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# Clinically Relevant Interactions between Hormones and Magnesium Metabolism – A Review

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## Zusammenfassung

In Untersuchungen an gesunden Probanden fanden sich tageszeitliche Schwankungen der Magnesium (Mg)-Gehalte von Serum/Plasma, Schweiß, Frauenmilch und Urin mit Maxima am Morgen und Minima um Mitternacht. Aufgrund enger Verknüpfungen mit dem Calcium (Ca)- und Kalium (K)-Haushalt und Wechselwirkungen dieser Kationen mit der therapeutischen Wirksamkeit von Lithium könnten diese Daten für psychiatrische Patienten relevant werden. Geringe Anstiege des Serum-Mg während der Wintermonate und eine Abnahme im Sommer sind komplexer Ursache. Die weiblichen Sexualhormone beeinflussen den Mg-Haushalt tiefgreifend. Während der Follikel-, besonders aber während der Lutealphase fallen die Serum-Mg-Spiegel ab und steigen während der Menses an. Ostradiol/Progesteron fördern die Einlagerung von Mg in das Skelett; deshalb sind die Serumgehalte unter Hormonbehandlung (hormonelle Kontrazeption, Osteoporosetherapie) erniedrigt – wie auch bei geschlechtsreifen Frauen im Vergleich zu gleichaltrigen Männern. Es sind einige Wechselwirkungen zwischen den Hormonen des Ca-Haushalts und dem Mg-Metabolismus bekannt. Ein kurzzeitiges alimentäres Mg-Defizit kann mit einer Erhöhung von PTH und unveränderten 1,25-$(OH)_2$-Vitamin D und Serum-Ca-Spiegeln, aber auch mit einer Abnahme von PTH und von 1,25-$(OH)_2$-Vitamin D sowie einer Hypokalziämie einhergehen. Ein chronisches Mg-Defizit ist häufig assoziiert mit einer Ca-resistenten, hypomagnesämischen Hypokalziämie und vermindertem PTH. Zu beachten ist, daß bei hypoparathyroiden Patienten die Wirksmakeit von Vitamin-D-Derivaten durch Mg-Gaben auch unabhängig von PTH wieder normalisiert werden kann. Da Mg für die Funktion der Adenylatcyclase benötigt wird (Parathyreoidea, Niere, Skelett), könnte der zugrundeliegende Mechanismus eine verminderte Bildung von cAMP sein. Während Mg-Infusionen ist bei Freiwilligen mit ausgeglichener Mg-Bilanz die PTH-Sekretion gehemmt; liegt ein Mg-Mangel vor, so wird die PTH-Sekretion erhöht. Bei Mg-verarmten Probanden war die basale und die durch Angiotensin-II stimulierte Aldosteronsekretion höher als bei

## Summary

Data obtained in volunteers point to diurnal variations in magnesium (Mg) concentrations in plasma/serum, sweat, breast milk and urine with peak times in the morning and a nocturnal minimum. Since Mg may modulate calcium (Ca) and potassium (K) metabolism and since these cations have been related to the therapeutic action of lithium, these data may be relevant for psychiatric patients. Small increases in serum Mg during winter and decreases during summer are probably complex in nature. Female sex hormones profoundly affect Mg metabolism. Plasma Mg decreases during the follicular, and especially the ovulatory phase of the menstrual cycle and increases during menses. Oestradiol/progesteron favour skeletal Mg uptake; accordingly serum Mg levels are lowered during homonal treatment (contraception, osteoporosis therapy) and in fertile women compared to age-matched males. There are close interrelations between Ca-regulating hormones and Mg metabolism. Short-term Mg deficiency may be associated with increased PTH and unaltered levels of 1,25-$(OH)_2$ vitamin D and serum Ca, or with decreased concentrations of PTH, 1,25-$(OH)_2$ vitamin D and serum Ca. Long-term Mg deficiency is frequently combined with (Ca-resistent) hypomagnesemic hypocalcemia and decreased PTH levels. However in hypoparathyroid patients, Mg may restore the calcemic response to vitamin D compounds independently of PTH. Since Mg is required for adenylate cyclase activity (parathyroid gland, kidney, bones) defective cAMP generation may be the common underlying mechanism. During Mg i.v. infusions, PTH secretion is depressed in Mg-sufficient volunteers and increased in Mg-deficient subjects. In Mg-deficient volunteers basal and angiotensin II-stimulated aldosterone levels were higher than in Mg-sufficient controls. On Mg i.v. infusions, plasma renin concentrations are increased after 60 minutes due to simultaneously released prostaglandins. After 3 hours, aldosterone levels were significantly decreased, perhaps mediated through Mg-induced intracellular Ca mobilization. Overactivation of the renin-angiotensin-aldosterone system in patients with heart failure was associated with pronounced hypo-

## Résumé

Lors de recherches chez des probandes en bonne santé on trouvait des fluctuations – toujours dépendantes de l'heure du jour – du taux de magnésium (Mg) dans le sérum/plasma, la sueur, le lait maternel et l'urine, avec des maxima les matins et des minima à minuit. À cause des tachements étroits avec le métabolisme du calcium (Ca) et le potassium (K), ainsi qu' à cause des corrélations de ces cations avec l'effectivité thérapeutique du lithium, ces donnés pourraient devenir relevantes pour les patients psychiatriques. Il y a des augmentations insignifiantes du taux de sérum-Mg pendant les mois d'hiver et une diminution en été, qui ont probablement une raison complexe naturelle. Les hormones sexuelles féminines exercent une influence profonde sur le métabolisme du Mg-pendant la phase folliculaire, mais surtout aussi pendant la phase ovulatoire les taux du Plasma Mg sont diminué, tandis qu'ils sont augmenté pendant la menstruation. L'ostradiole et le progestérone favorisent la mise en dépôt du Mg dans le squelette; c'est pourquoi les taux de sérum-Mg sont diminués pendant le traitement hormonale (contraception, thérapie ostéo-porotique), ainsi que chez les femmes fertiles, en comparaison des hommes du même âge. On connait quelques corrélations entre les hormones du taux de Ca et le métabolisme du Mg. On peut associer une manque alimentaire de Mg de peu de durée avec une augmentation du PTH et des taux inchangés de vitamine D 1,25-$(OH)_2$ et de sérum-Ca, mais aussi avec une diminution de PTH et de vitamine D 1,25-$(OH)_2$ et une hypocalcémie. On associe aussi une manque de Mg chronique avec une hypocalcémie hypomagnésiemme résistente au Ca avec un taux de PTH réduite. Il faut pourtant noter que – dans le cas des patients hyperparathyroïdes – le Mg pourrait normaliser la réponse calcémique aux complexes de vitamine D, indépendent du PTH. Etant donné que pour le fonctionnement de l'adenylata cyclase (parathyroïde, les reins, le squelette) le Mg est nécessaire, le mécanisme à la base pourrait être une formation diminuée de cAMP. Pendant les infusions de Mg i.v. la sécrétion de PTH est réduite chez les volontés, tandis que chez les volontés, qui souffraient d'une carence en Mg, la sécré-

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Kontrollen. Unter einer Mg-Infusion war das Plasma-Renin nach 60 Minuten aufgrund einer Freisetzung von Prostaglandinen erhöht. Nach 180 Minuten sank Aldosteron ab, möglicherweise aufgrund einer intrazellulären Ca-Mobilisierung. Bei Patienten mit Herzinsuffizienz war eine Überaktivierung des Renin-Angiotensin-Aldosteron-Systems mit einer ausgeprägten Hypomagnesämie assoziiert; hier hatte hochdosiertes Captopril einen moderaten Mg-sparenden Effekt. Die vorgestellten Befunde zeigen die Notwendigkeit auf, Wechselwirkungen zwischen Hormonen und dem Mg-Haushalt mehr Aufmerksamkeit in der Klinik zu zollen.

magnesemia. High-dosed captopril has a moderate Mg-sparing effect. These data point to the necessity to pay more attention to interactions between hormones and Mg metabolism in clinical medicine.

tion de PTH est augmentée. Les probandes souffrant d'une carence en Mg montraient des sécretions d'aldostérone basal et stimulé par l'angiotensine-II plus élevées que les groupes de contrôle. Pendant des infusions de Mg i.v. les concentrations de plasma rénine étaient élevées après 60 minutes, due à une libération des prostaglandines simultanée. Après trois heures, le taux d'aldostérone diminuait clairement, possiblement à cause d'une mobilisation intracellulaire de Ca. On associait une suractivité du système rénin-angiotensine-aldostérone, chez les patients souffrant d'une insuffisance cardiaque, avec une hypomagnésiémie prononcée. Dans ce cas que du Captopril à haut dosage a un effet modéré réducteur sur le Mg. Les donnés présentées démonstrent la necessité de porter plus d'attention sur les interactions entre les hormones et le métabolisme de Mg dans les cliniques.

## 1. Introduction

Magnesium (Mg) metabolism can be compared to an open three-compartment model with three main variables, namely: invasion (enteral absorption), distribution into bone and tissue compartments, and evasion (mainly renal excretion) [24]. These processes could be under hormonal control similar to the metabolism of calcium (Ca), sodium (Na) and potassium (K). However, smaller fluctuations of electrolytes are difficult to detect in biological fluids since no steady-state conditions are physiologically given. In addition, disturbances of Mg metabolism are obligatorily associated with secondary electrolyte alterations (Ca, Na, K) and vice-versa, which also stimulate hormonal control. Hence, data obtained in healthy volunteers, who may be rendered Mg-deficient or hypermagnesemic or be treated with hormones, are generally complex and therefore difficult to analyze. For patients this is true to an even larger extent. Therefore this review will concentrate on data obtained from healthy persons under physiological conditions and also with iatrogenic Mg deficiency and hypermagnesemia.

## 2. Diurnal variations and the effect of season, age and sex

Only few data have been published so far in the literature concerning the

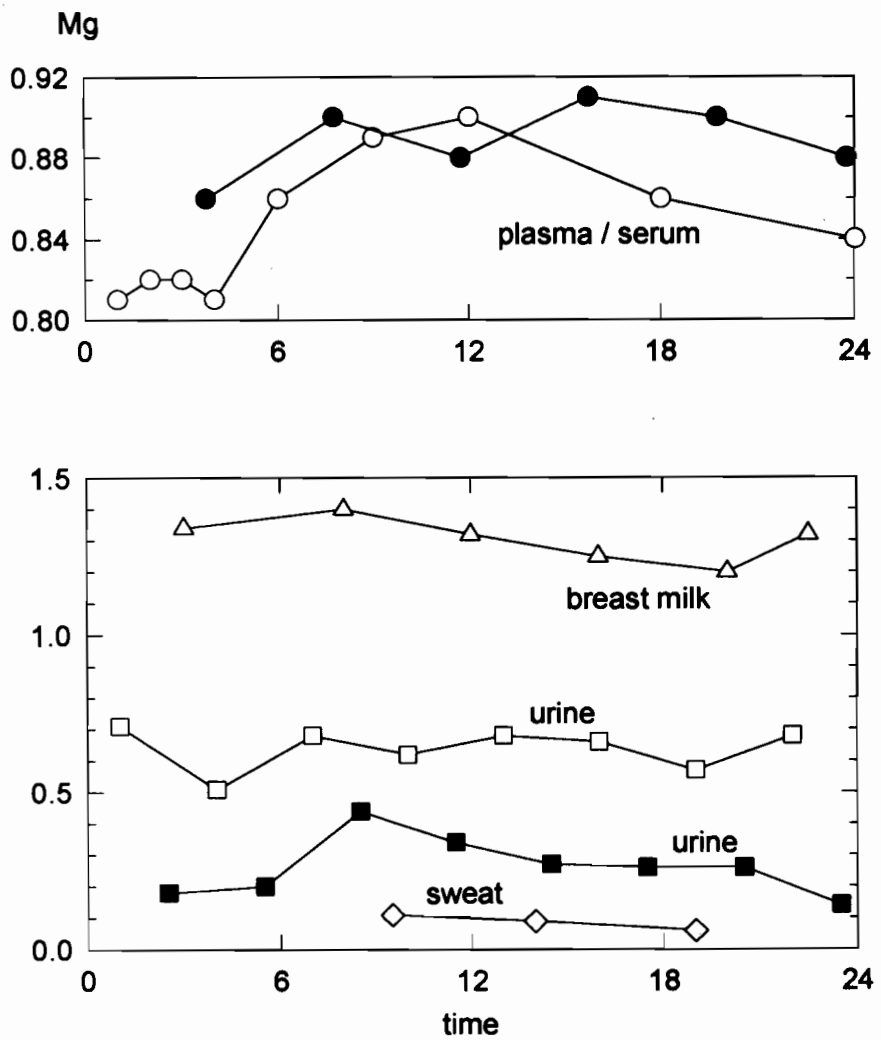


Fig. 1: Diurnal variations in magnesium concentrations in biological fluids (mmol/l); upper panel: plasma/serum [44, 12]; lower panel: breast milk [19] urine: mmol/mmol creatinine [21] resp. mmol/3 h [8], sweat [5].

behaviour of Mg levels in biological fluids during 24 hours. Generally, the volunteers under study had been fasted 10–12 hours prior in order to exclude effects of food-borne Mg. However, fasting is neither inert with respect to hormonal regulation. It should also be noted that the data stem from different populations under study. From fig. 1 it can be concluded that plasma/serum Mg [12, 44] as well as Mg levels of breast milk [19] and sweat [5] exhibit peak concentrations in the morning and lowest levels around midnight. Mg excretion also revealed an acrophase during the day and a nadir during 12 p.m. to 4 a.m. in two independent studies [21, 8]. However, *Kanabrocki* et al. [18] were not able to demonstrate a significant circadian rhythm in not fasted male volunteers. The suggested parallel course lets assume an efficient regulation of plasma Mg by the kidneys rather than an effect of urinary Mg excretion, respectively Mg retention, on plasma Mg. The hypothalamic-adrenal system might be involved, but nighttime renal conservation of Mg may also be due to increased levels of parathyroid hormone (PTH) since peak concentrations of PTH occur between 1 a.m. and 4 a.m. [21]. No data obtained in patients were found in the literature. This is the more surprising since changes in Mg, Ca and K metabolism have been related to circadian rhythms in several species and to the therapeutic action of lithium in psychiatric patients [20]. In addition to diurnal variations, slight seasonal effects on plasma Mg have been reported with somewhat higher levels during winter time and lower concentrations during summer [33, 42]. It is unknown whether or not hormones are involved. The same is true for the effect of age (fig. 2). There is no doubt that female sex hormones significantly affect Mg metabolism. *Deuster* et al. [9] have followed up plasma Mg levels during the menstrual cycle and detected lowest concentrations during the ovulatory phase and peak Mg levels during the menses (see fig. 2). In a large epidemiological study on a white US population *Lowenstein* et al. [23] reported lower serum Mg of women aged 20 to 35 years in comparison to males; this effect disappeared at higher age. Nearly identical curves were determined in plasma and in erythrocytes by *Gueux* et al. [16] studying a French population (see fig. 2). In addition, serum Mg levels of women taking hormonal contraceptives were slightly, but statistically significantly lower than in age-matched controls [43], and *Schlemmer* et al. [34] reported decreased urinary Mg excretion of postmenopausal women treated with oestrogens and cyclically with gestagens (fig. 3). Hence, there is no doubt that female sex hormones favour Mg uptake into bone within the process of mineralization. *Seelig* [35] has stressed that this may represent a situation with increased need for Mg to compensate for hypomagnesemia. Hypomagnesemia which frequently develops during the second half of pregnancy is probably different in origin and may be caused by increased urinary Mg losses, as proposed by *Spätling* et al. [41].

## 3. Calcium-regulating hormones and Mg deficiency

Calcium metabolism is sensitively controlled by several hormones. A decrease of plasma $Ca^{2+}$ is acutely corrected by the secretion of parathyroid hormone (PTH), mainly by mobilizing $Ca^{2+}$ from bone, by reducing its renal excretion and by increasing the urinary

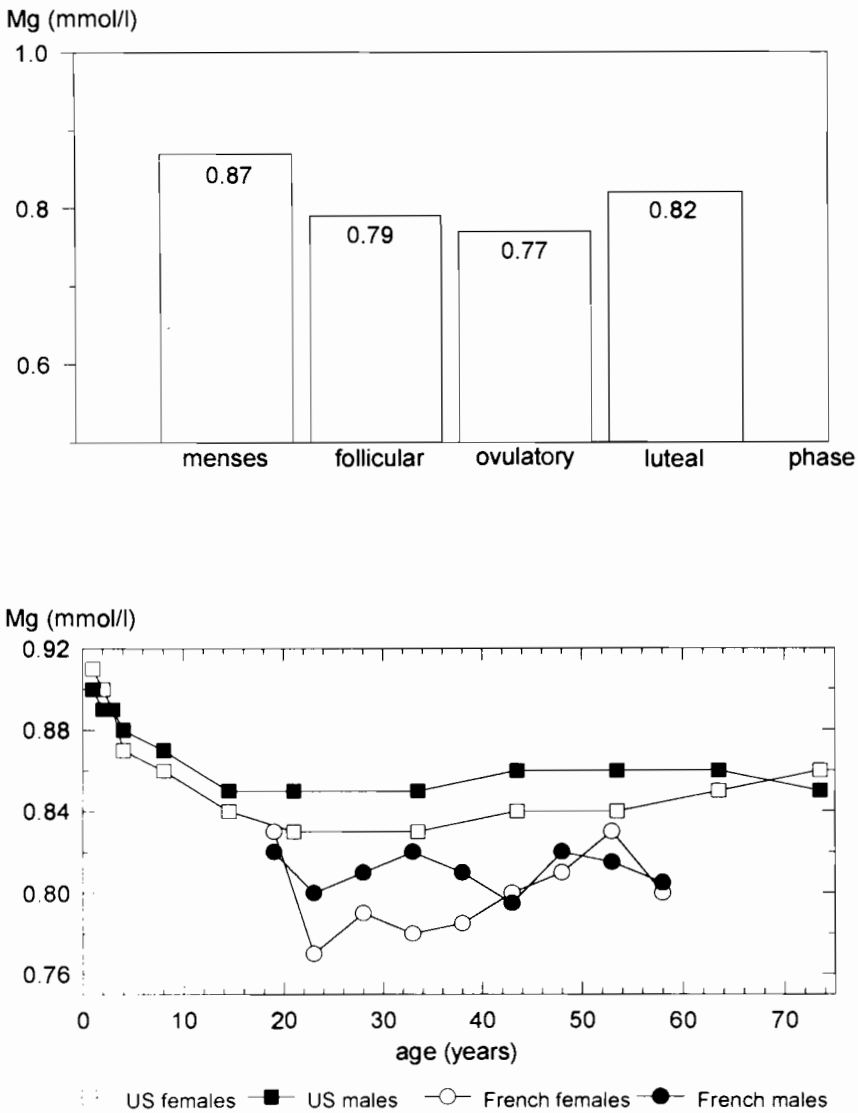


Fig. 2: Mean serum/plasma Mg levels (mmol/l) in women during the menstrual cycle [9], and the influence of age and sex [23, 16].

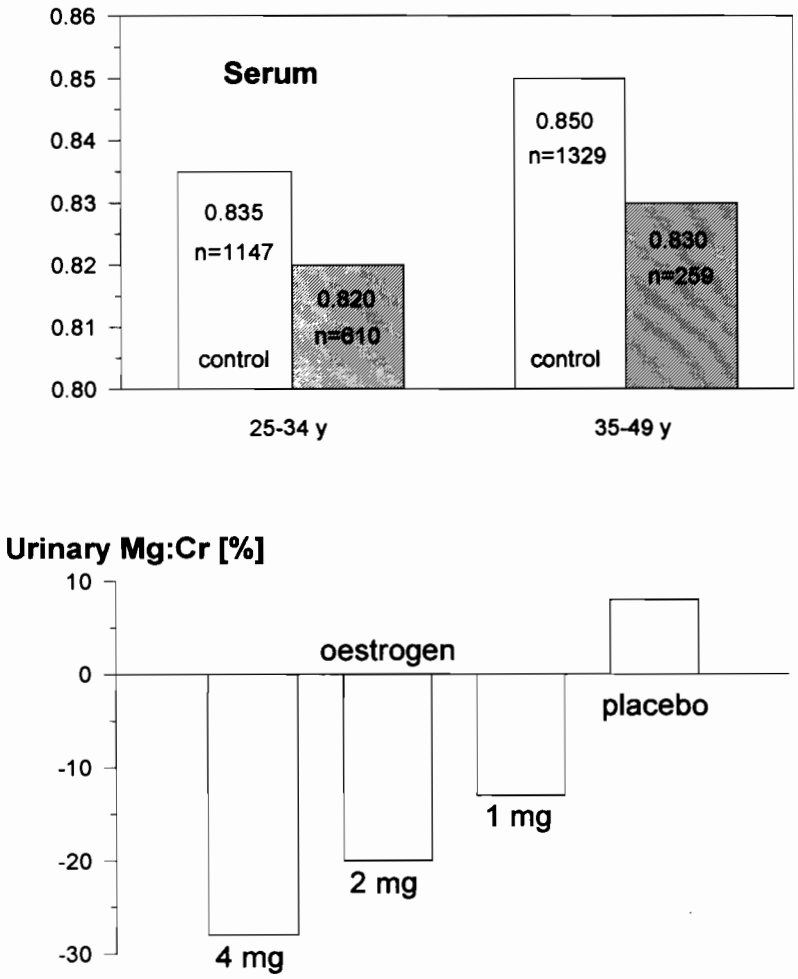


Fig. 3: The effect of hormonal contraceptives (upper panel [43]) and hormonal treatment with oestrogen/gestagen [34] on serum Mg, resp. urinary Mg excretion.

excretion of phosphate. The physiological antagonist of PTH is calcitonin at the level of the skeleton (with synergistic renal effects). Long-term effects are mainly mediated by vitamin D, respectively by its most active metabolite, 1,25-$(OH)_2$-vitamin D. 25-(OH)-vitamin D is built in the liver; then renal 1 α-hydroxylase converts it to 1,25-$(OH)_2$-vitamin D. PTH is a trophic factor for this renal enzyme being Mg-(resp. cAMP-)dependent in addition. Vitamin D favours the enteral absorption of Ca and phosphate and decreases renal Ca excretion [27]. Close, but complex and frequently inconsistent interrelationships between Mg and Ca are known since approximately 75 years. Human studies have shown that $Mg^{2+}$ may mimic the actions of $Ca^{2+}$, but may also be its natural antagonist. *Levine* and *Coburn* [22] have apostrophized this situation by choosing the title "Magnesium, the Mimic/Antagonist of Calcium" for their classical review article. Let us first discuss what happens during iatrogenic Mg deficiency. Considerable problems may arise when dietary daily Mg uptake shall be reduced to around 0.5 mmol (12 mg). *Shils* [38] chose a diet rich in cornstarch, casein and dextrose. Similarly the liquid diet used by *Rude* and coworkers contained as macronutrients 420 g of carbohydrate (corn syrup and sucrose), 12 g of fat (Lipomus®) and 81 g of calcium sodium caseinate together with micronutrients (vitamins and minerals) [31]. In the studies of *Rude* [30], *Ryzen* et al. [31], *Fatemi* et al. [14] and *Nadler* et al. [26] groups of 6 to 26 volunteers received the liquid diet during 21 days. Serum Mg decreased by 21% to 32% and urinary Mg excretion was drastically reduced. On the average, no statistically significant hypocalcemia developed and serum K, Na and P levels remained within the normal range. However, already in his earlier studies *Rude* [30] noted an unexplainable different reaction of PTH levels to Mg deficieny. There was a marked increase of more than 20% in half of the volunteers, whereas the remainder did not react. This phenomenon was studied in detail by *Fatemi* et al. [14]:

Of totally 26 volunteers, 23% exhibited an increase of immunoreactive PTH by 68% on the average; in this group serum Ca remained unalterated and 1,25-$(OH)_2$-vitamin D levels only insignificantly decreased by 9%. However, in 46% of the volunteers PTH levels decreased by 35%, as well as their serum Ca by 3% and their 1,25-$(OH)_2$-vitamin D by 29.3%. In the remainder (9%), PTH levels and the other parameters remained unchanged. These data of short-term studies point already to close interrelations between Mg and Ca metabolism and to compensatory hormonal regulation with considerable interindividual variation. In fact, in the long-term studies of *Shils* [38] the Mg-deficient diet was applied up to 117 days and serum Mg decreased by 79%. 6 of 7 volunteers developed pronounced hypocalcemia averaging to −32%, serum K and P levels declined by −37% and 20%, respectively, and metabolic alkalosis was present, in addition. Although not measured, it can be assumed that the levels of PTH and 1,25-$(OH)_2$-vitamin D had also declined under these drastic conditions. From these data it becomes overt that the manifestation of Mg deficiency-induced disturbances of Ca metabolism depends on the degree and duration of the Mg deficit, and perhaps also on (still unknown) individual factors. This is confirmed in clinical studies. For example, *Schimatschek* et al. [32] studying 1458 children with functional disorders, detected mild hypomagnesemia (< 0.76 mmol Mg/l) in 16% and 19% of the girls and boys, respectively. Hypomagnesemia plus hypocalcemia were present in 31% and 19.5% of these patients. *Yasui* et al. [49] have studied 63 aged patients (range: 65–85 years) and detected hypomagnesemia (0.6–0.8 mmol Mg/l) in 54%. In comparison to age-matched normo-

magnesemic controls, serum Ca was generally significantly decreased as well as PTH (carboxy-terminal and mid region fragments as well as intact PTH). Serum phosphate levels remained unaffected. Studying a total of 3 674 mostly surgical patients of a London teaching hospital, *Crook* [6] detected 26% of hypomagnesemia ($\leq$ 0.70 mmol Mg/l); 52 patients had severe hypomagnesemia ($\leq$ 0.50 mmol Mg/l). Of these 52 patients, 33% had concomitant hypophosphatemia, 40% had concomitant hypokalemia, and 17% had combined hypokalemia plus hypophosphatemia. Unfortunately, no hormones were measured nor plasma Ca levels reported. Nevertheless, these data resemble those of *Shils* [38] which had been gathered in long-term severe experimental Mg deficiency (see above).

## 4. The effect of Mg administration on Ca-regulating hormones in Mg-deficient subjects

In healthy men, the i.v. injection of $MgSO_4$ produces a significant decrease of PTH, being less pronounced than following the administration of equimolar amounts of $Ca^{2+}$; plasma Ca may be slightly decreased and urinary Ca excretion tends to increase [15].. *Fatemi* et al. [14] have described an opposite behaviour of PTH secretion in Mg-sufficient, respectively Mg-deficient volunteers, following the i.v. injection of $MgSO_4$ (fig. 4). PTH secretion was depressed in Mg-sufficient volunteers, as expected. However, in mildly Mg-deficient volunteers, acute hypermagnesemia was followed by a significant increase in PTH levels. This effect had already been described by *Rude* [29] in hypomagnesemic hypocalcemic patients independently from basal serum PTH concentrations (ranging from undetectable to 3 times the upper limit of normal). These data prove that PTH secretion is impaired during Mg deficiency thus contributing to hypocalcemia which may develop during Mg deficiency. Although serum Ca was not affected during these acute repletion studies it is easy to imagine that lowered levels would have normalized after longer Mg treatment (together with normalization of 1,25-$(OH)_2$-vitamin D levels). It is important to note that in hypoparathyroid patients Mg may restore the calcemic response to exogenous vitamin D compounds also independently of PTH. The underlying mechanism may be an impaired target responsiveness to these drugs which is restored by Mg supplementation. Hence, toxic hypercalcemia may result when Mg is given as ultimo ratio [2]. The question whether or not PTH regulates Mg metabolism cannot be definitely answered. It would make sense to assume renal Mg wasting together with hypercalcemia and hypercalciuria in primary hyperparathyroidism. However, *Elin* et al. [13] could not demonstrate a significant change of plasma Mg, neither in hyperparathyreoidism nor in hypoparathyreoidismus. These data were confirmed by *Claeyssens* et al. [3]; however in contrast to total Mg, ultrafiltrable Mg was significantly increased in their patients with primary hyperparathyreoidism. This points to

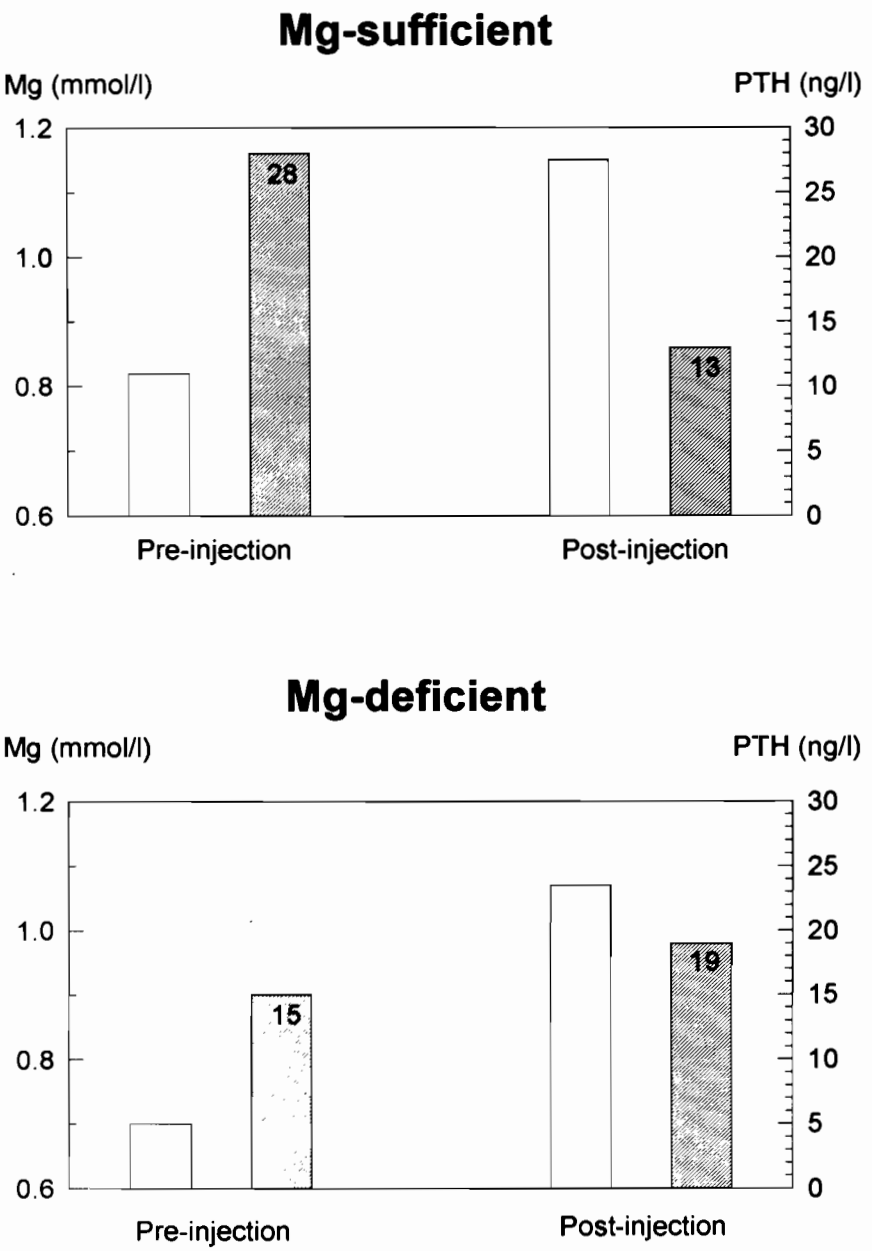


Fig. 4: Opposite acute effects of Mg i.v. on PTH levels in Mg-sufficient (upper panel) and Mg-deficient (lower panel) volunteers [14].

Tab. 1: Vitamin D metabolism and action during Mg deficieny (*Carpenter,* 1988; *Fatemi* et al., *Seelig,* 1990).

- Mg deficiency is frequently associated with hypocalcemia.
- Absorption of vitamin D and hepatic 25-hydroxylation is intact.
- Renal 1α-hydroxylase, yielding the active metabolite 1,25-$(OH)_2$-vit.D, needs PTH as a trophic factor and cAMP.
  Adenylate cyclase requires Mg for generating cAMP.
- 1,25-$(OH)_2$-vit.D levels may be, but aren't consistently low in Mg deficiency. Levels may be normalized by Mg supply, together with Ca concentrations.
- In hypoparathyroid patients, Mg may restore the calcemic response to vit.D compounds, independently of PTH, due to impaired / restored target issue responsiveness (skeletal and renal cAMP ?).
- Since Mg is required for adenylate cyclase activity (parathyroid, kidney, bones) defective cAMP generation may be the common underlying mechanism.

the necessity to follow up ionized $Mg^{2+}$ together with changes of PTH levels. In fact, *Dimai* et al. [10] were able to establish a close positive correlation of $Mg^{2+}$ with PTH in volunteers orally supplemented for 1 month with 15 mmol Mg per day. Since the serum concentrations of immunoreactive calcitonin are very low under physiological conditions no data concerning interactions with Mg are available. In patients with pathologically increased calcitonin levels, hypermagnesemia produced a striking fall of this hormone. The main data and conclusion of this section are summarized in tab. 1.

## 5. The renin-angiotensin-aldosterone system

In 1955, *Mader* and *Iseri* [25] reported a case of spontaneous hypomagnesemia, hypopotassemia, alkalosis and tetany due to primary hyperaldosteronism. Nevertheless the role of aldosterone in Mg homeostasis is not yet fully understood. When volunteers were rendered Mg-deficient during 3 weeks their plasma renin activity remained unchanged as well as serum and urinary K and Na [26], however their basal plasma aldosterone levels were significantly increased, and during a 3-hour angiotensin II infusion (7.2 pmol/kg BW/min) their rise in aldosterone concentration was twice that of Mg-sufficient controls. The underlying mechanisms are still unclear. In Mg-sufficient controls, the rise in aldosterone, produced by angiotensin II infusion, was significantly attenuated when Mg was infused simultaneously at a high concentration of 82.3 mmol/h. In agreement with these findings *Tranquilli* et al. [45] reported that the pressor effect of angiotensin II infusion (10 ng/kg/min) was abolished by Mg i.v. in pregnant women. In another study on Mg-sufficient volunteers, *Ichihara* et al. [17] infused 2.5 mmol Mg during 6 hours. After 60 minutes plasma renin activity was increased by 52%, probably due to an elevation of protaglandins since indomethacin (75 mg daily during 3 days) completely blocked this effect. Increased plasma renin concentration had already been described by *Dechaux* et al. who had infused 0.25 mmol Mg/kg BW during 90 minutes [7]. At 180 minutes, however, plasma aldosterone levels were significantly decreased by 33%. Since the latter effect could be blocked by pretreatment with the synthetic $Ca^{2+}$ antagonist diltiazem (90 mg daily during 3 days) *Ichihara* et al. [17] conclude that suppressed aldosterone production was mediated through Mg-induced intracellular $Ca^{2+}$ mobilization. Like in the others studies on volunteers, serum and urinary concentrations of Na, K, Ca and P remained unaffected. Putting the data together it seems likely that Mg infusion first induces prostaglandin release which in turn causes renin release. Prolonged infusion may inhibit aldosterone production by influencing the intracellular concentration of free $Ca^{2+}$. In patients with chronic heart failure the renin-angiotensin-aldosterone system is overactivated and pronounced chronic hypomagnesemia can be assumed. Interstingly, *Smetana* et al. [40] were able to establish a moderate Mg-sparing effect of the high-dosed (75 mg/day) ACE inhibitor captopril after 3 months, together with reduced aldosterone levels. This points to the possibility that the mineralocorticoids do adversely affect Mg balance. Since the Mg-sparing effect of captopril was however moderate, the authors recommend Mg supplementation in addition.

## 6. Stress hormones and others

Interactions between stress hormones and Mg metabolism have been earlier reviewed e.g. by *Classen* [4], *Seelig* [36] and *Smetana* [39]. Insulin favours cellular Mg uptake (for review see *Durlach* [11]). The question whether or not Mg deficiency may be associated with insulin resistance, as assumed by *Nadler* et al. [26], cannot be answered at present time since experimental data did not support this view [28]. Probably additional hormones and transmitters are involved in the pathogenesis of Mg deficiency, e.g. inflammatory cytokines and endothelin [47], or they are released by pharmacological doses of Mg [48]. However it remains open whether these factors regulate Mg metabolism.

## 7. Conclusion and outlook

The conclusion drawn by *Wallach* [46] at the 2nd International Magnesium Symposium in Montreal (June 1976) can be repeated 19 years later: Multiple interactions between Mg and the endocrine system have been demonstrated. In many cases, definitive studies have yet to be done and knowledge regard-

ing these interactions is still quite rudimentary. Perhaps the most important reason four our primitive state of knowledge is the fact that no endocrine secretion appears to exert an overriding control of Mg homeostasis. In this context, experimental data of *Shafik* and *Quamme* [37] should deserve special attention since these authors described renal Mg conservation during dietary Mg deficit already within 5 hours after starting the diet, i.e. long before plasma Mg decreased. The basis for this sensitive, rapid, and Mg-specific adaption – which could be hormonal – remains to be determined.

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