

Review Article

Hypomagnesemia and post-thyroidectomy hypocalcemia: molecular mechanisms and clinical potential

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Received January 6, 2018; Accepted July 2, 2018; Epub November 15, 2018; Published November 30, 2018

Abstract: Hypocalcemia, a common post-thyroidectomy complication, severely reduces patient quality of life. Numerous studies have suggested that hypomagnesemia is the key to post-thyroidectomy hypocalcemia. Magnesium (Mg) modulates calcium (Ca) homeostasis by regulating absorption or reabsorption of calcium ion (Ca^{2+}), activity of the Ca-sensing receptor (CaSR) signaling axis that mediates synthesis and secretion of parathyroid hormones (PTH), sensitivity of target organs to PTH, and synthesis of $1,25(\text{OH})_2\text{D}$. Therefore, this review focused on factors contributing to post-thyroidectomy hypocalcemia, effects of Mg on blood Ca, and related molecular mechanisms. Since Mg is important to the development and progression of post-thyroidectomy hypocalcemia, understanding underlying molecular mechanisms may help with postoperative clinical management and research.

Keywords: Thyroidectomy, hypocalcemia, hypomagnesemia, PTH, $1,25(\text{OH})_2\text{D}$

Introduction

In 2012, among people aged 0-74 years, 298,000 new cases of thyroid cancer were diagnosed, accounting for 2.1% of all newly diagnosed cancer cases [1]. In the US, 56,870 new cases of thyroid cancer were diagnosed in 2017. Thyroid cancer incidence in women was approximately 20.8/100,000 (4th most common cancer in women) [2]. Current therapeutic strategies for thyroid cancer are surgery-based [3], with hypoparathyroidism and recurrent laryngeal nerve injuries as common post-thyroidectomy complications [3]. Hypoparathyroidism-induced [4, 5] post-thyroidectomy hypocalcemia occurs in 0.33-83% of people after surgery [6-10]. Post-thyroidectomy hypomagnesemia occurs in 10-72% of patients [4, 8, 11-13] and is correlated with hypocalcemia ($r = 0.205$; $P = 0.022$) [14]. Studies have suggested that hypomagnesemia is a risk factor for post-thyroidectomy hypocalcemia [4, 8] and abnormal magnesium (Mg) metabolism may increase the duration and cost of postoperative hospitalization [15]. Thus, perioperative management of Mg is critical.

Mg^{2+} is the second most abundant cation, regulating calcium (Ca) homeostasis and acting as a cofactor for more than 300 reactions responsible for metabolism and protein and nucleotide synthesis [16]. This study examined factors contributing to post-thyroidectomy hypocalcemia, regulatory effects and mechanisms of Mg on Ca, interactions between Mg and Ca regulators such as parathyroid hormone (PTH), $1,25(\text{OH})_2\text{D}$, and underlying related molecular mechanisms.

Factors contributing to post-thyroidectomy hypocalcemia

Hypocalcemia may be asymptomatic (biochemical) or symptomatic (clinical) [9]. Asymptomatic hypocalcemia patients have serum Ca^{2+} levels lower than the normal range with no clinical symptoms, but symptomatic hypocalcemia patients have stinging pain or paresthesia, convulsions, muscle spasms, mental changes, arrhythmia and/or Chvostek's sign, Trousseau's sign, or QT interval prolongation. Symptomatic hypocalcemia patients may or may not have low serum Ca^{2+} and may require Ca and vitamin D supplementation [9]. Hypoparathyroidism is the

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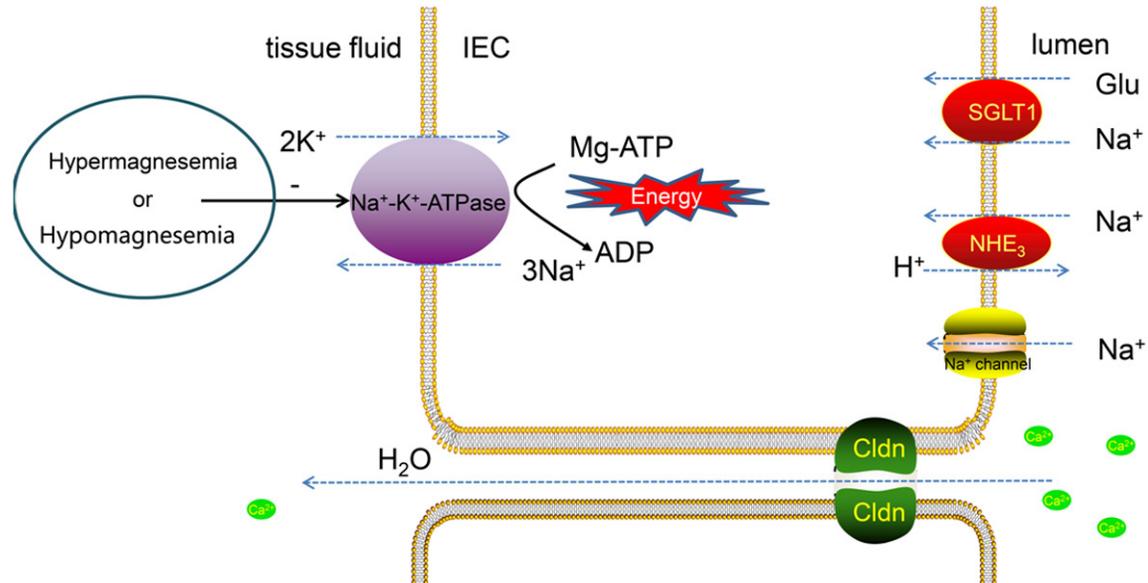


Figure 1. Involvement of magnesium in the process of Ca^{2+} absorption. Vectorial movement of Na^+ creates an osmotic gradient for water absorption from the intestine, which can create a concentration gradient to drive paracellular Ca^{2+} flux via convection/solvent drag. Mechanisms mediating Na^+ uptake can be divided into electroneutral and electrogenic transport. Electrogenic transport occurs via apical Na^+ channels expressed mainly in the distal colon and Na^+ /nutrient-linked cotransporters, especially Na^+ -dependent glucose cotransporters (SGLTs) expressed in the small intestine. Electroneutral Na^+ absorption occurs through the apically expressed Na^+/H^+ exchangers, where NHE3 appears to play a predominant role in Na^+ absorption from the small and large intestines. Na^+ efflux occurs across the basolateral membrane via the Na^+/K^+ -ATPase for both pathways. Na^+/K^+ -ATPase substrate is a complex of Mg-ATP. Hyper- and hypomagnesemia can inhibit Na^+/K^+ -ATPase activity. “-”: inhibiting.

most commonly recognized predictive factor for postoperative hypocalcemia [17-21]. Studies have reported that factors such as PTH levels in a specific time after surgery [18, 19, 21], levels of PTH decreasing between pre- and post-operative [8, 19, 20], measuring PTH and other item like blood Ca at the same time [18] could predict post-thyroidectomy hypocalcemia (sensitivity 91-100%, specificity 83-100%). However, which factor has the highest sensitivity and specificity for predicting postoperative hypocalcemia (asymptomatic or clinical hypocalcemia) remains unclear. Parathyroid gland (PG) injury, ischemia, and accidental removal are major causes of hypoparathyroidism [4, 22]. They occur typically during total thyroidectomy, removal of a large portion of the thyroid, malignant disease, a long disease course before surgery, or neck lymphadenectomies [23]. According to required time for PG function to be recovered, hypoparathyroidism has been categorized as transient or persistent. Transient hypoparathyroidism recovers in a few months (incidence 16.5-71%) [6, 7, 9], but persistent hypoparathyroidism requires more than one year for recov-

ery (incidence 0-10%) [6, 7]. Risk of transient hypoparathyroidism is greater for females, cases without using nanocarbon, PG autografts, PG accidental removal, and bilateral central compartment lymphadenectomies. Hypertension and tumors in the upper PG region of the thyroid may increase the risk of transient hypoparathyroidism becoming persistent hypoparathyroidism [24]. In addition to hypoparathyroidism, PG accidental removal or autografts (OR = 3.321), decreases in PTH exceeding 70% (OR = 6.69), thyroid malignancies (OR = 7.18), Grave's disease (OR = 2.4), and lymphadenectomies (OR = 2-5) increase the risk of postoperative hypocalcemia [5, 8, 25-27]. Other factors associated with postoperative hypocalcemia ($P < 0.05$) include toxic goiter, being female or older than 50 years-of-age, surgery lasting more than 120 minutes, and low pre-operative vitamin D [25-27].

Hypomagnesemia is also correlated with postoperative hypocalcemia ($r = 0.205$; $P = 0.022$) [14]. Mahmoud's group reported that patients with hypocalcemia on postoperative day 1 had

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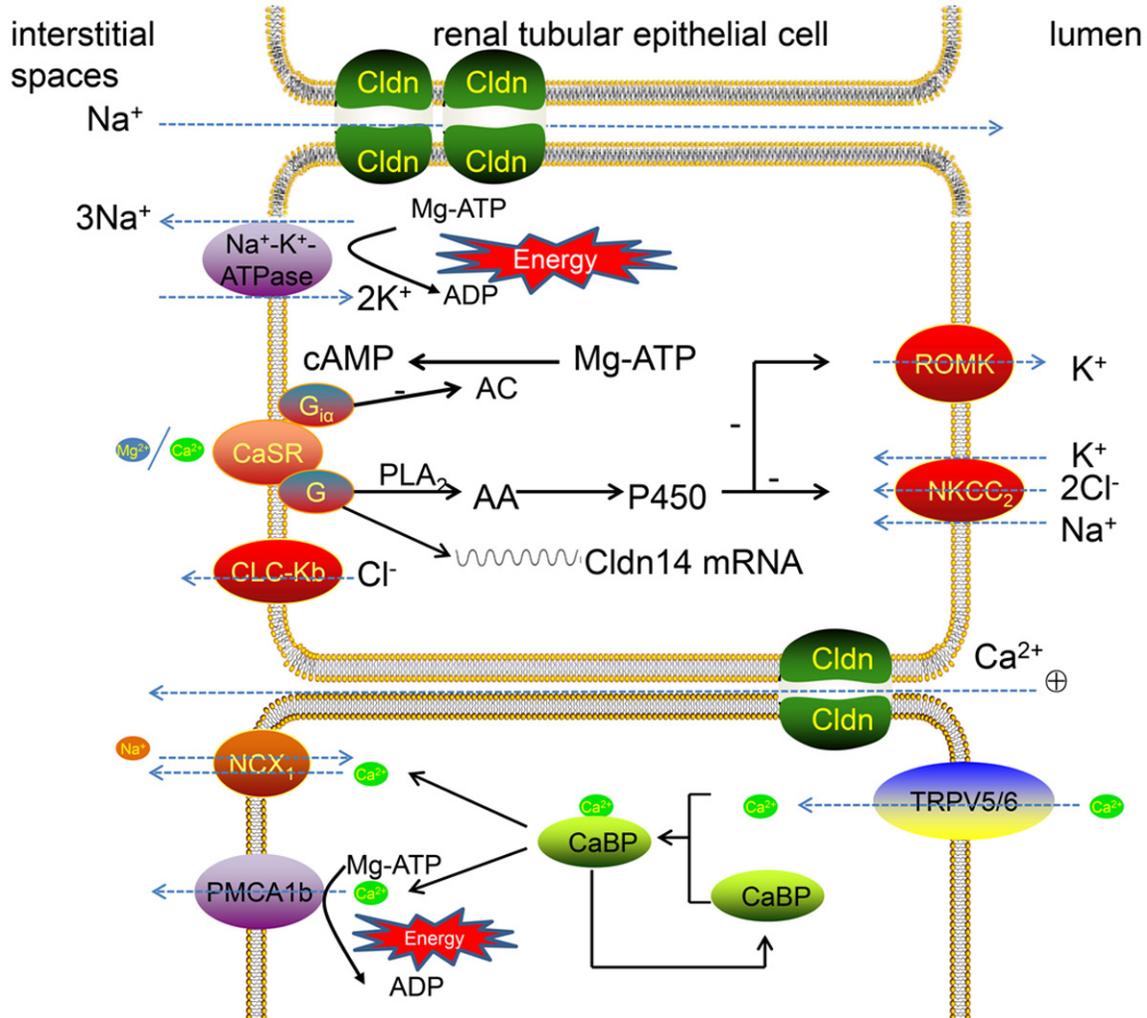


Figure 2. Participation of magnesium in Ca^{2+} reabsorption in kidney tubules. Ca^{2+} reabsorption across the proximal tubular and TAL epithelium via passive paracellular transport chiefly depends on a lumen-positive transepithelial voltage gradient acting to drive Ca^{2+} through the paracellular shunt. This lumen-positive transepithelial voltage gradient is generated by 2 interdependent mechanisms: NKCC2-dependent cotransport drives 1Na^+ , 1K^+ , and 2Cl^- ions across the apical membrane. This inward transport of monovalent ions relies on apical secretion of K^+ by renal outer medullary potassium (ROMK) channels and its subsequent recycling. K^+ efflux back into the lumen provides part of the lumen-positive potential difference. Inwardly transported Na^+ and the 2Cl^- ions exit basolaterally via the $\text{Na}^+\text{-K}^+\text{-ATPase}$ and chloride channels (CLC-Kb), respectively. Collectively, these transport processes create a lumen-positive voltage gradient of $\sim 5\text{-}10\text{ mV}$. Another mechanism is by the paracellular back flux of Na^+ which occurs when luminal Na^+ concentration is lower than that of the interstitium. This back flux of interstitial Na^+ amplifies the voltage gradient to $+30\text{ mV}$. Passive paracellular transport is regulated by CaSR. $\text{Mg}^{2+}/\text{Ca}^{2+}$ -mediated activation of the CaSR leads to reducing hormone-stimulated NaCl absorption via pertussis-toxin-sensitive inhibition of cAMP and production of arachidonic acid (AA) via stimulation of phospholipase A2 (PLA2). Cytochrome P450 (CYP450) metabolites of AA, 20-HETE, inhibits the 'loop'-diuretic-sensitive $\text{Na}^+\text{-K}^+\text{-}2\text{Cl}^-$ cotransporter in apical membranes and apical K^+ channels. Also, activation of CaSR increases expression of Cldn14 which forms an ionic barrier at the transcriptional level. In the distal nephron, Ca^{2+} is absorbed transcellularly. After entry of Ca^{2+} into the distal convoluted tubule (DCT2) and connecting tubule (CNT) through epithelial Ca^{2+} channels, TRPV5 and TRPV6, Ca^{2+} bound to calbindin diffuses to the basolateral membrane. There, Ca^{2+} is extruded via an Mg-ATP-dependent $\text{Ca}^{2+}\text{-ATPase}$ (PMCA1b) and a $\text{Na}^+\text{-Ca}^{2+}$ -exchanger (NCX1). "-": inhibiting; "⊕": higher potential.

0.125 mmol/L less Mg compared to controls with normal Ca ($P = 0.006$) [14]. Wang and colleagues suggested that postoperative Mg among postoperative hypocalcemia patients

and those with normal Ca were not statistically different ($P > 0.05$) [12], but other studies have suggested that hypomagnesemia increases incidence of postoperative hypocalcemia [4, 8,

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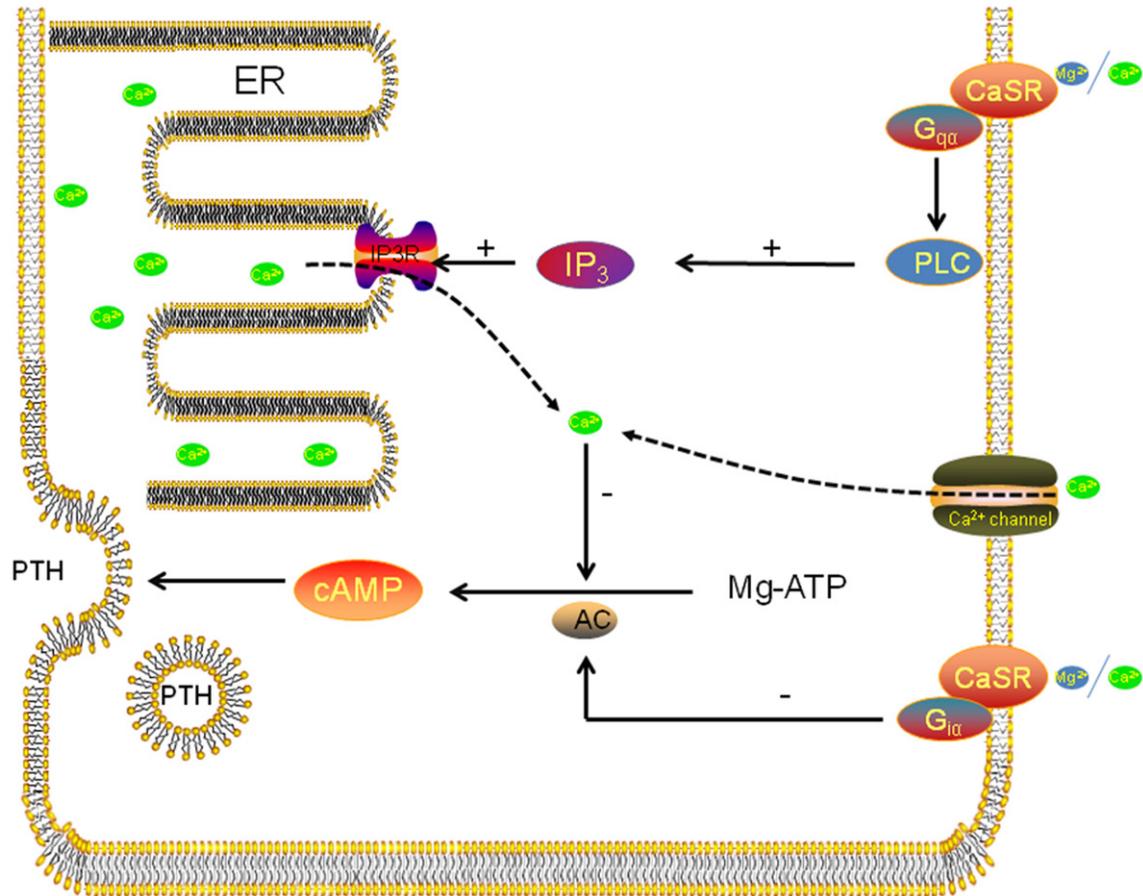


Figure 3. Signaling cascades mediated by CaSR in parathyroid chief cell. Activation of CaSR by extracellular Ca^{2+} / Mg^{2+} commonly elicits intracellular Ca^{2+} signals through interactions between the CaSR and phospholipase C (PLC), which are mediated by the $G_{q\alpha}$ or $G_{11\alpha}$ subunits of heterotrimeric G proteins. These interactions result in hydrolysis of phosphatidylinositol-4,5-bisphosphate by PLC to form inositol-1,4,5-trisphosphate (IP₃) and diacylglycerol. IP₃ binding and activating IP₃ receptors on the endoplasmic reticulum (ER) membrane elicit Ca^{2+} flux from Ca stores to the cytoplasm. Extracellular Ca^{2+} can also enter the cytoplasm via Ca channels. Increased cytosolic Ca^{2+} inhibits production of cAMP, essential for PTH secretion. CaSR also interacts with $G_{i\alpha}$ directly, which inhibits adenylate cyclase (AC) and reduces cellular cAMP. “-”: inhibiting; “+”: activating.

15]. Garrahy's group reported that asymptomatic hypocalcemia in hypomagnesemia patients was 2.65 times more frequent than in those without hypomagnesemia (RR = 2.65, 95% CI = 1.62-4.34) [4]. Luo's group identified the risk of asymptomatic hypocalcemia for hypomagnesemic patients to be 2.030 times greater than for those without hypomagnesemia (OR = 2.030, 95% CI = 1.146-3.595) [8]. Furthermore, Nellis and colleagues indicated that Mg metabolism disorders increased the risk of postoperative hypocalcemia by 11.71 times (OR = 12.71, 95% CI = 8.59-18.82) [15]. Therefore, hypomagnesemia has a substantial effect on the development and progression of postoperative hypocalcemia. Understanding how this occurs is essential.

Effects of Mg on Ca^{2+} absorption (reabsorption) and its molecular basis

Mg is a cofactor for many substrates and enzymes [16], required for absorption of Ca^{2+} in the intestines and Ca^{2+} reabsorption in renal tubules [28, 29]. Yamamoto and colleagues identified that, in hypocalcemic patients with concurrent Mg deficiency, oral Ca did not increase blood Ca levels [30]. Anast's group described a patient with hypoparathyroidism and concurrent hypomagnesemia [31] with consistently low blood Ca during 3 years of Ca treatment. After 24 hours of Mg treatment, blood Ca increased significantly and was normal 10 days later. Thus, hypomagnesemia negatively affects blood Ca. Other studies have

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indicated potential effects of Mg on absorption/reabsorption of Ca^{2+} . Kozakai's group reported that increasing Mg concentrations in sheep intestinal tracts significantly increased intestinal Ca^{2+} absorption and urinary Ca^{2+} excretion [32]. A rat study confirmed that mild Mg deficiencies significantly decreased urinary Ca^{2+} excretion [33].

Ca^{2+} may be absorbed (reabsorbed) through paracellular or transcellular pathways [34, 35]. The Na^+ - K^+ -ATPase on the basal membrane of epithelial cells transfers absorbed (reabsorbed) Na^+ to the interstitial fluid, generating an electrochemical gradient between the lumen and interstitial fluid (paracellular Ca^{2+} absorption in the intestine is facilitated by the chemical gradient, and paracellular Ca^{2+} reabsorption in renal tubules is facilitated by an electric gradient) [35] (**Figures 1 and 2**). The electrochemical gradient is the driving force for Ca^{2+} transport through paracellular pathways [36]. Na^+ - K^+ -ATPase transports ions by changing Na^+ - K^+ -ATPase conformation from E1 to E2 [37]. Binding and release between Mg and Na^+ - K^+ -ATPase facilitates transition of E1 to E2 conformations [38]. Energy required for this conformational change is provided by ATP in the form of a Mg-ATP complex that interacts with the ATPase [37]. In addition, Apell's group reported that Mg interacts with the α subunit extracellular functional domain of Na^+ - K^+ -ATPase [39]. The binding site is near the entrance of the access channel to ion-binding sites. Mg concentrations that are too high or too low reduce the affinity of Na^+ - K^+ -ATPase to Na^+/K^+ . Moreover, Mg^{2+} competitively occupies the Na^+/K^+ -binding site and reduces ion transport through the Na^+ - K^+ -ATPase.

In the thick ascending limb of Henle's loop (TAL), paracellular Ca^{2+} transport is regulated by CaSR (**Figure 2**) so antagonists of CaSR significantly increase paracellular reabsorption of Ca^{2+} in renal tubules. Efficiency of reabsorption is independent of extracellular PTH [40]. Like Ca^{2+} , Mg^{2+} also activates CaSR [41, 42]. Activation of CaSR inhibits activities of Na^+ - K^+ -2Cl⁻ symporters and potassium channels on renal tubule epithelial cell membranes, inhibiting ion reabsorption in renal tubules. Thus, decreased potential in renal tubules reduces potential-dependent Ca^{2+} reabsorption. Reduced countercurrent multiplication and water reabsorption inhibit urine concentration and

increase Ca^{2+} excretion via urine [43, 44]. Moreover, paracellular Ca^{2+} absorption (reabsorption) is regulated by ion channels formed by the claudin (Cldn) family, such as Cldn2, Cldn12, Cldn14, and Cldn16 [45]. Permeability of the ion channel is key to determining the capability of ion absorption (reabsorption) [46]. Cldn14 is commonly recognized as a component of non-selective cation barriers [47, 48]. Dimke's group reported that in TAL epithelial cells, activated CaSR increases Cldn14 mRNA expression 40 times and significantly inhibits paracellular Ca^{2+} flux [47]. In the transcellular pathway, Ca^{2+} in epithelial cells is first transported to the interstitial fluid through Ca pumps on the epithelial cell basal membrane [49]. Ca pump and Na^+ - K^+ -ATPase are both P-type pumps and require Mg as the cofactor in ion transport [50]. Differing from previous studies, Nagy's group demonstrated that Na^+ - K^+ -ATPase and Ca pump first interact with Mg and form ternary enzyme-metal-phosphate complexes to transport ions [50]. ATP provides energy for paracellular and transcellular pathways [35, 49]. Nagai and colleagues confirmed that Mg deficiency leads to low cellular ATP [51]. In addition, Mg is involved in synthesis and metabolism of PTH and $1,25(\text{OH})_2\text{D}$, which regulate Ca^{2+} absorption/reabsorption [28]. Currently, there is no molecular or cellular evidence supporting a direct effect of hypomagnesemia or hypermagnesemia on paracellular or transcellular Ca^{2+} flux. There are no data regarding Mg-ATP synthesis or the function of Na^+ - K^+ -ATPase or Ca pump in epithelial cells derived from patients with concurrent hypocalcemia and hypomagnesemia. Nevertheless, Mg is important for Ca^{2+} absorption (reabsorption). Current mechanistic studies may offer a preliminary basis for the role of hypomagnesemia in development and progression of postoperative hypocalcemia.

Mg and Ca regulators and related mechanisms

Mg not only directly participates in Ca^{2+} absorption (reabsorption) but also is directly involved in synthesis and/or secretion of Ca regulators, such as PTH and $1,25(\text{OH})_2\text{D}$. PTH increases blood Ca by mobilizing bone Ca into the blood and promoting Ca^{2+} reabsorption in distal renal tubules. PTH also activates α -hydroxylase in renal juxtaglomerular cells and converts 25-hydroxyvitamin D (25-OH-D) into $1,25(\text{OH})_2\text{D}$,

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which is the activated form, and promotes Ca^{2+} absorption in the intestines and Ca^{2+} reabsorption in renal tubules [52, 53]. Therefore, factors that regulate synthesis and/or secretion of PTH not only directly regulate function of PTH for modulating blood Ca but also control Ca homeostasis by regulating $1,25(\text{OH})_2\text{D}$ synthesis. In addition to Ca^{2+} , Mg^{2+} is a cation important to PTH synthesis and/or secretion [28, 42, 54, 55]. The role of Mg^{2+} in PTH synthesis and/or secretion is similar to the role of Ca^{2+} . It functions in a concentration-dependent manner. Both hypomagnesemia and hypermagnesemia inhibit PTH synthesis and/or secretion and Mg directly participates in synthesis of $1,25(\text{OH})_2\text{D}$.

Hypermagnesemia inhibits PTH synthesis and/or secretion

Clinical studies have shown that blood Mg is negatively correlated with blood PTH. Compared to low PTH patients, those with high PTH have significantly lower mean blood Mg [56-60]. *In vitro* studies have revealed that increased Mg inhibits PTH synthesis and/or secretion in PG cells [61-64], perhaps by extracellular Mg^{2+} binding with extracellular CaSR at the cation binding site, mimicking the effects of Ca^{2+} [41, 42]. Activated CaSR interacts with G protein which couples with its functional domain and activates phospholipase C (PLC). Cytoplasmic Ca^{2+} is then increased via the PLC-IP3 pathway [65, 66]. In addition, extracellular Ca^{2+} influxes through voltage-gated channels on cell membranes, increasing intracellular Ca^{2+} [67, 68]. Cytoplasmic Ca^{2+} inhibits adenylate cyclase (AC) activity through the G protein subunit Gi , which subsequently decreases intracellular cyclic adenosine monophosphate (cAMP) and inhibits synthesis and/secretion of PTH [41] (**Figure 3**). CaSR inhibition attenuates the inhibitory effects of Mg^{2+} on synthesis and/secretion of PTH [69]. Thus, inhibiting the affinity of IP3 to its receptor, AC activity, or cAMP synthesis decreases synthesis and/or secretion of PTH in PG cells. Furthermore, compared with low Mg^{2+} at 0.5 mM, high Mg^{2+} at 2.0 mM increased expression of CaSR, vitamin D receptor (VDR), and fibroblast growth factor receptor1 (FGFR1) by 2.2-3.9 fold in PG cells. Interactions of these three receptors with their ligands inhibited secretion of PTH [64]. Therefore, Mg^{2+} , at high concentrations, reduces synthesis and/secretion of PTH through direct and indirect mechanisms.

CaSR mediates the inhibitory effects of Mg^{2+} and Ca^{2+} on synthesis and/or secretion of PTH. Its affinity to Mg^{2+} is significantly lower than for Ca^{2+} . Mg^{2+} concentrations required to activate CaSR are 3 times greater than Ca^{2+} concentrations required to activate CaSR [41]. Moreover, the regulatory effects of Mg^{2+} on PTH are extracellular Ca^{2+} concentration-dependent [54, 63, 64, 70], although the exact correlation is not known. Brown's group reported that Ca^{2+} enhances inhibitory effects of Mg^{2+} on PTH secretion [70]. When extracellular Ca^{2+} concentrations were 0, 0.5 mM, and 1 mM, Mg^{2+} at 10-15 mM, 3 mM, and 1.8 mM, respectively, reduced secretion of PTH to 5% of the maximum PTH secretion. Rodriguez-Ortiz and colleagues reported that with increased Ca^{2+} (from 0.8 mM to 1.5 mM), the inhibitory effects of Mg^{2+} at 2.0 mM on PTH secretion were attenuated but the maximum inhibitory effects of Mg^{2+} on PTH secretion occurred at Ca^{2+} of 1.0 mM [63]. Thus, while Ca^{2+} and Mg^{2+} activate CaSR and inhibit synthesis and/or secretion of PTH, their inhibitory effects are not additive. The mechanisms are not clear but potential mechanisms include the following: Ca^{2+} influx through Ca^{2+} channel, both Ca^{2+} and Mg^{2+} activating CaSR, and regulation of the affinity of CaSR to $\text{Ca}^{2+}/\text{Mg}^{2+}$ by extracellular $\text{Mg}^{2+}/\text{Ca}^{2+}$ [70].

Regulatory role of hypomagnesemia in PTH synthesis and/or secretion

A survey mentioned in a review demonstrated that ~48% of North Americans took in less Mg than required in 2011-2012, accounting for 89% of teenage females, 55-58% of people aged 51-70 years, and 70-80% of individuals aged over 71 years old [29]. In pigs with Mg deficiency, Mg in soft tissues, red blood cells, and bones are significantly reduced. This has been noted in humans, too [29]. With insufficient Mg intake, the body may show normal blood Mg levels and be asymptomatic but Mg in soft tissues and bones may significantly decrease, causing chronic latent Mg deficiency (CLMD) [16]. Hypomagnesemia occurs in 10-72% of post-thyroidectomy patients [4, 8, 11-13]. The cause for this is unclear but may be related to CLMD. In addition, Wilson's group reported that postoperative hypomagnesemia may be related to other conditions, including blood dilution and renal Mg^{2+} excretion elevation caused by intravenous fluid and decreased

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Mg²⁺ intestinal absorption and Mg²⁺ renal reabsorption caused by postoperative hypoparathyroidism [11].

Another study suggested that patients with hypomagnesemia had significantly lower PTH compared to controls with normal blood Mg [71]. Secondary hyperparathyroidism (SHPT) is a common complication in patients with chronic kidney disease [72] and hypocalcemia promotes the development and progression of SHPT by increasing synthesis and/or secretion of PTH and hyperproliferation of parathyroid cells [73]. However, if a patient also has hypomagnesemia, hypocalcemia does not elevate PTH [74] and levels of PTH may be even lower [31, 75]. Treatment with Mg for hypomagnesemia and low PTH rapidly restores serum PTH and Ca²⁺ to normal ranges [31]. Post-thyroidectomy hypomagnesemia is also correlated with low PTH [12]. Thus, Mg deficiency may lead to PTH synthesis and/or secretion abnormalities. Mennes and colleagues reported that PTH levels increased 2 fold in hypomagnesemia patients within 2 minutes of intravenous administration of Mg [74]. Therefore, hypomagnesemia-induced PG abnormalities may be a secretion abnormality. An *in vitro* study validated that Mg²⁺ deficiency inhibits function of the PG: PTH secretion was < 50% of the maximum when Mg²⁺ was 0.1 mM [69].

Hypomagnesemia may inhibit PTH synthesis and/or secretion through the following mechanisms: 1) Mg participates in synthesis of the second messenger cAMP. The substrate of AC is the Mg-ATP complex [76]. Mg²⁺ deficiency limits Mg-ATP to cAMP conversion catalyzed by AC. Rude's group identified that increased Mg-ATP concentrations (from 0.2 to 1.5 mM) significantly elevated cAMP [77]; 2) Mg participates in activation of AC [76]. Secretion of PTH is regulated by the Ca-CaSR signaling axis. CaSR is a G protein (Gs and Gi)-coupled receptor and Gs activates AC. Under basal conditions, Gs form homodimers through its β subunit to inhibit its activity. Upon stimulation (such as activation of CaSR), Gs $\alpha\beta$ interacts with GTP γ to form a complex, which releases its β subunit in the presence of Mg, leaving free and active Gs α that activates AC and promotes generation of cAMP. With Mg deficiency, activation of Gs protein is blocked and cAMP generation decreases [76]; 3) Mg decreases affinity of IP₃ to its receptor and inhibits IP₃-induced Ca²⁺ release from cal-

cium stores [78]; 4) Mg²⁺ deficiency leads to PTH resistance. Patients with hypomagnesemia have less urine cAMP, compared to healthy controls [62]. Intravenous treatment with PG extracts alone did not elevate urine cAMP but intravenous treatment with PG extracts after 4 days of Mg therapy significantly elevated urine cAMP [62]. Fatemi's group reported that patients with hypomagnesemia had significantly lower 1,25(OH)₂D, compared with controls, and PTH supplementation for patients with hypomagnesemia produced smaller elevations in 1,25(OH)₂D than for patients without hypomagnesemia [54]. Thus, hypomagnesemia may lead to renal PTH resistance. This may be caused by inhibiting PTH function on target cells which depends on catalysis of Mg-ATP through AC [79]. With Mg²⁺ deficiencies, the Mg-ATP complex is reduced [79] and AC activity is inhibited [76]. However, the blood Mg threshold leading to decreased intracellular Mg²⁺ and functional abnormalities of intracellular signaling molecules remains unclear.

Mg and 1,25(OH)₂D interactions and underlying mechanisms

1,25(OH)₂D promotes absorption (reabsorption) of Ca²⁺ [28]. Thus, regulating 1,25(OH)₂D synthesis can indirectly affect absorption (reabsorption) of Ca²⁺ and Ca homeostasis. Approximately 29.9-85% of thyroidectomy patients have low 25-OH-D prior to surgery [80-82]. Al-Khatib and colleagues reported that 43.6% of patients with low serum 25-OH-D developed postoperative hypocalcemia, but only 3.1% of patients with normal 25-OH-D did so (n = 213) [81]. Lee's group reported that, although 25-OH-D in postoperative hypocalcemia patients and normal Ca controls were not significantly different (P = 0.94), patients with low 25-OH-D were more likely to develop postoperative hypocalcemia (65.9% vs. 51.6%) [82]. In addition, a survey of adolescents from Iran revealed a correlation between blood Mg and serum 25-OH-D (r = 0.276, P = 0.0001) [83]. Increasing Mg intake decreased the risk of vitamin D deficiency, significantly [84]. Thus, Mg is key to synthesis and metabolism of 25-OH-D. Previous studies have shown that vitamin D is synthesized in the skin and transported to the liver after binding with vitamin D binding protein (VDBP). Vitamin D is then catalyzed by 25-hydroxylase and converted to 25-OH-D, which is subsequently transported to the kid-

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ney after binding with VDBP and catalyzed by 1- α -hydroxylase to 1,25(OH)₂D. VDBP, 25-hydroxylase, and 1- α -hydroxylase require Mg as a cofactor. With Mg deficiencies, these proteins are deactivated. Transport and hydroxylation of vitamin D are inhibited, consequently inhibiting synthesis of 25-OH-D and 1,25(OH)₂D [85-87]. Moreover, 1,25(OH)₂D also promotes intestinal absorption of Mg²⁺ [88, 89]. Mg deficiency inhibits 1,25(OH)₂D synthesis, which reduces intestinal absorption of 1,25(OH)₂D. Therefore, Mg deficiencies and 1,25(OH)₂D synthetic issues exacerbate each other. Increasing blood Mg promotes synthesis of 25-OH-D and 1,25(OH)₂D, increases activity of VDBP, and subsequently enhances transport of 1,25(OH)₂D to target organs [90].

Clinical management of post-thyroidectomy hypocalcemia concurrent with hypomagnesemia

Ca should be monitored with PTH, constantly, after thyroidectomies. For those that are symptomatic or asymptomatic but have persistent hypocalcemia, Ca and vitamin D supplementation should be considered [91]. If corrective Ca is < 1.8 mmol/L (normal range 2.2-2.6 mmol/L), Ca gluconate should be given intravenously (iv) until serum Ca normalizes. For those with mild but symptomatic hypocalcemia (1.8-2.2 mmol/L), low dose oral Ca and vitamin D is worth consideration. For patients with persistent hypoparathyroidism, treatment should last more than 6 months to control symptoms and maintain blood Ca [92].

Other studies concerning postoperative hypocalcemia have shown that symptoms such as convulsions and muscle spasms are related to both hypocalcemia and hypomagnesemia [11]. Compared with patients with only hypocalcemia, those with hypomagnesemia were more likely to have symptoms (83% vs. 30%) [11]. Bilezikian's group indicated that in patients with symptomatic hypocalcemia that required Ca treatment, hypomagnesemia should be considered [93]. Hypomagnesemia may increase postoperative hypocalcemia by modulating absorption (reabsorption) of Ca²⁺, PTH synthesis and/or secretion, sensitivity to PTH in target organs, and synthesis of 1,25(OH)₂D. Furthermore, Mg²⁺ participates in many ATP-related reactions. It is involved in various physiological functions, such as neuromuscular

excitability, cell membrane permeability, ion channel modulation, mitochondrial function, cell proliferation, and apoptosis [94]. When Mg is low (0.5 mmol/L < [Mg²⁺] < 0.66 mmol/L), patients may be asymptomatic. When Mg is severely low (< 0.5 mmol/L), several hypocalcemia-like symptoms may manifest [94]. Persistent hypomagnesemia may also be related to glucose metabolism disorders, hypertension, atherosclerosis, osteoporosis, and asthma [94]. In addition, Nellis and colleagues revealed that Mg metabolism disorders correlate with duration and cost of post-thyroidectomy hospitalization ($r = 0.6306$, $P < 0.001$). Compared to patients with hypocalcemia, patients with both hypocalcemia and Mg metabolism disorders required longer hospitalizations and incurred more treatment costs (0.8 days vs. 2.3 days; \$1,265 vs. \$3,121). Anast's group suggested that Ca treatment did not restore blood Ca level in patients with postoperative hypocalcemia and hypomagnesemia, but Ca and Mg treatment rapidly restored serum Ca²⁺ within 24 hours [31]. Therefore, for patients with post-thyroidectomy symptomatic hypocalcemia, blood Ca, Mg, and PTH should be monitored [11] and hypomagnesemia should be treated [95] to recover Ca and PTH [31, 96], reducing symptoms [11] and duration and cost of hospitalization [15]. Shoback indicated that blood Mg does not accurately reflect body Mg stores [96]. Therefore, for patients with hypocalcemia and concurrent low blood Mg (below the normal range or near the lower limit of normal), Mg treatment should be considered as well as regular Mg tests to monitor Mg deficiencies [96]. Patients with low blood Mg may be given oral Mg. Those with severe Mg deficiencies may require intravenous treatment [96]. Drip speed should be controlled to prevent excessive urinary loss of Ca²⁺ and Mg²⁺.

Conclusion

Postoperative hypocalcemia is a complication of thyroidectomies. Low Mg contributes to its development and progression [4, 56-59]. Mg likely regulates absorption (reabsorption) of Ca²⁺, modulates PTH synthesis and/or secretion, and participates in the generation of PTH resistance by activating CaSR and functioning as an intermediate signal molecule in the Ca-CaSR axis. Mg also participates in synthesis of 1,25(OH)₂D. After thyroidectomies, blood PTH, Ca, and Mg should be monitored. Hy-

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pocalcemic patients should be treated with Ca and vitamin D (oral or iv) based on the severity of deficiency. Patients symptomatic with low Mg or hypomagnesemia should be treated with Mg. Blood Mg should be monitored as well.

Acknowledgements

The authors would like to acknowledge the National Natural Science Foundation (NSFC) of China for funding (No. 81672885, 81372860).

Disclosure of conflict of interest

None.

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