Drug-induced alterations in Mg$^{2+}$ homoeostasis

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ABSTRACT

Magnesium (Mg$^{2+}$) balance is tightly regulated by the concerted actions of the intestine, bone and kidneys. This balance can be disturbed by a broad variety of drugs. Diuretics, modulators of the EGFR (epidermal growth factor receptor), proton pump inhibitors, antimicrobials, calcineurin inhibitors and cytostatics may all cause hypomagnesaemia, potentially leading to tetany, seizures and cardiac arrhythmias. Conversely, high doses of Mg$^{2+}$ salts, frequently administered as an antacid or a laxative, may lead to hypermagnesaemia causing various cardiovascular and neuromuscular abnormalities. A better understanding of the molecular mechanisms underlying the adverse effects of these medications on Mg$^{2+}$ balance will indicate ways of prevention and treatment of these adverse effects and could potentially provide more insight into Mg$^{2+}$ homoeostasis.

INTRODUCTION

Mg$^{2+}$, the second most abundant intracellular divalent cation, is of central importance for a broad variety of physiological processes, including intracellular signalling, neuronal excitability, muscle contraction, bone formation and enzyme activation. Its overall balance is tightly regulated by the concerted actions of the intestine, bones and kidneys, keeping plasma Mg$^{2+}$ levels within the range of 0.70 to 1.10 mmol/l. Disturbance of this balance can have serious consequences. Symptoms of hypomagnesaemia include tetany, seizures and cardiac arrhythmias, whereas hypermagnesaemia may cause various cardiovascular and neuromuscular abnormalities. Drugs can interfere with Mg$^{2+}$ homoeostasis in multiple ways. The aim of the present review is to provide an overview of the various drugs that are known to influence Mg$^{2+}$ homoeostasis and to give some insights into the underlying physiological mechanisms.

MAGNESIUM HOMOEOSTASIS

Mg$^{2+}$ transport can take place via two routes: an active transcellular pathway or a passive paracellular route. The transcellular transport of Mg$^{2+}$ is less well defined than that of for instance Ca$^{2+}$. TRPM (transient receptor potential melastatin) 6 and 7 cation channels are thought to be responsible for Mg$^{2+}$ transport into the cell. TRPM6 is most abundantly expressed in the intestine, kidney and lung, whereas TRPM7 is expressed ubiquitously [1]. Transport of Mg$^{2+}$ from the tubular or intestinal lumen into the cell is, therefore, considered to be responsible for Mg$^{2+}$ transport into the cell. TRPM6 is most abundantly expressed in the intestine, kidney and lung, whereas TRPM7 is expressed ubiquitously [1]. Transport of Mg$^{2+}$ from the tubular or intestinal lumen into the cell is, therefore, considered to be mediated predominantly via TRPM6, whereas TRPM7 appears responsible for cellular Mg$^{2+}$ homoeostasis. A role for TRPM7 and even for TRPM6–TRPM7 heterotetrameric complexes in the apical transport of Mg$^{2+}$ has, however, also been suggested [2,3]. A recent study by Ryazanova et al. [4] has shown that heterozygote TRPM7-deficient mice develop hypomagnesaemia due...
to a defect in intestinal absorption of Mg\(^{2+}\), whereas renal Mg\(^{2+}\) excretion is appropriately low, indicating TRPM7 does play an important role in intestinal Mg\(^{2+}\) homeostasis. Specific Mg\(^{2+}\)-binding proteins involved in cytosolic diffusion have not been identified to date. The calbindin proteins, primarily responsible for cytosolic Ca\(^{2+}\) transport, have been shown to also bind Mg\(^{2+}\), but the physiological relevance of this observation remains to be determined [5]. The molecular identity of the basolateral extrusion mechanism for Mg\(^{2+}\) remains to be defined as well. Extrusion of Mg\(^{2+}\) must occur against an electrochemical gradient, implicating its dependence on a primary or secondary active transport process, a Mg\(^{2+}\) pump or a Na\(^{+}\)/Mg\(^{2+}\) exchanger are most frequently suggested [6,7]. Alternatively, Mg\(^{2+}\) can be absorbed passively via paracellular transport route. For this latter process, tight-junction proteins from the claudin family are important, as they can determine both size and charge selectivity of the paracellular transport [8].

**Intestine**

In the intestine, Mg\(^{2+}\) is primarily derived from dietary sources, such as green leafy vegetables, nuts and whole grains. Approximately 300 mg of Mg\(^{2+}\) is ingested on a daily basis, of which 25–75% is absorbed in the adult, depending on the availability and needs of the body [6,9]. When Mg\(^{2+}\) intake is normal, the transcellular pathway, involving TRPM6, is responsible for approximately 30% of absorption, a fraction that increases when dietary intake is low [10]. Paracellular transport depends on the transepithelial electrical voltage, which is approximately 5 mV lumen-positive with respect to blood. Luminal Mg\(^{2+}\) concentrations range from 1 to 5 mmol/l depending on dietary contents, providing a transepithelial chemical concentration gradient which further enhances absorption [10]. Paracellular transport takes place via tight junctions and is responsible for approximately 70% of Mg\(^{2+}\) absorption when luminal concentrations are high. For the intestine, Mg\(^{2+}\)-specific paracellular channels have not yet been found; however, the observation that, for instance, claudin-2 and -12 are vitamin D-regulated indicates that it is likely that a similar pathway is involved in intestinal paracellular transport of divalent cations [11].

**Bone**

Approximately 50% of the total Mg\(^{2+}\) body content resides within the skeleton as part of hydroxyapatite crystals. The stores in bone serve as a buffer from which Mg\(^{2+}\) can be released when plasma levels are low and into which Mg\(^{2+}\) can be stored when circulating Mg\(^{2+}\) levels are excessive [12]. In animals maintained on a low-Mg\(^{2+}\) diet, bone Mg\(^{2+}\) content is reduced, as is bone mineral density [13]. To date, our understanding of the mechanisms responsible for the mobilization of Mg\(^{2+}\) into and out of these skeletal stores remains insufficient.

**Kidney**

In the kidney, approximately 2.5 g of Mg\(^{2+}\) is filtered by the glomeruli on a daily basis. Approximately 95% of this filtered load is reabsorbed along the different parts of the nephron via both paracellular and transcellular processes (Figure 1) [14]. In the PT (proximal tubulus), 10–30% is reabsorbed [15,16]. Generally, this occurs via a paracellular process, most likely depending on Na\(^{+}\)-driven water transport that increases the intraluminal Mg\(^{2+}\) concentration of the pro-urine along its way through the PT; the small lumen-positive potential in the PT also adds driving force [17–19]. The exact mechanism, however, remains to be elucidated. Paracellular Mg\(^{2+}\) transport in the nephron predominates in the TAL (thick ascending limb) of the nephron, where 40–70% of the filtered Mg\(^{2+}\) is reabsorbed [20]. Here, Mg\(^{2+}\) reabsorption is mainly driven by the lumen-positive transepithelial voltage. NKCC2 (Na\(^{+}\)-K\(^{+}\)-2Cl\(^{−}\) co-transporter) serves as an apical entry mechanism for Na\(^{+}\), K\(^{+}\) and Cl\(^{−}\). ROMK (renal outer medullary K\(^{+}\) channel) 2 allows for apical recycling of K\(^{+}\) back into the tubular lumen, thereby generating a lumen-positive voltage of approximately 5–10 mV. Cl\(^{−}\) exits via the basolateral membrane via CLC-Kb (Cl\(^{−}\) channel Kb). At the basolateral side, the Na\(^{+}\)/K\(^{+}\)/-ATPase constitutes the initial driving force for Na\(^{+}\) transport in the TAL. Here, the paracellular Mg\(^{2+}\) reabsorption depends on the lumen-positive transepithelial voltage and is facilitated by claudin-16 and -19, which are two tight-junction proteins that operate together to form a cation-permeable channel [21]. At the basolateral side, CaSR (Ca\(^{2+}\)-sensing receptor) can modulate transport in response to changes in concentration of extracellular cations, reducing transport upon stimulation [22]. In the DCT (distal convoluted tubule) the final 5–10% of Mg\(^{2+}\) is reabsorbed in an active transcellular manner [23]. The tubular epithelium in this part of the nephron consists of a high-resistance epithelium with a lumen-negative voltage of approximately −5 mV. Apical reabsorption occurs via TRPM6, which can be stimulated via the basolateral EGFR [EGF (epidermal growth factor) receptor] [24]. Kv1.1, an apically located K\(^{+}\) channel, establishes a favourable luminal membrane potential facilitating an increase in the driving force for Mg\(^{2+}\) reabsorption via TRPM6 [25]. The Na\(^{+}\)/K\(^{+}\)/-ATPase at the basolateral membrane provides the Na\(^{+}\) gradient that is utilized by the apical NCC (Na\(^{+}\)/Cl\(^{−}\) co-transporter) to transport NaCl into the cell, while K\(^{+}\) that enters at the basolateral side in this process is recycled via Kir4.1. The Mg\(^{2+}\) reabsorption in the DCT defines the final urinary Mg\(^{2+}\) excretion, as there is no significant reabsorption of Mg\(^{2+}\) beyond the DCT.

**HYPOMAGNESAEMIA**

Hypomagnesaemia is defined as a serum Mg\(^{2+}\) concentration of less than 0.70 mmol/l. Muscle cramps,
Drug-induced alterations in Mg²⁺ homeostasis

Figure 1  Schematic representation of the nephron and electrolyte handling in the TAL of Henlé and DCT
(A) Approximately 95% of the Mg²⁺ filtered in the glomerulus is reabsorbed from the pro-urine along the different segments of the nephron. Of this filtered Mg²⁺ load, 10–30% is reabsorbed in the PT, followed by an additional 40–70% in the TAL. The DCT is responsible for the transport of the final 5–10% of Mg²⁺ back into the blood. CNT, connecting tubule; TDL, thin descending limb. (B) In the TAL, NCC2 allows apical entry of Na⁺, K⁺ and Cl⁻. ROMK2 recycles K⁺ back into the tubular lumen. Cl⁻ exits via the basolateral membrane via CLC-Kb. At the basolateral side, the Na⁺/K⁺-ATPase constitutes the initial driving force for Na⁺ transport in the TAL. Paracellular Mg²⁺ absorption is facilitated by claudin-16 and claudin-19 (CLDN16/19). CaSR will reduce the absorption upon stimulation by extracellular cations. (C) In the DCT, Mg²⁺ absorption via TRPM6 depends on the membrane potential, which is set by Kv1.1 and can be stimulated via EGFR. The Na⁺/K⁺-ATPase at the basolateral membrane provides an Na⁺ gradient that is used by NCC on the apical cell membrane. K⁺ that enters the cell in this process is recycled via Kir4.1.

tetany and muscular weakness are the main complaints of hypomagnesaemic patients [26]. Cardiovascular abnormalities, such as arrhythmias and convulsions, have also been described. Hypomagnesaemia is, however, often associated with multiple biochemical abnormalities such as hypokalaemia and hypocalcaemia. It is, therefore, difficult to ascribe specific clinical manifestations solely to hypomagnesaemia. In this regard, important lessons can be learned from patients with isolated forms of hypomagnesaemia, such as isolated dominant [OMIM (Online Mendelian Inheritance in Man) #154020, #176260 and #613882] and isolated recessive (OMIM #611718) hypomagnesaemia. It must, however, be noted that these cases reflect only the chronically Mg²⁺-depleted state.

Isolated dominant hypomagnesaemia can be caused by mutations in the FXYD2 gene, encoding the γ-subunit of the Na⁺/K⁺-ATPase. The two index patients described, with serum Mg²⁺ levels of approximately 0.4 mmol/l, suffered from generalized convulsions and severe mental retardation was present in one of the patients. Remarkably, other family members with low serum Mg²⁺ levels (0.32–0.65 mmol/l) showed no symptoms of hypomagnesaemia [27–29]. In isolated autosomal-dominant hypomagnesaemia due to mutations in KCNA1 (encoding Kv1.1), serum Mg²⁺ levels <0.40 mmol/l were found in an index patient suffering from recurrent muscle cramps, tetanic episodes, tremor and muscular weakness. Serum Mg²⁺ values of 0.37 and 0.25 mmol/l with normal serum Ca²⁺ and K⁺ values were reported in affected family members during severe attacks of cramps and tetany [25]. In another form of dominant hypomagnesaemia caused by mutations in the CNNM2 gene (encoding cyclin M2), the index patient had a serum Mg²⁺ level of 0.36 mmol/l and suffered from weakness of the limbs, vertigo and headaches, but no other electrolyte abnormalities were described [30,31]. Recessive hypomagnesaemia resulting from mutations in the EGF gene also leads to isolated hypomagnesaemia. Two sisters were described with generalized seizures during infancy, and were found to have serum Mg²⁺ levels of 0.53–0.66 mmol/l with no other clear clinical symptoms [32].

Chronic depletion of Mg²⁺, as reflected by the low serum Mg²⁺ levels, generally becomes clinically evident in patients with serum Mg²⁺ concentrations...
of <0.40 mmol/l. As mentioned above, hypocalcaemia (muscle cramps and tetany) and hypokalaemia (muscle weakness), when occurring secondary to hypomagnesaemia, will contribute to the clinical phenotype. Hypokalaemia associated with hypomagnesaemia is often refractory to treatment by K\(^+\) and can only be properly corrected when Mg\(^{2+}\) is co-administered. The decreased intracellular Mg\(^{2+}\) concentration resulting from Mg\(^{2+}\) deficiency, releases the Mg\(^{2+}\)-mediated inhibition of ROMKs, thereby increasing K\(^+\) excretion [33]. Hypocalcaemia secondary to hypomagnesaemia has been hypothesized to originate from inappropriately low PTH (parathyroid hormone) secretion, the release of which depends on an intracellular signalling cascade that requires Mg\(^{2+}\). In addition, the responsiveness of target organs to PTH stimulation seems to be reduced [34,35]. Hypocalcaemia secondary to hypomagnesaemia with low PTH secretion is mostly seen when serum Mg\(^{2+}\) levels are extremely low [36]. Treatment is only successful when hypomagnesaemia is addressed together with the hypocalcaemia, as Ca\(^{2+}\) supplementation alone will not suffice [34].

**Assessment of Mg\(^{2+}\) status**

In clinical practice total serum Mg\(^{2+}\) is most commonly used to assess the Mg\(^{2+}\) status in patients. This parameter does not necessarily reflect the true total body Mg\(^{2+}\) content, as normal serum Mg\(^{2+}\) levels may be present despite intracellular depletion. Using ion-selective electrodes it is possible to measure solely ionized Mg\(^{2+}\). Some studies indicate that ionized Mg\(^{2+}\) is a better representative of the Mg\(^{2+}\) status compared with total serum Mg\(^{2+}\), whereas others find both parameters equally representative. The Mg\(^{2+}\) content of erythrocytes, leucocytes and platelets has also been suggested as potential biomarkers for the assessment of Mg\(^{2+}\) status. However, their usefulness and reliability are currently under debate. Alternatives such as measuring Mg\(^{2+}\) content of bone, teeth, muscle, hair or nails are either too invasive, too laborious or not reliable to use in daily clinical practice [37]. An easy non-invasive method is to analyse urinary Mg\(^{2+}\) excretion. As renal Mg\(^{2+}\) excretion will decrease in response to deficiency, this is an important parameter during assessment of Mg\(^{2+}\) status [37].

The Mg\(^{2+}\) status can also be evaluated in balance studies by determining Mg\(^{2+}\) faecal as well as renal excretion after oral loading or intravenous infusion. Since the results of these tests are partly dependent on the renal function, the risk of false-negative and false-positive outcomes should be taken into account. Owing to these and other limitations, balance studies are not frequently performed [38]. For some minerals, radioactive isotopes can be used to assess the mineral balance. For safety reasons radioactive isotopes are not often employed for balance studies in humans, but in animal models they can be useful and are, therefore, frequently applied. The use of radioactive Mg\(^{2+}\) isotopes for balance studies is unfortunately limited by the short Mg\(^{2+}\) isotope half-lives, which range from 21 h to just milliseconds. Stable Mg\(^{2+}\) isotopes such as \(^{25}\)Mg or \(^{26}\)Mg can be distinguished from \(^{24}\)Mg using inductively coupled plasma mass spectrometry. Owing to their relatively high natural abundance, high doses of the enriched isotopes are required for analytical precision, making this type of experiments not only technically demanding, but also relatively expensive [39].

In conclusion, a simple, rapid and accurate test to assess total body Mg\(^{2+}\) status is lacking. Until adequate alternatives become available, the combined determination of serum Mg\(^{2+}\) and urinary Mg\(^{2+}\) excretion remains the only practical test to assess Mg\(^{2+}\) status.

**Treatment of hypomagnesaemia**

The route of administration of Mg\(^{2+}\) supplements depends on the severity of clinical findings and the origin of the hypomagnesaemia. Patients can be treated with oral supplements, with intramuscular injections or with intravenous infusions [40]. Intravenous administration is the most effective in restoring serum Mg\(^{2+}\) to normal levels and is, therefore, the best treatment in cases of severe hypomagnesaemia. The disadvantage is that patients have to visit the hospital on a regular basis if frequent treatment is required. Oral supplements do not require hospital visits; however, not all patients tolerate oral supplementation of Mg\(^{2+}\) due to their cathartic effect at higher dosages. Solubility and bioavailability vary greatly between various Mg\(^{2+}\) supplements. In general, organic Mg\(^{2+}\) salts have a higher solubility and bioavailability compared with inorganic Mg\(^{2+}\) salts, making them more suitable for oral Mg\(^{2+}\) replacement therapy. It should be noted that, in cases of severe hypomagnesaemia or Mg\(^{2+}\) deficiency due to intestinal malabsorption, oral Mg\(^{2+}\) supplements may not be sufficient to restore serum Mg\(^{2+}\) levels to normal.

**DRUG-INDUCED HYPOMAGNESAEMIA**

A summary of the drugs described below is provided in Table 1 and Figure 2.

**Diuretics**

Diuretics increase urinary output and are widely used in the treatment of hypertension, heart failure and kidney diseases. They may cause hypermagnesuria, leading to possible hypomagnesaemia and Mg\(^{2+}\) depletion. Three types of diuretics are known to influence Mg\(^{2+}\) homeostasis, namely osmotic diuretics, loop diuretics and thiazide-type diuretics.
### Table 1  Drug-induced changes in Mg²⁺ homoeostasis

<table>
<thead>
<tr>
<th>Drug/compound</th>
<th>Reference(s)</th>
<th>Drug/compound</th>
<th>References</th>
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<tr>
<td><strong>Hypomagnesaemia</strong></td>
<td></td>
<td><strong>Hypermagnesaemia</strong></td>
<td></td>
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<tr>
<td>Diuretics</td>
<td></td>
<td>Epsom salt poisoning</td>
<td>[103,106–108]</td>
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<td>Osmotic diuretics</td>
<td>[41]</td>
<td>Overdose using Mg²⁺ as a cathartic</td>
<td>[108,110,111]</td>
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<tr>
<td>Loop diuretics</td>
<td>[41,42]</td>
<td>Antacids</td>
<td>[112–115]</td>
</tr>
<tr>
<td>Thiazide-type diuretics</td>
<td>[43–49]</td>
<td>Laxative abuse</td>
<td>[119,121,122]</td>
</tr>
<tr>
<td>EGFR modulators</td>
<td></td>
<td>Enemas containing Mg²⁺</td>
<td>[107,123,124]</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>[32,50–55]</td>
<td></td>
<td></td>
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<tr>
<td>Erlotinib</td>
<td>[56]</td>
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<tr>
<td>PPIs</td>
<td>[57–65]</td>
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<td>Antimicrobials</td>
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<td></td>
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<tr>
<td>AGAs</td>
<td>[66–73]</td>
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<tr>
<td>Pentamidine</td>
<td>[74–78]</td>
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<tr>
<td>Sirolimus</td>
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<tr>
<td>Foscarnet</td>
<td>[83,84b]</td>
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<tr>
<td>Calcineurin inhibitors</td>
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<tr>
<td>FK506</td>
<td>[92–95]</td>
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<tr>
<td>Cisplatin/carboplatin</td>
<td>[96–101]</td>
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</table>

**Figure 2  Overview of drugs causing hypomagnesaemia**

Overview of the six classes of drugs described causing hypomagnesaemia. Effects of individual drugs on key players in Mg²⁺ homoeostasis in cells of the TAL and DCT are displayed. Pentamidine and cisplatin are not known to have an effect on specific proteins involved in Mg²⁺ homoeostasis, but have been shown to be toxic to/accumulate in DCT cells respectively.
Osmotic diuretics

Osmotic diuretics (such as mannitol) are solutes that are not absorbed or only partly absorbed from the renal tubular lumen. They diminish salt and water reabsorption by increasing the flow rate thereby reducing, among others, serum Mg\(^{2+}\) levels [41].

Loop diuretics

Loop diuretics (such as furosemide, bumetanide, torsemide and ethacrynic acid) act in the TAL by competing for the Cl\(^{-}\) site on NKCC2. Inhibition of apical Cl\(^{-}\) reabsorption and diminished basolateral Cl\(^{-}\) efflux lead to a loss of lumen-positive potential, thus resulting in a diminished driving force for paracellular cation reabsorption [42]. Therefore the use of loop diuretics may lead to renal Mg\(^{2+}\) wasting and hypomagnesaemia due to reduced paracellular Mg\(^{2+}\) reabsorption via claudin-16 and -19 [41].

Thiazide-type diuretics

Thiazide-type diuretics comprise a class of diuretics derived from benzothiadiazine, but also drugs with similar action that do not have the thiazide chemical structure such as chlortalidone and metolazone. Thiazides enhance renal Na\(^{+}\) excretion by inhibiting NCC in the DCT cells [43]. Thiazide treatment leads to hypomagnesaemia as well as hypocalciuria [44,45]. In contrast with the effects of thiazide-type diuretics on Ca\(^{2+}\) balance, which seem to differ in short- and long-term treatment, the effect of thiazides on Mg\(^{2+}\) reabsorption only becomes apparent upon chronic treatment [46]. Hypomagnesaemia has been suggested to result from K\(^{+}\) deficiency, increased passive Mg\(^{2+}\) secretion or decreased active Mg\(^{2+}\) reabsorption in the DCT [47-49]. Chronic administration of thiazides enhances renal Mg\(^{2+}\) excretion and specifically reduced renal expression levels of TRPM6 in a mouse model. In the same study, it was shown that TRPM6 expression levels were severely decreased in NCC-knockout mice. Therefore the pathogenesis of hypomagnesaemia in chronic thiazide treatment appears to result from specific TRPM6 down-regulation in the DCT [46].

EGFR modulators

EGF is an important growth factor that is synthesized as a pre-proprotein, which is cleaved and subsequently processed into the mature EGF [50–51a]. EGF acts by binding with high affinity to EGFR, which is generally localized at the basolateral cell surface, thereby stimulating the intrinsic protein tyrosine kinase activity of the receptor and activating intracellular signalling cascades. EGF is overexpressed in a broad variety of tumour cells, making it an effective target for anticancer treatments. In the nephron, EGF is expressed along the TAL and DCT [32].

In 2007, Groenestege et al. [32] presented two sisters with low serum Mg\(^{2+}\) concentrations and an inappropriately high fractional excretion of Mg\(^{2+}\). They identified a mutation in the pro-EGF gene that, upon closer investigation, was found to cause a defect in the sorting of the pro-EGF, resulting in impaired basolateral sorting. Owing to the resulting lack of release of the hormone on the basolateral side, the EGFR in the DCT could not be stimulated. This study demonstrated that TRPM6 activity was increased upon binding of EGF to EGFR, making EGF the first magnesiotropic hormone. The increased activity results from an increase in the mobility and cell-surface expression of TRPM6 [52]. These findings matched perfectly with earlier observations that certain EGFR-targeting chemotherapeutic agents cause hypomagnesaemia. There are actually two main classes of anticancer agents that affect the EGFR: those targeting the extracellular ligand-binding domain (such as cetuximab and panitumumab) and drugs that block the intracellular tyrosine kinase domain (such as erlotinib and gefitinib).

Cetuximab (erbitux)

Cetuximab is a chimaeric (mouse/human) monoclonal antibody, which functions as an EGFR antagonist by preventing the binding of EGF and triggering the internalization of the receptor, consequently leading to inhibition of EGFR activation. Approximately 1.5 years after its release by the U.S. FDA (Food and Drug Administration) in 2004, a warning was released concerning the relationship between severe hypomagnesaemia and cetuximab treatment. Several groups have performed retrospective studies to determine the incidence of cetuximab-induced hypomagnesaemia [53,54]. These studies are, however, hindered by the fact that Mg\(^{2+}\) levels are not commonly determined in all patients. In a prospective study, it was shown that in most patients serum Mg\(^{2+}\) concentrations during EGFR-targeting treatment had decreased compared with baseline measurements [55]. In total, 54% of the treated patients developed hypomagnesaemia (defined as serum Mg\(^{2+}\) levels <0.65 mmol/l), and in 6% of all patients hypomagnesaemia was severe (serum Mg\(^{2+}\) levels <0.4 mmol/l). Clinically significant hypocalcaemia was rare and not progressive upon treatment. Careful monitoring of serum Mg\(^{2+}\) levels is, therefore, essential during treatment.

Erlotinib (tarceva)

Erlotinib is a tyrosine kinase inhibitor that acts on EGFR. It binds in a reversible fashion to the ATP-binding site of the receptor. For the signal to be transmitted, two members of the EGFR family need to dimerize. The two halves of the dimerized EGFR then autophosphorylate each other using one ATP molecule. The autophosphorylation causes a conformational change in the intracellular structure of EGFR, which is essential for the activation of the
intracellular signalling cascade that takes place upon binding of EGF to EGFR. By inhibiting the binding of ATP, autophosphorylation is not possible and the signal is blocked. To date, reports on erlotinib-induced hypomagnesaemia in patients are lacking. A recent study by Dimke et al. [56] determined the effect of erlotinib on Mg²⁺ homeostasis. In vivo studies showed a small, but significant, effect on serum Mg²⁺ levels; furthermore, mice failed to decrease renal fractional excretion of Mg²⁺ in reaction to reduced Mg²⁺ levels. Although TRPM6 expression was lowered at the mRNA level, no changes were found at the protein level. Erlotinib failed to inhibit EGF-induced changes in TRPM6 activity at physiological concentrations [56]. Taken together, these observations indicate that the effect of erlotinib on Mg²⁺ homeostasis is minimal. Nevertheless, in the case of erlotinib treatment in patients predisposed to developing hypomagnesaemia, extra caution is warranted.

The dissimilarity between anti-EGFR antibodies and EGFR tyrosine kinase inhibitors on Mg²⁺ handling is still not fully understood; most probably differences in the bioavailability of erlotinib and cetuximab play a decisive role in the aetiology of EGFR modulator-induced hypomagnesaemia [56].

**PPIs (proton pump inhibitors)**

PPIs belong to the most widely prescribed classes of drugs in the world. In 2006, two cases of PPI-induced hypomagnesaemia were published by Epstein et al. [57]. Since then, several groups have described similar findings in patients using PPIs [58–62]. The exact prevalence remains unknown; however, the growing number of case reports indicates that these patients might represent the ‘tip of an iceberg’.

Patients generally suffer from hypomagnesaemia and often have secondary hypocalcaemia and hypokalaemia. Long-term use seems to play a role, as all patients were using PPIs for more than 1 year. Remarkably, patients recover relatively quickly upon discontinuation and relapse within days when medication is restarted. This could indicate that PPIs might have a relatively subtle effect on Mg²⁺ homeostasis, which only becomes overt when Mg²⁺ stores are completely depleted. Indeed, Mg²⁺ retention upon intravenous infusion is high, suggesting severe depletion of the body’s Mg²⁺ stores. Urinary Mg²⁺ excretion is low, indicating intact renal function. Taken together, these findings point towards an intestinal abnormality as the most likely problem underlying PPI-induced hypomagnesaemia. Studies examining the effect of PPIs on the intestinal absorption of various salts have not identified differences in the absorption of Mg²⁺ [63,64]. All studies were, however, performed after short-term PPI use and were based on faecal excretion analysis; a long-term effect or a subtle effect for which this technique is not sensitive enough and can, therefore, not be excluded.

Several explanations have been suggested in the published case reports. First, Mg²⁺ absorption might depend on the stomach’s acidity for solubilization. Achlorhydria caused by PPIs could, therefore, reduce Mg²⁺ availability for absorption, resulting in diminished Mg²⁺ absorbed in the intestine. A second explanation would be an increase in intestinal Mg²⁺ loss via secretion; considerable amounts of Mg²⁺ can be excreted in the intestine, and thus a shift in the balance between Mg²⁺ absorption and secretion in the intestine could result in net Mg²⁺ loss. Thirdly, active transcellular or passive paracellular Mg²⁺ absorption could be impaired. TRPM6 activity is positively regulated by extracellular protons, and an inhibitory effect of PPIs on the colonic H⁺/K⁺-ATPase (a homologue of the gastric H⁺/K⁺-ATPase that is inhibited by PPIs) could reduce TRPM6 activity due to a decreased level of excreted protons. Recently, Thongon and Krishnamra [65] have shown that omeprazole treatment of Caco-2 monolayers can decrease paracellular cation permeability leading to suppression of passive Mg²⁺ absorption. A clear molecular explanation for this observation is still lacking.

More studies need to be performed to determine the incidence of PPI-induced hypomagnesaemia and to unravel the underlying mechanisms. Meanwhile, physicians should be aware of this serious side effect of PPIs. Patients suffering from hypomagnesaemia due to PPIs can be treated with supplements or switched to a histamine H₂ receptor antagonist.

**Antimicrobials**

**AGAs (aminoglycoside antibiotics)**

AGAs such as gentamycin, tobramycin and amikacin are widely used in the treatment of severe bacterial infections of the abdomen and urinary tract because of their high efficacy. Side effects can, however, be serious, with nephrotoxicity and ototoxicity occurring in up to 35% of the treated patients. As many as 25% of the patients will develop hypomagnesaemia due to renal Mg²⁺ loss [66]. The effect of AGAs on Mg²⁺ balance is not directly dose-dependent, but seems to be related to the cumulative doses of AGAs received by the patient during treatment. Onset of hypomagnesaemia can take up to 2 weeks and can persist after cessation of AGA treatment for several months [67]. Hypermagnesuria is generally accompanied by hypercalciuria, which suggests that AGAs exert an effect on renal solute transport in those tubular segments where both Ca²⁺ and Mg²⁺ are reabsorbed, i.e. the TAL and DCT. AGAs do not accumulate in the more distal parts of the nephron, but up to 10% of the administered dose accumulates in the renal cortex, especially in the PT cells, where intracellular accumulation of AGAs leads to damage as indicated by the increase in specific biomarkers [68,69]. Animal experiments have shown renal Mg²⁺ wasting in the absence of renal failure.
or tubular morphology abnormalities [70]. In a recent study, Tzovaras et al. [71] found no correlation between changes in Mg\(^{2+}\) and Ca\(^{2+}\) excretion with alterations in urine lactate, alanine or hippurate used as markers for nephrotoxicity. Together, these findings indicate that the proximal and distal renal tubular dysfunction as a result of AGA treatment is caused by two independent processes. AGAs can function as polyvalent cations and can thus stimulate the CaSR [72,73]. Activation of the CaSR by polyvalent cations could inhibit the passive reabsorption of Ca\(^{2+}\) and Mg\(^{2+}\) in the TAL and active absorption in the DCT. Indeed, Sassen et al. [70] have shown a decreased expression of NKCC2 and an increased expression of CaSR in the TAL of gentamycin-treated rats. The reduced NKCC2 expression would result in a decrease in the lumen-positive membrane voltage and is, therefore, likely to contribute to the increased urinary Ca\(^{2+}\) and Mg\(^{2+}\) excretion resembling the response to furosemide treatment.

**Pentamidine**

Pentamidine is an antimicrobial used in the prevention or treatment of pneumocystic pneumonia in immuno-compromised patients. Treatment with pentamidine can lead to severe symptomatic hypomagnesaemia secondary to renal Mg\(^{2+}\) wasting, typically in association with hypocalcaemia, which has been observed to continue for up to 2 months after cessation of pentamidine treatment [74–76]. The exact molecular mechanism underlying this renal Mg\(^{2+}\) leakage is unknown; however, autopsy studies in AIDS patients has shown pentamidine accumulation in renal tissue from 1 day to 1 year after the completion of therapy [77,78]. In addition, the epithelium of the DCT was degenerated, suggesting that pentamidine-induced hypomagnesaemia might be the result of diminished active Mg\(^{2+}\) reabsorption in the kidney.

**Rapamycin (sirolimus)**

Rapamycin is a macrolide antibiotic derived from fungus. It was the first inhibitor of the mTOR (mammalian target of rapamycin) pathway approved by the FDA and it is frequently used to prevent post-transplant organ rejection. Treatment with rapamycin is associated with increased renal Mg\(^{2+}\) excretion resulting in hypomagnesaemia [79], da Silva et al. [80] showed a marked decrease in both plasma K\(^{+}\) and Mg\(^{2+}\) in sirolimus-treated rats. In addition, increased urinary excretion of Na\(^{+}\), K\(^{+}\) and Mg\(^{2+}\) was found, whereas the glomerular filtration rate remained unchanged. Sirolimus treatment reduced the expression of NKCC2 and AQP2 (aquaporin 2), whereas TRPM6 expression was increased, which could represent either a direct stimulatory effect of sirolimus or a compensatory response [80]. Recently, Ikari et al. [52] demonstrated in an in vitro study that rapamycin inhibits the EGF-mediated increase in TRPM6 expression by reducing mRNA stability. Clinical implications of these findings remain to be determined; however, they indicate hypomagnesaemia due to rapamycin treatment is the result of a defect in Mg\(^{2+}\) absorption by DCT cells.

**Amphotericin B**

Amphotericin B is an antifungal drug that is mainly used to treat various systemic fungal infections in immunocompromised patients or for parasitic protozoan infections. Amphotericin B causes renal injury leading to renal insufficiency, urinary K\(^{+}\) wasting and hypokalaemia, Mg\(^{2+}\) wasting and hypomagnesaemia, metabolic acidemia due to distal renal tubular acidosis, and polyuria [81]. Barton et al. [82] found reduced serum Mg\(^{2+}\) levels and an increase in renal Mg\(^{2+}\) excretion upon treatment with amphotericin B. They also showed that the effect is reversible and Mg\(^{2+}\) homoeostasis returns to normal baseline levels upon discontinuation of treatment [82]. To date, no molecular data explaining amphotericin B-induced hypomagnesaemia are available.

**Foscarnet (trisodium phosphonoformate hexahydrate)**

Foscarnet is a pyrophosphate analogue that inhibits many viral DNA polymerases [83]. It is used to treat cytomegalovirus and acyclovir-resistant mucocutaneous herpes simplex virus disease in immunocompromised patients. Its side effects include hypomagnesaemia, hypocalcaemia and hypokalaemia [84]. Being a pyrophosphate analogue, foscarnet is a potent chelator of divalent cations. Thus complexes readily form with Mg\(^{2+}\) and Ca\(^{2+}\), and a linear relationship exists between serum divalent ions and circulating plasma foscarnet concentrations [84a,84b]. This suggests that foscarnet-induced hypomagnesaemia is solely the result of the physical interaction between foscarnet and Mg\(^{2+}\). It would be interesting, however, to investigate whether adaptational changes occur in expression of, for example, TRPM6.

**Calcineurin inhibitors**

Calcineurin inhibitors such as CsA (cyclosporin A; ciclosporin) and FK506 are immunosuppressant drugs that are widely prescribed in post-transplantation immunosuppression and for numerous immunological disorders. Calcineurin inhibitors are known to cause renal injury, hypertension and tubular dysfunction with disturbances of mineral metabolism. Both drugs commonly lead to hypomagnesaemia due to renal Mg\(^{2+}\) wasting, hypercalciuria and hypokalaemia [85].

**CsA**

CsA is known to cause nephrotoxicity in a dose-dependent and reversible manner [86–88]. CsA treatment also frequently results in a disruption of mineral homoeostasis, with 10–36% of CsA-treated patients developing hypomagnesaemia [88,89]. In vitro, CsA
significantly reduces the expression of Claudin-16 and TRPM6, but not TRPM7, at both the mRNA and protein levels; for TRPM6, the decreased expression is mediated by the inhibition of c-Fos transcription [89,90]. A recent study has described an increase in the fractional excretion of Mg\(^{2+}\) in rats as a result of CsA treatment [91]. The study also showed a reduction in the expression levels of TRPM6, TRPM7, NCC and EGF; whereas reduced expression of EGFR or claudin-16 was not found [91]. Together, these findings indicate CsA reduces renal Mg\(^{2+}\) reabsorption in the DCT, possibly via the down-regulation of TRPM6.

**FKS06 (tacrolimus)**
FKS06 treatment is frequently associated with an inappropriately high fractional excretion of Mg\(^{2+}\) and Ca\(^{2+}\) [92]. Nijenhuis et al. [93] found decreased renal levels of TRPV5 (transient receptor potential vanilloid 5), calbindin-D28K and TRPM6 mRNA expression in the kidneys of rats treated with FKS06. The expression of specific DCT markers was unaltered, excluding the possibility that the reduction in Mg\(^{2+}\) reabsorption is the result of a general toxic effect of FKS06 on DCT cells [93]. It has been shown that FKS06 treatment results in decreased intracellular Mg\(^{2+}\) concentrations in human osteoblast cells, suggesting that changes in Mg\(^{2+}\) homeostasis might also be involved in the reduced bone mineralization caused by FKS06 treatment [94]. A recent study has shown that FKS06 can suppress VDR (vitamin D receptor) expression; the renal loss of both Mg\(^{2+}\) and Ca\(^{2+}\) occurring despite increased vitamin D levels suggests a possible aetiological role of vitamin D resistance [95]. Further studies are needed to unravel the underlying molecular mechanisms.

**Cisplatin**
Cisplatin (cis-diammine dichloroplatinum) is widely used to treat various solid tumours. Among the various side effects, nephrotoxicity is generally considered the most important since it is the main dose-limiting factor in the treatment of patients [96]. Hypomagnesaemia due to renal Mg\(^{2+}\) wasting is common in cisplatin-treated patients; an additional effect of reduced intestinal absorption of Mg\(^{2+}\) cannot be excluded as the absorption of several electrolytes has been shown to be reduced by cisplatin treatment [97]. The incidence of Mg\(^{2+}\) deficiency is >30% and is augmented with increased dosage or prolonged duration of treatment [98]. Interestingly, hypomagnesaemia caused by cisplatin treatment seems to be Mg\(^{2+}\)-specific, with hypocalcaemia and hypokalaemia only occurring with prolonged and severe Mg\(^{2+}\) deficiency [97]. Cisplatin predominantly accumulates in the PT and DCT, but effects of cisplatin may persist long after all inorganic platinum has disappeared from renal tissue [99,100]. In addition, hypomagnesaemia and cisplatin accumulation appear to enhance each other in a vicious circle in which cisplatin treatment causes renal Mg\(^{2+}\) loss and the resulting hypomagnesaemia stimulates cisplatin accumulation in the kidney [101].

**HYPERMAGNESAEAMIA**

Hypermagnesaemia causes a broad variety of symptoms depending on the serum Mg\(^{2+}\) levels (Table 2) [26,102,103]. In the case of a relatively mild degree of hypermagnesaemia, patients may suffer from nausea, vomiting and flushing. Within the asymptomatic and mildly symptomatic stages of hypermagnesaemia (between 1.1 and 3.0 mmol/l), there is also the therapeutic range in which hypermagnesaemia can be used to control convulsions [104]. When the plasma Mg\(^{2+}\) levels increase further, symptoms become increasingly dangerous, eventually leading to a comatose state and/or asystole. As the renal response to high Mg\(^{2+}\) levels is extremely efficient, hypermagnesaemia is relatively rare and primarily observed in patients with renal insufficiency. It has, however, also been detected in individuals with normal renal function as a result of exogenous administration via oral, intravenous or rectal routes [105]. A summary of the effects of the compounds described below is provided in Table 1.

**Epsom salt poisoning**
The heptahydrate of MgSO\(_4\), also known as Epsom salt, is often used as bath salt in flotation therapy, but it is also applied as a home remedy for numerous ailments, including abdominal pain, constipation, sprains and muscle strains. Accidental excessive ingestion can lead to severe hypermagnesaemia. Several fatal or almost fatal cases of hypermagnesaemia due to Epsom salt poisoning have been reported in which patients used Epsom salt gargles, Epsom salt enemas or simply ingested several tablespoons of Epsom salt in an attempt to heal various ailments [103,106–108].

| Table 2 Symptoms of hypermagnesaemia |
|-----------------|-----------------|
| Serum Mg\(^{2+}\) level (mmol/l) | Symptoms |
| 0.7–1.1 | None; normal serum level |
| 1.1–2.0 | Asymptomatic |
| 2.0–3.0 | Nausea, vomiting, cutaneous vasodilation, headaches, hyporeflexia and lethargy |
| 3.0–5.0 | Unresponsiveness, loss of deep tendon reflexes, electrocardiographic changes, such as prolongation of QRS, PR and QT intervals, bradycardia and hypotension |
| >5.0 | Complete heart block, respiratory paralysis, coma and shock |
| >8.0 | Asystole and death |
**Overdose using Mg\(^{2+}\) as a cathartic**

Gastrointestinal decontamination after a toxic ingestion typically involves three actions, all aiming to minimize absorption of ingested poisons: gastric emptying by aspiration and lavage, administration of an absorbing agent such as active charcoal to bind the toxic agent, and catharsis [109]. Cathartics decrease absorption of toxic substances by accelerating the transport of both the toxic substance and the charcoal–substance complex through the intestine, thereby reducing the bodies exposure time to the toxins. Mg\(_3\)(C\(_6\)H\(_5\)O\(_7\))\(_2\) (magnesium citrate) is often used as a cathartic after oral poisoning or overdosing, and is considered safe in patients with normal renal function. Upon multiple doses, however, this treatment can lead to severe hypermagnesaemia [108,110,111]. Careful monitoring of serum Mg\(^{2+}\) levels during treatment of patients with multiple doses of Mg\(_3\)(C\(_6\)H\(_5\)O\(_7\))\(_2\) is, therefore, strongly advised.

**Antacids**

Many types of antacids contain Mg(OH)\(_2\). Available as over-the-counter drugs, Mg\(^{2+}\)-based antacids such as milk of magnesia are generally considered to be safe. The Mg\(^{2+}\) load posed by these drugs can indeed, under normal circumstances, easily be excreted via the kidneys. However, when renal function is compromised or when extreme amounts are ingested, hypermagnesaemia may develop [112–115].

**Laxative abuse**

Various compounds containing Mg\(^{2+}\) [such as Mg\(_3\)(C\(_6\)H\(_5\)O\(_7\))\(_2\), Mg(OH)\(_2\) and MgSO\(_4\)] can be used as laxatives. They increase the faecal water content, leading to softer stools and eventually diarrhoea. This has long been ascribed to the increased osmotic pressure in the colon due to large amounts of unabsorbed Mg\(^{2+}\) and SO\(_4^{2-}\) Two recent studies, however, have found that the Mg\(^{2+}\)-induced diarrhoea is not solely the result of increased osmotic pressure. Upon treatment with Mg\(^{2+}\) salts, aquaporin-3 expression in the Caco-2 cell line increases in a Mg\(^{2+}\)-specific manner, inducing an increase in water permeability [116,117]. This increase in aquaporin-3 expression was also observed in rats [118]. High dosages and impaired renal function increase the risk of hypermagnesaemia due to the use of laxatives [119,120]. In addition in children and laxative abusers, such as for instance patients with eating disorders, laxatives can lead to hypermagnesaemia [119,121,122].

**Enemas**

In the past, Mg\(^{2+}\)-containing enemas were applied in cases of obstipation. We now know that in the large intestine substantial quantities of Mg\(^{2+}\) can be absorbed, explaining the numerous cases of fatal hypermagnesaemia occurring even in patients with normal renal function [107,123,124]. As several safe alternatives are available nowadays, the use of Mg\(^{2+}\)-containing enemas is no longer recommended.

**Treatment of hypermagnesaemia**

Treatment of hypermagnesaemia should primarily be aimed at lowering plasma Mg\(^{2+}\) levels. However, when serious complications of Mg\(^{2+}\) intoxication are present, intravenous administration of low doses of Ca\(^{2+}\) may quickly reduce the severity of symptoms due to the antagonistic effect of Ca\(^{2+}\) on Mg\(^{2+}\). It is, therefore, the advised initial treatment in the case of lifethreatening situations. In addition, haemodialysis may be used to quickly reduce serum Mg\(^{2+}\) levels in severe cases [125,126]. Next, oral intake and/or intravenous administration of Mg\(^{2+}\) salts should be discontinued immediately to avoid further intoxication. Subsequently, renal Mg\(^{2+}\) excretion could be stimulated by intravenous administration of furosemide and saline to ensure high urine output and to prevent volume depletion [127].

**SUMMARY**

Tightly controlled Mg\(^{2+}\) balance is essential for ample physiological processes and consequently disturbance of this balance can have serious clinical consequences. There is a large variety of drugs that influence Mg\(^{2+}\) homoeostasis in various ways, causing either hypo- or hyper-magnesaemia. A better understanding of the mechanisms that are underlying the drug-induced changes in Mg\(^{2+}\) homoeostasis could allow the development of drugs with less side effects and thus better patient care. The discovery of novel key players in Mg\(^{2+}\) homeostasis could help to further elucidate the molecular pathways involved in (re)absorption of Mg\(^{2+}\) as well as its regulation.

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