining positive magnesium balance.<sup>72</sup> A placebo-controlled trial in young women who were supplemented with 100 mg magnesium per day (basal magnesium intake 250 mg) was inadequate for positive or even zero magnesium balance even though the supplemented women had a higher magnesium excretion in urine, indicating a higher total absorption.<sup>5</sup> In other words, young women may be in negative magnesium balance despite consuming 350 mg of magnesium per day. However, one double-blind metabolic balance study in postmenopausal Caucasian women showed that 318 mg of magnesium per day was enough to remain in positive balance, but 118 mg/day was inadequate.<sup>73</sup> A more recent balance study in postmenopausal women found that while a diet containing 399 mg of magnesium per 2000 kcal was able to produce a positive magnesium balance, a diet containing ~100 mg of magnesium per 2000 kcal was inadequate.<sup>74</sup> Other data have found negative magnesium balance in men with osteoporosis or psychoneurosis consuming 240 mg/day of magnesium.<sup>75</sup> Another study noted negative magnesium balance (–122 mg) in those consuming 322 mg/day of magnesium on top of a high-fibre diet.<sup>76</sup> In other words, context matters (overall dietary pattern, patient population and background medication).

One of the most comprehensive reviews in the literature on this subject suggests that in healthy adults only around 180 mg of magnesium per day is required to maintain balance in healthy individuals (even when taking into account magnesium sweat losses). This analysis pooled magnesium data from 27 different tightly controlled balance studies (lasting more than 27 days) conducted in the USA.<sup>77</sup> However, it must be noted that this analysis does not take into account the numerous disease states, medications, stress and dietary factors that increase magnesium requirements.

Based on the National Health and Nutrition Examination Survey (NHANES) data, 64% of women aged 51–70 years old do not achieve the EAR for this age group (265 mg/day),<sup>77</sup> with an estimated average magnesium intake of just 246 mg/day (NHANES 2001–2002) and only 238 mg/day (NHANES 1999–2000). Magnesium

**Table 1** Magnesium requirements based on older balance studies<sup>37</sup>

Age	Requirement
Infants	150–200 mg/day
Children	200–250 mg/day
Adults	250–300 mg/day
Lactating women	400 mg/day

intake for Mexican and African–American women of the same age group is even lower (185 mg/day and 169 mg/day, respectively, and 176 mg/day and 150 mg/day in those reporting no dietary supplement use).<sup>77</sup> Thus, the elderly population is especially at risk of magnesium deficiency due to low intake but also increased risk for chronic diseases that predispose to magnesium deficiency (ageing also reduces magnesium absorption from the diet, ie, achlorhydria). **Table 1** covers the magnesium requirements from older balance studies.

### CAUSES OF MAGNESIUM DEFICIENCY

Numerous factors can lead to magnesium deficiency, such as kidney failure,<sup>78</sup> alcohol consumption<sup>79</sup> and malabsorption issues (magnesium is absorbed in the small intestine and in the colon<sup>3</sup>; thus, patients with intestinal or colon damage such as Crohn's disease, irritable bowel syndrome, coeliac disease, gastroenteritis, idiopathic steatorrhoea, ulcerative colitis, resection of the small intestine, ileostomy patients or patients with ulcerative colitis may have magnesium deficiency). Renal tubular acidosis, diabetic acidosis, prolonged diuresis, acute pancreatitis, hyperparathyroidism and primary aldosteronism can also lead to magnesium deficiency.<sup>80</sup> A meta-analysis of 13 studies in almost 5500 patients found that magnesium levels were significantly lower in patients with metabolic syndrome versus controls.<sup>81</sup> The intravenous magnesium tolerance test has confirmed that children with type 1 diabetes have intracellular magnesium deficiency.<sup>82</sup> This is likely due to osmotic diuresis and increased magnesuria caused by high glucose levels and damage to the renal tubules. Patients with type 2 diabetes have been found with lower magnesium levels compared with healthy controls (0.79 mmol/L vs 0.88 mmol/L).<sup>83</sup>

Supplementing with calcium can lead to magnesium deficiency due to competitive inhibition for absorption,<sup>84</sup> and oversupplementing with vitamin D may lead to magnesium deficiency via excessive calcium absorption and hence increase the risk of arterial calcifications.<sup>85</sup> Use of diuretics and other medications can also lead to magnesium deficiency.

Over 42% of young (aged 15–18 years) sportsmen (volleyball players and rowers) are magnesium-deficient based on a high retention after an oral magnesium load. The authors of the study concluded '...the magnesium load test a more sensitive indicator of latent Mg deficiency than the serum Mg level which is maintained at

### Box 1 Renal magnesium wasting<sup>145</sup>

- ▶ Diagnosis: urinary magnesium excretion >24 mg/day in the presence of hypomagnesaemia (<0.7 mmol/L).<sup>145</sup>
- ▶ Causes
  - Bartter's syndrome.
  - Gitelman's syndrome.
  - Diabetes.
  - Hypercalcaemia.
  - Diuretics.
  - Cisplatin.
  - Aminoglycosides.
  - Pentamidine.
  - Cyclosporin.
  - Calcitriol deficiency.

a relatively stable level and declines only in severe deficiency'.<sup>86</sup> Another study concluded '...athletes suffer from a magnesium deficiency, partially due to physical exercise'.<sup>87</sup> At a minimum, approximately 15 mg of magnesium is lost in sweat per day, but losses are probably greater especially in conditions of increased perspiration (exercise, heat and humidity).<sup>88</sup> **Box 1** covers renal magnesium wasting. **Box 2** provides a comprehensive list of potential causes of magnesium deficiency.

### CLINICAL SIGNS OF MAGNESIUM DEFICIENCY

'...magnesium is essential for the normal metabolism of potassium and of calcium...the occurrence in clinical situations of otherwise unexplained hypokalemia and hypocalcemia should suggest the possibility of significant magnesium depletion'.<sup>89</sup>

Among the most common laboratory signs of magnesium deficiency are low potassium and calcium levels, as well as low urine and/or faecal magnesium. The most common neurological side effect with magnesium depletion is the Trousseau sign; that is, 'To elicit the sign, a blood pressure cuff is placed around the arm and inflated to a pressure greater than the systolic blood pressure and held in place for 3 min. This will occlude the brachial artery. In the absence of blood flow, the patient's hypocalcemia and subsequent neuromuscular irritability will induce spasm of the muscles of the hand and forearm. The wrist and metacarpophalangeal joints flex, the DIP and PIP joints extend, and the fingers adduct'.<sup>90</sup> Other signs of magnesium deficiency included tremor, fasciculations ('a brief spontaneous contraction that affects a small number of muscle fibres'),<sup>91</sup> spontaneous carpopedal spasm (painful cramps of the muscles in your hands and feet) and generalised spasticity.<sup>89</sup> Other clinical features of magnesium deficiency include mental disturbances such as depression, confusion, agitation, hallucinations, weakness, neuromuscular irritability (tremor), athetoid movements and convulsive seizures.<sup>80</sup>

A full list of potential clinical and lab signs of magnesium deficiency are summarised in **box 3** and **box 4**.



**Box 2** Causes of magnesium deficiency<sup>4</sup>

- ▶ Acetaminophen toxicity.<sup>146</sup>
- ▶ Alcoholism.
- ▶ Aluminium<sup>8</sup> (environmental and dietary).
- ▶ Aldosteronism.<sup>3 147</sup>
- ▶ Alcohol.<sup>148</sup>
- ▶ Ageing<sup>149</sup> (hypochlorhydria, ie, decreased acid in the stomach).
- ▶ Antacids<sup>149 150</sup> (including ranitidine and famotidine).
- ▶ Bariatric surgery (small intestinal bypass surgery).<sup>151</sup>
- ▶ Calcium supplements (or a high calcium to magnesium diet).
- ▶ Caffeine.<sup>152</sup>
- ▶ Cancer.<sup>153</sup>
- ▶ Coeliac disease.<sup>154</sup>
- ▶ Colon removal.<sup>155</sup>
- ▶ Chronic stress.<sup>156</sup>
- ▶ Cisplatin.<sup>157–161</sup>
- ▶ Crohn's disease.<sup>162</sup>
- ▶ Cyclosporin.<sup>163–166</sup>
- ▶ Type 1 and type 2 diabetes<sup>83 167</sup> (uncontrolled glucose levels).
- ▶ Diarrhoea.
- ▶ Diet high in fat or sugar.<sup>152 168</sup>
- ▶ Digoxin.<sup>169</sup>
- ▶ Diuretics<sup>170–172</sup>—non-potassium-sparing diuretics (thiazide and loop diuretics).
- ▶ Excessive ingestion of poorly absorbable magnesium<sup>173</sup> (such as magnesium oxide), leading to diarrhoea and magnesium loss.
- ▶ Emotional and/or psychological stress<sup>174</sup> (overactivation of the sympathetic nervous system).
- ▶ Enzymatic dysfunction<sup>175</sup> (impaired magnesium distribution).
- ▶ Oestrogen therapy<sup>176</sup> (shifts magnesium to soft and hard tissues lowering serum levels).
- ▶ Excessive or prolonged lactation.<sup>177</sup>
- ▶ Excessive menstruation.<sup>152</sup>
- ▶ Fasting<sup>178</sup> (or low magnesium intake).
- ▶ Foscarnet.<sup>179</sup>
- ▶ Gentamicin<sup>180</sup> and tobramycin.<sup>181</sup>
- ▶ Hyperparathyroidism and hypoparathyroidism.
- ▶ Hyperthyroidism.
- ▶ Kidney diseases<sup>182–184</sup> (glomerulonephritis, pyelonephritis, hydronephrosis, nephrosclerosis and renal tubular acidosis).
- ▶ Heart failure.<sup>185</sup>
- ▶ Haemodialysis.<sup>186</sup>
- ▶ High phosphorus in the diet<sup>152</sup> (soda, inorganic phosphates contained in many inactive ingredients in processed foods).
- ▶ Hyperinsulinaemia<sup>187</sup> (and insulin therapy).<sup>179</sup>
- ▶ Insulin resistance<sup>188</sup> (intracellular magnesium depletion).
- ▶ Laxatives.<sup>23</sup>
- ▶ Low salt intake.<sup>189</sup>
- ▶ Low selenium intake.<sup>152</sup>

Continued

**Box 2** Continued

- ▶ Gastrointestinal disorders<sup>190</sup>—malabsorption syndromes (coeliac disease, non-tropical sprue, bowel resection, Crohn's disease, ulcerative colitis, steatorrhoea), prolonged diarrhoea or vomiting.
- ▶ Liver disease<sup>191</sup> (acute or chronic liver disease, including cirrhosis).
- ▶ Metabolic acidosis<sup>167 192 193</sup> (latent or clinical).
- ▶ Pancreatitis<sup>194–197</sup> (acute and chronic).
- ▶ Parathyroidectomy.
- ▶ Pentamide.<sup>179</sup>
- ▶ Peritoneal dialysis.<sup>198</sup>
- ▶ Porphyria with inappropriate secretion of antidiuretic hormone.
- ▶ Pregnancy.
- ▶ Proton pump inhibitors.<sup>199 200</sup>
- ▶ Strenuous exercise.<sup>201</sup>
- ▶ Tacrolimus.<sup>179</sup>
- ▶ Vitamin B<sub>6</sub> (pyridoxine) deficiency.<sup>71 202</sup>
- ▶ Vitamin D excess or deficiency<sup>85 152 184 203</sup> (chronic kidney disease and liver disease can prevent the activation of vitamin D).

Magnesium deficiency is extremely hard to diagnose since symptoms are generally non-specific, there are numerous contributing factors, and there is no simple easy way to diagnose magnesium deficiency.<sup>29 80</sup> However, one study concluded: 'There is Mg deficiency in many patients with variant angina and it is corrected after treatment with calcium antagonists'.<sup>92</sup> The authors noted that the mean 24-hour magnesium retention of an intravenous magnesium load was 60% in those with variant angina versus 36% in controls despite both groups having the same normal serum magnesium levels (2.1 mg/dL).

Gastrointestinal loss of magnesium can be determined by increased renal conservations of magnesium measured by a fractional magnesium excretion of less than 2%.<sup>93</sup> Renal magnesium wasting can be determined by a fractional magnesium excretion above 2% in patients with normal renal function.

**Thoren's intravenous magnesium load test (16 hours)**

Thoren has suggested that if less than 70% of a 30 mEq (~365 mg) to 40 mEq (~486 mg) of parenteral magnesium given over an hour to an adult is excreted in the following 16 hours, this may indicate magnesium deficiency. In other words if you give ~400 mg of magnesium intravenously over 1 hour, if 70% or more of that dose (so 280 mg or more) is not excreted in the urine over the next 16 hours, this likely indicates magnesium deficiency even in the presence of normal magnesium levels.<sup>37</sup> An important flaw of this test is in patients who have renal damage who are spilling magnesium out in the urine who could appear magnesium-replete but in actuality could be magnesium-deficient (in this instance the magnesium in the serum would likely be low or low-normal).

**Thoren's intravenous magnesium load test for diagnosing magnesium deficiency**

1. Provide ~360–480 mg of magnesium intravenously over 1 hour

**DIAGNOSING MAGNESIUM DEFICIENCY**

'The existence of subacute or chronic magnesium deficiency is difficult to diagnose. Because the tissues damaged by magnesium depletion are those of the cardiovascular, renal and the neuromuscular systems, early damage is not readily detectable. It is postulated that long-term suboptimal intakes of magnesium may participate in the pathogenesis of chronic diseases of these systems'.<sup>88</sup>

**Box 3** Potential clinical signs of magnesium deficiency<sup>88 204 205</sup>**Less severe signs**

- ▶ Aggression.<sup>152</sup>
- ▶ Anxiety.
- ▶ Ataxia.
- ▶ Chvostek sign<sup>80</sup> (twitching of the facial muscles in response to tapping over the area of the facial nerve).
- ▶ Confusion.
- ▶ Cramps (spontaneous carpopedal spasm or painful cramps of the muscles in your hands and feet).
- ▶ Disorientation.
- ▶ Fasciculations ('a brief, spontaneous contraction affecting a small number of muscle fibres, often causing a flicker of movement under the skin. It can be a symptom of disease of the motor neurons').<sup>91</sup>
- ▶ Hyper-reflexia.
- ▶ Irritability.
- ▶ Muscular weakness.
- ▶ Neuromuscular irritability.
- ▶ Pain or hyperalgesia<sup>206</sup> (decreases the nociceptive threshold).
- ▶ Photosensitivity.<sup>207</sup>
- ▶ Spasticity.
- ▶ Tetany<sup>204</sup> (involuntary muscle spasms).
- ▶ Tinnitus<sup>208</sup> (ringing in the ears).
- ▶ Tremors.
- ▶ Trousseau sign.
- ▶ Vertigo.
- ▶ Vitamin D resistance.

**Severe signs**

- ▶ Arrhythmias (caused by overexcitation of the heart due to enhanced depolarisation susceptibility, especially torsades de pointes or ventricular tachycardia with a prolonged QT interval).
- ▶ Calcifications (soft tissue).
- ▶ Cataracts.<sup>209</sup>
- ▶ Convulsions.
- ▶ Coronary artery disease.
- ▶ Depressed immune response.<sup>210</sup>
- ▶ Depression.<sup>211</sup>
- ▶ Hearing loss.<sup>152 212</sup>
- ▶ Heart failure.
- ▶ Hypertension.
- ▶ Migraines/headaches.
- ▶ Mitral valve prolapse.<sup>213</sup>
- ▶ Osteoporosis.
- ▶ Parathyroid hormone resistance and impaired parathyroid hormone release/function.<sup>214</sup>
- ▶ Psychotic behaviour.
- ▶ Seizures<sup>215</sup> (overexcitation of the nervous system (nerve cells), which are more likely to fire due to a reduced electric potential difference between the outer and inner surfaces of the membrane).<sup>2</sup>
- ▶ Sudden cardiac death.
- ▶ Tachycardia.

2. If <70% of the magnesium load comes out in the urine over 16 hours, this is highly suggestive of magnesium deficiency.

Healthy subjects have been noted to have an intravenous magnesium load retention between 2% and

**Box 4** Lab and ECG signs of magnesium deficiency<sup>89</sup>

- ▶ Hypomagnesaemia.
- ▶ Hypocalcaemia.
- ▶ Hypokalaemia.
- ▶ Prolonged QTc.
- ▶ ST segment depression<sup>115</sup> (in animals).

8%.<sup>47</sup> Corroborating these findings are another study that found an average magnesium retention from an intravenous load to be 6.3% in healthy patients aged 18–66 years old.<sup>94</sup> The 97.5% fractile was retention of 27.5%. A large percentage of patients who are considered healthy can be magnesium-deficient. Based on these results an intravenous magnesium load retention above 27.5% is highly suggestive of magnesium deficiency. In fact, one study in healthy patients found a 6% 24-hour magnesium retention after an intravenous magnesium load in young controls but a 28% retention in the elderly, suggesting that a large percentage of the elderly population is magnesium-deficient.<sup>95</sup> The authors of the study concluded: 'This study suggests that a significant subclinical magnesium deficit, not detected by serum magnesium, was present in many of these healthy elderly subjects. Magnesium supplementation improved magnesium status and renal function'.<sup>95</sup> If using 2 SD above the mean intravenous magnesium retention in normal younger healthy patients, an abnormally high magnesium retention would be approximately 28%. This suggests that about half of all elderly patients may be magnesium-deficient (a level very close to the 27.5% retention level found as the upper bound in healthy patients aged 18–66 years).<sup>94</sup>

The intravenous magnesium load test has been given as 0.2 mmol/kg MgSO<sub>4</sub> over 4 hours<sup>96</sup> (or around 340 mg of magnesium for a 70 kg person). One procedure has given magnesium sulfate MgSO<sub>4</sub> (0.2 mmol/kg body weight) in 250 mL of 5% dextrose in water at 09:00 over 4 hours. Twenty-four-hour urine samples were then collected starting from the initiation of the infusion to determine 24-hour urinary magnesium excretion. Baseline 24-hour urinary magnesium excretion was then subtracted from postinfusion 24-hour urinary magnesium excretion. The magnesium retention was then calculated by the total amount of magnesium infused – (postinfusion 24-hour urinary magnesium – baseline 24-hour urinary magnesium) × 100/total amount of magnesium infused.<sup>96</sup> **Box 5** provides measurements to diagnose magnesium deficiency from best to worst. **Box 6** provides a summary of causes of hypermagnesaemia. **Box 7** covers treatments for hypermagnesaemia.

**TREATMENT OF MAGNESIUM DEFICIENCY**

One group of authors concluded: 'When magnesium substitution is started, the minimum dose to be applied is 600 mg magnesium per day. The therapy should proceed



**Box 5** Measurements to diagnose magnesium deficiency (best to worst)**Reliable methods**

- ▶ Retention of magnesium load (intravenous or oral) after its administration<sup>80 216</sup> is likely the best indicator of magnesium deficiency. However, the retention test assumes normal kidney function for intravenous magnesium loads and normal gastrointestinal and renal function for oral load tests and is cumbersome and invasive.
- ▶ Mononuclear cell magnesium<sup>217 218</sup> and muscle magnesium content<sup>219</sup> (muscle biopsy).

**Less reliable methods**

- ▶ Hair magnesium content<sup>220 221</sup> (one study concluded: 'magnesium hair concentration may be an easier, cheaper and less invasive indicator of body magnesium depletion').<sup>220</sup>
- ▶ Bone magnesium (magnesium depletion in the coccyx may indicate magnesium deficiency).<sup>8 23</sup>
- ▶ Ratio of ionised magnesium to total magnesium<sup>222</sup> (serum or plasma).
- ▶ Ionised magnesium levels<sup>223 224</sup> (serum or erythrocytes, ionised magnesium is the physiologically active magnesium not bound to proteins). However, this biomarker is controversial and not always available in clinical labs and hard to measure reliably.
- ▶ Lymphocyte magnesium.<sup>225</sup>
- ▶ Urinary or faecal magnesium excretion<sup>8 89</sup> (low or high levels may indicate deficiency).
- ▶ Urinary fractional magnesium excretion >4%<sup>226</sup> (some authors have suggested >2% in those with normal kidney function).<sup>93</sup>
- ▶ Total erythrocyte magnesium levels<sup>227</sup> (magnesium deficiency has been suggested when erythrocyte magnesium levels are <1.65 mmol/L).<sup>13</sup>
- ▶ Total serum magnesium levels.
- ▶ It is important to note that choosing only one of the aforementioned methods of measuring magnesium deficiency is not appropriate for diagnosing magnesium deficiency. In general, either symptoms of magnesium deficiency must accompany the more reliable methods to diagnose magnesium deficiency (eg, intravenous/oral magnesium load, mononuclear cell or muscle), or two or more of the reliable measurements (eg, intravenous/oral magnesium load, mononuclear cell or muscle) should be used in supporting a diagnosis of magnesium deficiency.

for more than one month, and then continue with a dose that holds the serum value not lower than 0.9 mmol/L magnesium'.<sup>36</sup> The authors noted that using a cut-off of 0.75 mmol/L for magnesium deficiency misses 50% of those with true magnesium deficiency.

**Box 6** Causes of hypermagnesaemia

- ▶ Oversupplementation (mainly from magnesium containing antacids).<sup>228</sup>
- ▶ Kidney damage.<sup>229</sup>
- ▶ Inflammation and cellular injury<sup>230</sup> (significant increases in total and ionised magnesium in animals during endotoxin challenge).

**Box 7** Treatment of hypermagnesaemia<sup>230</sup>

- ▶ Diuresis or dialysis<sup>231</sup> (to increase renal elimination of magnesium).
- ▶ Supportive care.

**CONSEQUENCES OF MAGNESIUM DEFICIENCY****Hypertension**

'Magnesium status has a direct effect upon the relaxation capability of vascular smooth muscle cells and the regulation of the cellular placement of other cations important to blood pressure - cellular sodium:potassium (Na:K) ratio and intracellular calcium (iCa(2+)). As a result, nutritional magnesium has both direct and indirect impacts on the regulation of blood pressure and therefore on the occurrence of hypertension'.<sup>97</sup>

It must be remembered that there is magnesium-ATP-driven sodium-potassium pump and calcium pump.<sup>97</sup> Magnesium deficiency leads to dysfunction of the Na-K-ATPase depleting intracellular K and increasing intracellular sodium and calcium in cardiac and smooth muscle cells. This can cause vasoconstriction of venous smooth muscles and arteries causing hypertension.<sup>3</sup> Magnesium deficiency may also predispose to an increased response to vasoconstrictors, such as angiotensin II and catecholamines.<sup>98</sup>

Many patients with hypertension are treated with thiazide and loop diuretics, both of which deplete the body of magnesium,<sup>99</sup> and giving patients with hypertension who are receiving long-term thiazide diuretics oral magnesium supplementation significantly reduces blood pressure.<sup>99</sup> In fact, the high intracellular calcium induced by magnesium deficiency may induce both insulin resistance and hypertension.<sup>100</sup> A meta-analysis of randomised, double-blind, placebo-controlled trials in normotensive and hypertensive adults found that 368 mg/day of magnesium for a median of 3 months significantly reduces systolic blood pressure by 2.00 mm Hg and diastolic blood pressure by 1.78 mm Hg.<sup>101</sup> In fact, a meta-analysis of seven studies encompassing 135 patients with hypertension on antihypertensive medications with a mean starting blood pressure >155 mm Hg found that magnesium supplementation reduced blood pressure by -18.7/-10.9 mm Hg.<sup>102</sup> Another meta-analysis of 22 trials using a mean dose of 410 mg of magnesium found a significant reduction in systolic (3-4 mm Hg) and diastolic (2-3 mm Hg) blood pressure. The effect on blood pressure was greater when magnesium doses >370 mg/day were used.

Low magnesium levels can promote endothelial cell dysfunction, potentially increasing the risk of thrombosis and atherosclerosis.<sup>103</sup> Magnesium deficiency also promotes a proatherogenic phenotype in endothelial cells.<sup>104</sup> Hypomagnesaemia can impair the release of nitric oxide from the coronary endothelium,<sup>105</sup> while magnesium therapy can improve endothelium-dependent vasodilation in patients with coronary artery disease.<sup>105</sup> Since nitric oxide is both a vasodilator and an

inhibitor of platelet aggregation, this makes magnesium supplementation a promising therapy in the treatment of hypertension and coronary artery disease. Indeed, magnesium therapy may enhance prostacyclin release from the vascular wall.<sup>106</sup>

### Atherosclerosis and calcifications

Magnesium deficiency and magnesium depletion in soft tissues can cause calcifications in the heart, liver and skeletal muscles.<sup>107</sup> Magnesium deficiency may be a leading cause of kidney disease as it leads to swelling of the tubular epithelium, apatite crystal deposition in the proximal convoluted tubules, loops of Henle, collecting tubules and in the pars recta.<sup>108</sup> Thus, magnesium deficiency damages the kidneys due to calcium deposits and may cause numerous electrolyte abnormalities (a common problem in patients with chronic kidney disease). Other studies in animals show that magnesium deficiency causes cardiac necrosis and calcifications.<sup>109</sup> Magnesium deficiency can calcify the descending limb of the loop of Henle, which may lead to dehydration and volume depletion by reducing water reabsorption.<sup>108</sup> A greater intake of magnesium is associated with having a lower risk of an elevated coronary artery calcification score,<sup>110</sup> and supplementing with magnesium has been found to improve endothelial function in patients with coronary artery disease.<sup>111</sup>

One animal study noted: ‘...the degree of lipid deposition in the aorta of cholesterol-fed rabbits can be significantly enhanced by feeding a magnesium-deficient diet... The calcification of the inflammatory granuloma of the aortas and the atrophy and degeneration of muscle fibres with inflammatory connective tissue proliferation in the myocardium and in the stomach and skeletal muscles were only observed in rabbits fed a magnesium deficient diet’.<sup>112</sup> In other words, eating a diet deficient in magnesium predisposes to atherosclerosis, calcification of the aorta, degeneration of myocardial muscle fibres and inflammatory connective tissue throughout the body. This study suggests that low magnesium intake increases inflammation.

Inadequate dietary magnesium intake increases atherosclerotic plaque development in rabbits<sup>113</sup> and induces myocardial fibrosis similar to what is found in human cardiomyopathy/endomyocardial fibrosis.<sup>114</sup> A diet deficient in magnesium in the Cebus monkey causes an increase in serum cholesterol, ST segment depression and atherosclerotic plaques in the aorta,<sup>115</sup> whereas magnesium fortification in drinking water inhibits atherogenesis in female and male Low-density lipoprotein (LDL)-receptor-deficient mice fed a high-cholesterol diet.<sup>116 117</sup>

Magnesium treatment for 3 months in patients with ischaemic heart disease increases the apolipoprotein A1:apolipoprotein B ratio by 13%, decreases the apolipoprotein B concentrations by 15%, and decreases very-low-density lipoprotein concentrations by 27%.<sup>118</sup> Magnesium therapy also tended to increase high-density lipoprotein. The authors of the study concluded: ‘...magnesium

deficiency might be involved in the pathogenesis of ischemic heart disease by altering the blood lipid composition in a way that disposes to atherosclerosis’.<sup>118</sup> In hypomagnesaemic kidney transplant recipients, magnesium supplementation significantly decreases total cholesterol, low-density lipoprotein and total cholesterol:high density lipoprotein ratio.<sup>119</sup> Magnesium deficiency may enhance vascular endothelial injury, promoting the development and progression of atherosclerosis.<sup>120</sup>

Magnesium deficiency may supersaturate bodily fluids with octacalcium phosphate calcifying soft tissues, whereas magnesium therapy may stop or even prevent soft tissue calcifications.<sup>121</sup> Magnesium deficiency in Yorkshire swine induces numerous calcifications and smooth muscle cell degeneration, and promotes atherosclerosis in combination with an atherogenic diet.<sup>122</sup> Hamsters fed a magnesium-deficient diet develop myocardial necrosis, calcifications and cardiomyopathy. These effects of magnesium deficiency seem to be secondary to the inhibition of the Na-K-ATPase and the calcium overload that follows in cardiac myocytes.<sup>123</sup> Triglyceride-rich lipoproteins from magnesium-deficient rats are more susceptible to oxidation.<sup>124</sup> Thus, magnesium deficiency predisposes to lipoprotein peroxidation and atherosclerosis. Perhaps most importantly, patients in the intensive cardiac care unit have been noted to have low blood mononuclear cell magnesium levels.<sup>125</sup> The authors summarised their findings as the following: ‘We conclude that the incidence of intracellular Mg deficiency in patients with cardiovascular disease is much higher than the serum magnesium would lead one to suspect, and may contribute to clinical cardiovascular morbidity’.<sup>125</sup>

### Arrhythmias

‘Although available on order by physicians, the lack of routine serum Mg analysis as part of the ‘electrolyte panel’ impedes the diagnosis of clinical Mg deficiency. Renal loss of Mg resulting from the widespread use of loop diuretics is responsible for significant numbers of patients with Mg deficiency and hypomagnesemia. Life-threatening cardiac arrhythmias and seizures represent the most serious manifestation of clinical hypomagnesemia and Mg depletion [...] Hypomagnesemia is one of the most frequent serum electrolyte abnormalities in current clinical practice. Routine inclusion of serum Mg analysis in the electrolyte panel will enhance the clinical recognition and treatment of hypomagnesemic Mg-depleted patients. Failure to respond to treatment of recurrent ventricular tachycardia/fibrillation to usual antiarrhythmic therapy in patients with acute myocardial infarction, idiopathic dilated cardiomyopathy, and congestive heart failure should alert the clinician to consider administering intravenous Mg’.<sup>126</sup>

As noted previously, magnesium deficiency reduces cardiac Na-K-ATPase, leading to higher levels of sodium and calcium and lower levels of magnesium and potassium in the heart. This increases vasoconstriction in the coronary arteries, which can induce coronary artery spasms,

myocardial infarction and arrhythmias.<sup>127</sup> Considering that around 25% of all myocardial infarctions are not due to atherosclerotic plaque rupture, coronary artery spasm induced by magnesium deficiency may explain some of these events.

In one metabolic study of 22 postmenopausal women, a low-magnesium diet (containing around 130 mg/day) significantly increased both supraventricular and supraventricular plus ventricular beats based on Holter monitor. The authors of the study concluded: 'The recommended dietary allowance of 320 mg/day seems correct; 130 mg is too little. Persons who live in soft water areas, who use diuretics, or who are predisposed to magnesium loss or ectopic beats may require more dietary magnesium than would others'.<sup>128</sup> Another study in postmenopausal women found that a low-magnesium diet (approximately 100 mg/day) can induce atrial fibrillation and increases glucose levels.<sup>129</sup> Patients with diabetes mellitus and arrhythmia have been noted to have lower serum levels of ionised magnesium.<sup>130</sup> Thus, it appears that low dietary intake of magnesium or low magnesium levels can predispose to arrhythmias. Diuretics and digoxin also cause magnesium depletion, making the heart more susceptible to the development of arrhythmias.<sup>131</sup>

Hypomagnesaemia may induce arrhythmias including torsades de pointes ventricular tachycardia.<sup>132</sup> Magnesium therapy may be useful in the treatment of refractory ventricular tachycardia, ventricular fibrillation, multifocal atrial tachycardia, atrial fibrillation and supraventricular tachycardia.<sup>133</sup> A meta-analysis of 19 randomised trials using magnesium orotate found a significant reduction in first-degree mitral valve prolapse, grade I regurgitation, supraventricular and ventricular premature contraction, and paroxysmal supraventricular tachycardia.<sup>134</sup>

### Coronary artery disease

'...low heart muscle magnesium may contribute to sudden death after myocardial infarction. Western diets are probably often low in magnesium, so that the magnesium in hard drinking water may help to protect its consumers from ischemic heart disease...Increasing the magnesium content of the diet may help to prevent ischemic heart disease, and there is already evidence that magnesium salts can have beneficial effects on established heart disease'.<sup>131</sup>

Autopsy studies have revealed lower magnesium content in both infarcted and non-infarcted heart muscle in those who have died of a myocardial infarction.<sup>131</sup> Furthermore, autopsy studies have noted that those dying from accidents have lower heart muscle magnesium in soft-water drinking areas versus those from hard-water areas. This suggests that patients who have lower than normal magnesium concentrations in their heart muscle may be more likely to die suddenly after a myocardial infarction. Indeed, there are numerous studies indicating an increased rate of death from heart disease in low-magnesium drinking water areas.<sup>131</sup>

Magnesium is required for the formation and activation of ATP and is essential for heart muscle contraction and oxidative phosphorylation in heart mitochondria.<sup>131</sup> There is also a rapid loss of myocardial magnesium during anoxia, suggesting that chronic angina leads to magnesium deficiency. Chipperfield and Chipperfield<sup>131</sup> noted: 'Magnesium-deficient diets...predispose animals to the development of myocardial fiber necrosis. Administration of magnesium salts has been shown to reverse many of the changes in animal models of heart disease...There is also good evidence from some animal studies that pretreatment with magnesium salts protects against many of the changes in the heart caused by anoxia...' In other words, consuming a diet high in magnesium may prevent the harms from an acute ischaemic events.

Just 42–64 days on a diet low in magnesium (~101 mg/day) produced atrial fibrillation and flutter in three of five postmenopausal women (ages 47–75 years). Moreover, the arrhythmias responded quickly to magnesium supplementation. During the low-magnesium diet, glucose levels increased and red blood cell superoxide dismutase decreased. The authors of the study concluded: 'A dietary intake of about 4.12 mmol (~101 mg/day, my insertion) Mg/8.4 MJ is inadequate for healthy adults and may result in compromised cardiovascular health and glycemic control in postmenopausal women'.<sup>129</sup>

In a randomised, double-blind, placebo controlled study on 350 patients with acute myocardial infarction, intravenous magnesium sulfate given immediately after completion of thrombolytic therapy significantly reduced all-cause mortality (3.5% vs 9.9%,  $P < 0.01$ ) and ventricular arrhythmias (13% vs 48.6%,  $P = 0.00001$ ).<sup>135</sup> There was also a numerical reduction in reinfarction (8.8% vs 12.7%,  $P$  value not significant).

Magnesium deficiency in swine leads to proaggregatory and procoagulation alterations,<sup>136</sup> and in humans leads to increased thromboxane synthesis.<sup>137</sup> In rats, magnesium deficiency increases thromboxane B<sub>2</sub> outflow.<sup>138</sup> Magnesium treatment has been found to inhibit thrombus formation (as measured by platelet-dependent thrombosis) in patients with stable coronary artery disease by 35%.<sup>105</sup> These effects are additive to that of aspirin and are independent of platelet aggregation. One author concluded: 'High dose of intravenous magnesium can inhibit thrombus formation and is associated with suppression of platelet aggregation. Magnesium treatment can dose-dependently inhibit a wide variety of agonists of platelet aggregation, such as thromboxane A<sub>2</sub> and stimulate prostacyclin synthesis. The molecular basis for these effects is likely modulated via reduction of intracellular calcium mobilization'.<sup>105</sup> Thus, magnesium may prevent thrombotic events and may also protect cardiac cells against ischaemia.<sup>139</sup>

Platelet-dependent thrombosis is significantly higher in patients with stable coronary artery disease with low intracellular magnesium levels.<sup>140</sup> Administration of



### Box 8 Possible cardiovascular manifestations of magnesium deficiency

- ▶ Hypertension.
- ▶ Arrhythmias.
- ▶ Calcifications.
- ▶ Atherosclerosis.
- ▶ Heart failure.
- ▶ Increased platelet reactivity and thrombosis.
- ▶ Myocardial infarction.
- ▶ Stroke.
- ▶ Sudden cardiac death.

intravenous magnesium to healthy volunteers significantly inhibits both ADP-induced platelet aggregation by 40% and binding of fibrinogen or surface expression of GMP-140 by 30%.<sup>141</sup> Thus, magnesium therapy also has antiplatelet effects. In rats, intravenous magnesium therapy inhibits arterial thrombi after vascular injury.<sup>142</sup> All of these suggest that magnesium is an anti-thrombotic and antiplatelet agent and that magnesium deficiency may promote thrombosis. Furthermore, magnesium deficiency appears to be more prevalent in patients with coronary artery disease or ischaemic heart disease, suggesting a need for magnesium treatment.<sup>143 144</sup> Box 8 provides a summary of possible cardiovascular manifestations of magnesium deficiency.

### CONCLUSION

Subclinical magnesium deficiency is a common and under-recognised problem throughout the world. Importantly, subclinical magnesium deficiency does not manifest as clinically apparent symptoms and thus is not easily recognised by the clinician. Despite this fact, subclinical magnesium deficiency likely leads to hypertension, arrhythmias, arterial calcifications, atherosclerosis, heart failure and an increased risk for thrombosis. This suggests that subclinical magnesium deficiency is a principal, yet under-recognised, driver of cardiovascular disease. A greater public health effort is needed to inform both the patient and clinician about the prevalence, harms and diagnosis of subclinical magnesium deficiency.

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## Correction: *Subclinical magnesium deficiency: a principal driver of cardiovascular disease and a public health crisis*

DiNicolantonio JJ, O'Keefe JH, Wilson W. Subclinical magnesium deficiency: a principal driver of cardiovascular disease and a public health crisis. *Open Heart* 2018;5:e000668. doi: 10.1136/openhrt-2017-000668.

The following sentence in the abstract 'Certain individuals will need to supplement with magnesium in order to prevent suboptimal magnesium deficiency, especially if trying to obtain an optimal magnesium status to prevent chronic disease.' should be: 'Certain individuals will need to supplement with magnesium in order to prevent subclinical magnesium deficiency, especially if trying to obtain an optimal magnesium status to prevent chronic disease.'

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