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Magnesium in disease

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Abstract
Although the following text will focus on magnesium in disease, its role in healthy subjects during physical exercise when used as a supplement to enhance performance is also noteworthy. Low serum magnesium levels are associated with metabolic syndrome, Type 2 diabetes mellitus (T2DM) and hypertension; consequently, some individuals benefit from magnesium supplementation: increasing magnesium consumption appears to prevent high blood pressure, and higher serum magnesium levels are associated with a lower risk of developing a metabolic syndrome. There are, however, conflicting study results regarding magnesium administration with myocardial infarction with and without reperfusion therapy. There was a long controversy as to whether or not magnesium should be given as a first-line medication. As the most recent trials have not shown any difference in outcome, intravenous magnesium cannot be recommended in patients with myocardial infarction today. However, magnesium has its indication in patients with torsade de pointes and has been given successfully to patients with digoxin-induced arrhythmia or life-threatening ventricular arrhythmias. Magnesium sulphate as an intravenous infusion also has an important established therapeutic role in pregnant women with pre-eclampsia as it decreases the risk of eclamptic seizures by half compared with placebo.

Keywords: cardiovascular disease; diabetes mellitus; magnesium; metabolic syndrome; pre-eclampsia/eclampsia

Introduction

Magnesium has numerous physiological functions in the body—in health as in disease (also see de Baaij *et al.* [1] in this supplement). With regard to muscle function, magnesium affects oxygen uptake, energy production and electrolyte balance. Magnesium requirement is higher during sports, particularly during strenuous workouts, as when sweating copiously, the need for magnesium increases considerably. During physical exercise, magnesium is redistributed within the body to accommodate altered metabolic needs. Essential minerals, or the use of magnesium supplements, are recommended to enhance performance. Athletes usually consume sufficient minerals—including magnesium—via high-energy diets. However, this is not always the case when restricting or reducing diets to maintain or reduce body weight. This can result in insufficient magnesium intake and a subsequent decrease in physical performance [2, 3]. While even a marginal magnesium deficiency can impair exercise performance, magnesium supplementation can also boost training performance in athletes, particularly in magnesium-deficient individuals [2, 4]. Therefore, dietary magnesium supplementation in sports should be considered.

Whether magnesium supplementation is effective in reducing muscle cramps needs to be further evaluated, as noted in the conclusion of a recent evidence-based review of symptomatic treatment for muscle cramps [5]. Evidence is scarce and only two Class-II evidence trials were included in the assessment (excluded studies were those dealing with muscle cramps because of medical conditions such as cirrhosis and haemodialysis as well as trials during pregnancy). In one of these two trials included in the review, dosages of an equivalent of 12.3 mmol (300 mg) of magnesium given as magnesium citrate were studied in 46 patients suffering from chronic persistent leg cramps, and a trend in favour of magnesium for reducing muscle cramps was reported ($P = 0.07$) [6]. The second trial, which included 45 patients with nocturnal leg cramps, and in which 36 mmol (900 mg) magnesium citrate was given, did not reveal any significant effect on the number of muscle cramps [7]. Nonetheless, there is some evidence supporting magnesium administration in pregnant women suffering from cramps using a proposed dose of 5 mmol magnesium as a mixture of lactate and citrate in the mornings and 10 mmol in the evenings [8]. Still, these data remain controversial. In a more recent, double-blind placebo-controlled trial including 38 pregnant women suffering from leg cramps, magnesium supplementation (15 mmol/day) did not reveal any beneficial effect of magnesium on the frequency and intensity of leg cramps compared to placebo [9].

Magnesium and the metabolic syndrome

The metabolic syndrome is a disease of modern times. It is an increasing problem in developed and developing countries and is characterized by the simultaneous presence of several metabolic risk factors. It was estimated in 2002 that one quarter of American adults suffer from metabolic

syndrome [10]. Generally, the triad of obesity, hypertension and impaired glucose tolerance, as in diabetes mellitus (insulin resistance), is referred to as the metabolic syndrome. Dyslipidaemia [11], prothrombotic states (high fibrinogen and plasminogen activator inhibitor-1) and an activated acute-phase response (elevated C-reactive protein) may all also contribute to the disorder [12, 13]. To dissect the factors responsible for each single condition, the various diseases underlying the metabolic syndrome will be discussed separately in detail.

One common feature in patients with Type 2 diabetes mellitus (T2DM), hypertension and low levels of high-density lipoprotein cholesterol (HDL-C) appears to be a deficiency of magnesium. However, no data have been published about serum magnesium levels in people with the metabolic syndrome until recently [13, 14]. In 2002, results from a cross-sectional population-based study revealed an association between serum magnesium levels and the metabolic syndrome: Mexicans in their 40s with a metabolic syndrome ($n = 192$) were compared with an age-matched healthy control group ($n = 384$) [13]. Serum magnesium levels $\leq$0.74 mmol/L (1.8 mg/dL), corresponding to the lowest quartile of distribution were defined as low. Using this definition, serum magnesium levels were low in 66% of the patients with the metabolic syndrome compared with 4.9% in the control population ($P < 0.00001$). There was a strong independent association between serum magnesium levels below this threshold and the prevalence of the metabolic syndrome [odds ratio 6.8; 95% confidence interval (CI) 4.2–10.9] [13]. In a further cross-sectional analysis based on 11 686 women, originally participating in the Women's Health Study (WHS), an inverse correlation of magnesium intake and the prevalence of the metabolic syndrome was seen in those above the age of 45 years [15]. The relationship between magnesium intake and the metabolic syndrome was also studied prospectively in younger individuals, i.e. in 5115 young Americans (aged 18–30 years), initially free of metabolic syndromes and diabetes, who were enrolled in the Coronary Artery Risk Development in Young Adults (CARDIA) study from 1985 to 1986. A total of 4637 participants were included in the analysis, and 74% showed up for the 15-year examination in 2000–2001. Within this follow-up period, 608 incident cases of metabolic syndrome were diagnosed. The findings showed that young adults with a higher magnesium intake had a lower risk of developing metabolic syndrome and that this risk was dose dependent [16].

- The metabolic syndrome is an increasing health problem in the westernized world, and is characterized by a combination of metabolic risk factors.
- Low serum magnesium levels are associated with a higher prevalence of the metabolic syndrome.
- Higher dietary magnesium intake is associated with a lower risk of developing a metabolic syndrome.

Magnesium and diabetes mellitus

T2DM is often associated with hypomagnesaemia [17], and incidence rates of 13.5–47.7% have been reported [18]. Hypomagnesaemia can be defined as serum magnesium concentrations $\leq$0.65 mmol/L (1.6 mg/dL) or $\geq$2 SD below the average in the general population [19, 20]. Hereditary factors, poor dietary intake, autonomic dysfunction, altered insulin metabolism, glomerular hyperfiltration, osmotic diuresis, recurrent metabolic acidosis, hypophosphataemia and hypokalaemia may all contribute to hypomagnesaemia in diabetic patients [18].

Magnesium deficiency has also been linked to the development of the disease as well as its severity: the lower the magnesium level the faster the deterioration of renal function in Type 2 diabetics [20]. Moreover, correction of hypomagnesaemia via dietary magnesium supplementation improved glucose handling and insulin response in elderly and non-insulin-dependent diabetics [21]. Several investigators have therefore addressed the topic of magnesium status and dietary magnesium intake, especially in diabetes mellitus.

In epidemiological studies, an inverse correlation between magnesium intake and the risk of developing diabetes mellitus was found [22–24]. The WHS enrolled a cohort of 39 345 US women aged at least 45 years. During a follow-up period of 6 years, on average, 918 women developed T2DM. The trial results support a protective role for higher magnesium intake and a reduced risk of developing T2DM, in particular in the subgroup of overweight women [24]. In two other large prospective studies—the Nurses' Health Study (NHS) initiated in 1976 and the Health Professionals Follow-up Study (HPFS), which began in 1986—an inverse correlation between magnesium intake and the risk of developing T2DM was observed for women as well as for men [23]. The investigators examined the association between magnesium intake and risk of T2DM in 85 060 women and 42 872 men without any previous history of diabetes, cardiovascular disease or cancer at baseline. After 18 years follow-up, 4085 cases of T2DM were documented in women, and after 12 years follow-up, 1333 T2DM cases were found in men. When comparing the highest and lowest magnesium consumption, the relative risk for T2DM was in the highest-magnesium group 0.66 in women, (95% CI 0.60–0.73, $P < 0.001$) and 0.67 in men (95% CI 0.56–0.80, $P < 0.001$) [23]. Furthermore, in the Atherosclerosis Risk in Communities Study (ARIC), a low serum magnesium level was found to be a strong independent predictor of incident T2DM among middle-aged white participants [22]. Recently, a meta-analysis of seven prospective cohort studies and 286 668 participants revealed that magnesium intake was inversely associated with the incidence of T2DM. The authors suggested that an increased consumption of magnesium-rich food, such as whole grains, beans, nuts and green vegetables, might reduce the risk for T2DM [25] (Figure 1).

Findings from large observational studies, carried out in various other regions in the world, have had similar results. For instance, in a large, population-based prospective study including 64 191 middle-aged Chinese women, a non-linear inverse association between calcium and magnesium consumption and the incidence of T2DM was observed after 7 years follow-up. Future controlled studies must, however, investigate whether the intake of these elements is protective for the development of T2DM in this population [26]. Moreover, it was noted in an assessment of 1453 adults in Australia that hypomagnesaemia was on average 8.6 times more common in patients with diabetes and 10.5-fold higher in newly diagnosed diabetics than in healthy individuals [17]. This observation, however, did not hold true for the precursor states of diabetes, as no differences were

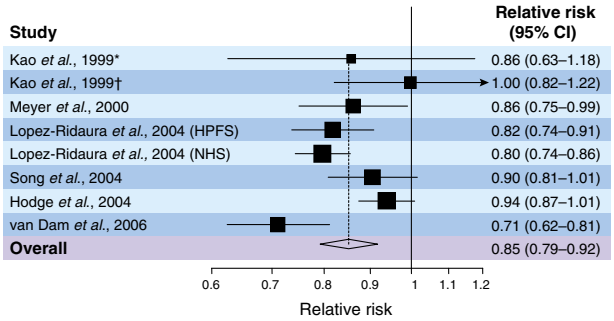

Fig. 1. Association between magnesium intake (for a 100 mg/day increase) and incidence of T2DM. In the various trials, the study-specific relative risk was assessed (squares) [25]. The diamond represents the overall relative risk. Reprinted from Larson *et al.* [25], Copyright © 2007, John Wiley and Sons. *, Black participants; †, White participants; HPFS, Health Professionals' Follow-up Study; NHS, Nurses' Health Study.

observed between healthy controls and individuals with impaired glucose tolerance or impaired fasting glucose levels [17]. In the European Prospective Investigation Into Cancer and Nutrition (EPIC)-Potsdam Study which included 9702 men and 15 365 women, dietary intake of fibre and magnesium was evaluated by validated food questionnaires assessing the risk of T2DM [27]. In light of the evidence from this investigation and a meta-analysis including various previous studies, the authors summarized that higher magnesium intake, along with higher fibre consumption, might be able to decrease the risk of developing T2DM [27].

But conflicting data also exist: in a cohort of 17 592 Japanese between 40 and 65 years of age, investigators observed that dietary magnesium intake was inversely associated with diabetes incidence in both genders [28]. In contrast, a prospective Japanese study including 25 872 men and 33 919 women, aged 45–75 years, with no history of diabetes, demonstrated only a small correlation in men after 5 years of observation. They noted that magnesium intake might not be appreciably associated with the risk of T2DM in Japanese adults. The authors conceded that magnesium might improve insulin resistance but had no clear explanation for the smaller risk association among these Japanese patients compared with western populations. They further speculated that the observed differences could be ascribed to the lean body mass of Asian populations [29]. The US Black Women's Health Study (BWHS) showed that a diet rich in magnesium was shown to be associated with a substantially lower risk of T2DM in a prospective cohort study including 41 186 participants with an 8-year follow-up (1995–2003) [30]. In contrast, however, little or no association was observed among black participants in the ARIC study, possibly because any modest benefit from magnesium was overshadowed by the extraordinarily high incidence of T2DM in blacks. Nonetheless, as mentioned above, there was a strong correlation between low-serum magnesium levels and the incidence of T2DM in middle-aged white participants of the same trial [22]. As a consequence of the aforesaid observations, a controversy has ensued concerning the causal association between hypomagnesaemia and the risk for diabetes mellitus. In addition, hypomagnesaemia was identified as a risk factor for the development and progression of diabetic retinopathy [31]. Finally, lower magnesium levels also appear to be associated with a more rapid decline of renal function in patients with T2DM [20]. Patients with serum magnesium levels between 0.82 and 1.03 mmol/L (2.0–2.5 mg/dL) had the lowest deterioration of renal function and the best glycaemic control. Therefore, these levels were suggested as target serum magnesium levels for diabetic patients [18].

Possible underlying mechanisms

The mechanisms whereby hypomagnesaemia may induce or worsen existing diabetes are not well understood. It has been suggested that magnesium regulates cellular glucose metabolism directly because it serves as an important co-factor for various enzymes and acts as a second messenger for insulin [32–34] (also see Jahnen-Dechent and Ketteler [35] in this supplement).

It was also observed that insulin enhances intracellular magnesium uptake [36] and this in turn mediates diverse effects ascribed to insulin [32]. Furthermore, hypomagnesaemia may induce altered cellular glucose transport, reduced pancreatic insulin secretion, defective post-receptor insulin signalling and/or altered insulin–insulin receptor interactions [18] and thus aggravate insulin resistance [37].

Therapeutic considerations

Two studies investigated the effect of magnesium supplementation in non-diabetic insulin-resistant individuals: one study in 60 non-diabetic hypomagnesaemic subjects describes in a double-blind, placebo-controlled randomized trial over 3 months, that daily administration of 300 mg (12.3 mmol) magnesium significantly improved insulin sensitivity [38]. These data were confirmed in a very recent placebo-controlled randomized trial in 52 normomagnesaemic, but overweight and insulin-resistant subjects, in which Mg supplementation over 6 months resulted in a significant improvement of fasting plasma glucose and insulin sensitivity indices compared to placebo [39].

Whether patients with established T2DM benefit from the administration of magnesium was evaluated in a meta-analysis of nine randomized-controlled trials enrolling 370 participants [40]. Dosage, indications and inclusion criteria varied. Number of patients in the single studies were relatively small and the outcome variable. Oral magnesium supplementation at a median dose of 15 mmol/day used as adjunct therapy for 4–16 weeks was found to be significant regarding lowering fasting glucose levels, but only marginally effective in lowering HbA1C and increasing HDL-C [40]. One of these studies was performed in hypomagnesaemic patients and revealed the most promising results [41]. Another study, investigating the effect on lipid profiles which was not considered in the meta-analysis cited above, as a combination of magnesium and vitamin C and E was used, saw an increase in HDL-C and Apo A1 but no other changes in lipids including triglycerides [42].

Magnesium supplements alone [43] or in combination with other supplements (i.e. Zinc, vitamin E, C and B complex) [44] have also been described as being useful in treating diabetic neuropathy [43, 44] and depression [45].

In conclusion, daily magnesium administration may play a role in pre-diabetic and/or diabetic subjects, but more and larger trials are needed to establish its definitive role.

- Magnesium intake is inversely associated with T2DM incidence.
- Low serum magnesium levels might confer an increased risk of developing T2DM.
- An optimal serum magnesium concentration in diabetics has not been published so far. However, serum magnesium levels of 0.82–1.03 mmol/L seem to be favourable.
- Daily supplementation of at least 15 mmol magnesium may be beneficial in pre-diabetic and T2DM patients in improving insulin resistance.

Magnesium and cardiovascular disease

Death from cardiovascular disease is common and demographical changes mean that deaths from this cause are likely to increase even further. Many cardiovascular disorders are associated with changes in magnesium levels; in particular, those affecting the myocardium and involving blood pressure control [31].

The investigators of a recent epidemiological study—a 5-year follow-up of the population-based Study of Health in Pomerania (SHIP) ($n = 212\ 157$)—found that low serum magnesium levels predicted cardiovascular and all-cause mortality [46]. They were also able to show that low serum magnesium concentrations—regardless of other cardiovascular risk factors—were associated with the long-term gain of left ventricular mass [47], a significant predictor for adverse cardiovascular events.

Magnesium and hypertension

Not only left ventricular hypertrophy but also high blood pressure has been linked to hypomagnesaemia. An inverse relationship between magnesium and blood pressure is apparent according to various study results [18]. Some data even support a role for magnesium in the pathophysiology of essential hypertension [48–50]. Moreover, investigators reported that doses of anti-hypertensive drugs needed to be higher in patients with a magnesium deficiency than in those without [51].

For the most part, results of clinical trials showed magnesium deficiency (in serum and/or tissue) to a certain degree in hypertensive subjects, linking low magnesium levels to a significant undesirable effect on blood pressure [52]. Total magnesium content in red blood cells, as measured by atomic absorption spectroscopy, was significantly reduced in patients with essential hypertension [53]. In the ARIC study, serum magnesium levels in hypertensive white men and women, and in black men, were inversely related to systolic blood pressure (Figure 2) [54]. This study included a total of 15 248 participants, aged 45–64 years.

Not all investigators detected low magnesium serum concentrations in people with hypertension. Hiraga *et al.* [55]—conceding that they were not able to provide an explanation—even observed increased cytosolic-free magnesium concentrations in essential hypertension. Despite these inconsistencies in respect to magnesium status and high blood pressure, some hypertensive individuals consistently demonstrate hypomagnesaemia. Among those are patients with obesity, insulin resistance, hypertriglyceridaemia, severe forms of hypertension, hyperaldosteronism (i.e. volume-dependent hypertension), pregnancy-induced hypertension as well as patients of African-American descent [56–58]. Patients with high blood pressure, therefore, do not seem to represent a homogeneous group. It was speculated that reduction in total intracellular magnesium may only play a role in certain subgroups of patients who—for the time being—cannot be identified with specific clinical characteristics [53]. Obviously, magnesium deficiency is not present in all hypertensive patients. Conversely, not all individuals with hypomagnesaemia suffer from high blood pressure [58]. Moreover, when interpreting the results of older investigations, one has to bear in mind that only recently have certain highly specific techniques become available, such as selective fluorescent Mg^{2+} probes and Mg^{2+}-specific ion-selective electrodes, and these may account for some degree of variation between older and more recent studies.

Whereas serum magnesium-concentrations are not always directly related to arterial hypertension or the development of blood pressure over time [47], reviews of epidemiological and observational studies have shown an inverse relationship between dietary magnesium intake and blood pressure levels [59]. Substantial epidemiological evidence for a correlation between magnesium and blood pressure is derived from the Honolulu Heart Study [49]. In this trial, 61 dietary variables were investigated in 615 men of Japanese descent living in Hawaii and who had no history of hypertension. The results revealed that among these variables, it was dietary magnesium consumption that showed the strongest inverse association with blood pressure.

Similar associations were observed in the ARIC trial between dietary magnesium intake and systolic blood pressure in white women and in blacks (Figure 3) and for diastolic blood pressure [54]. A comprehensive meta-analysis on this subject, however, demonstrated a huge variability of the results without a significant association between magnesium intake and blood pressure [50].

Possible underlying mechanisms. In spite of considerable research, the exact underlying causes for altered magnesium metabolism in hypertensive individuals remain unclear. It is assumed that inadequate dietary magnesium intake or a malfunction in magnesium metabolism can lead to vasospasm and endothelial damage [60–62]. Magnesium deficiency—in particular when combined with stress and catecholamine secretion—might lead to enhanced entry of calcium into vascular smooth muscle cells, which in turn can result in increased arteriolar tone and coronary spasm. Hypertension and its complications may also be the final consequences of increased calcium influx and contraction of arterial smooth muscle cells [31, 63, 64]. Moreover, it was observed that magnesium—often referred to as a 'natural calcium antagonist' (also see Jahnen-Dechent and Ketteler [35] in this supplement)—acts on most types of calcium channels in vascular smooth muscle cells exerting substantial arterial blood pressure-lowering properties, resulting in a reduction of peripheral and cerebral vascular resistance. Apparently, vasodilation is mediated by blocking calcium influx and competitive inhibition of calcium binding [65]. *In vivo* and *in vitro* studies in animals (pregnant rats) demonstrated magnesium-induced relaxation of smooth muscle. Such findings suggest the vasodilatory potential of magnesium in large arteries such as the aorta [66–68], in smaller resistance vessels as the mesenteric arteries and in the cerebral arteries [65, 69–72]

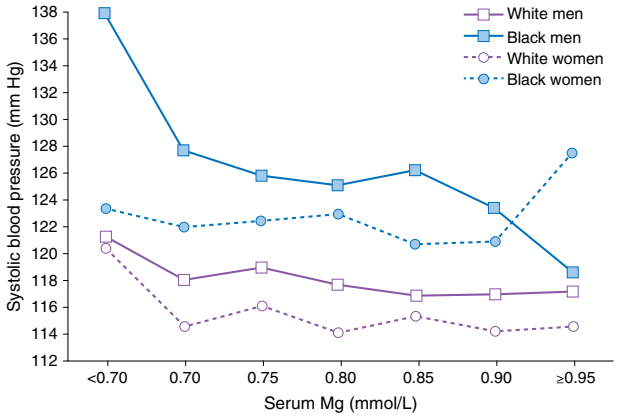

Fig. 2. Race- and gender-specific, age- and body mass index-adjusted average systolic blood pressure according to the serum magnesium level in participants without cardiovascular disease [54]. Magnesium serum levels were inversely related to systolic blood pressure except in black women in whom there was a U-shaped association. Subjects who received anti-hypertensive medication were excluded from the analyses (ARIC study). Reprinted from Ma *et al.* [54], Copyright (1995), with permission from Elsevier.

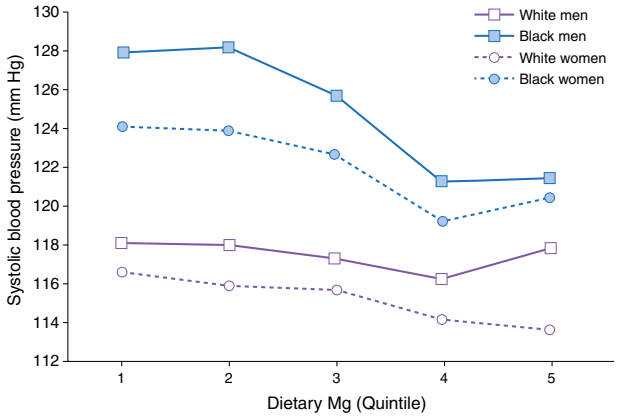

Fig. 3. Magnesium consumption and systolic blood pressure (ARIC study) [54]. Dietary magnesium intake led to considerable effects on systolic blood pressure parameters in white women and in blacks. Race- and gender-specific, age and body mass index-adjusted average systolic blood pressure according to dietary magnesium intake in participants lacking cardiovascular disease. Those on anti-hypertensive medication are also excluded. Reprinted from Ma *et al.* [54], Copyright (1995), with permission from Elsevier.

(Figure 4). These and similar data indicate that vascular tone can be modified by decreasing blood pressure via minor changes in magnesium levels [73].

Therapeutic considerations. Although previous studies evaluating anti-hypertensive effects of magnesium supplementation also produced contradictory results, the therapeutic value of magnesium in hypertension was mentioned as early as 1925 [74]. Since then, considering the inexpensive nature of magnesium, researchers have suggested a putative role for magnesium in the routine management of hypertension [14, 75, 76].

In one trial, oral magnesium supplementation was associated with small, but consistent and significant, reductions in mean 24-h systolic and diastolic blood pressure in individuals with mild hypertension ($n = 48$) [48]. When magnesium concentrations were assessed after magnesium supplementation, serum and intracellular levels had indeed increased, as did magnesium excretion via the urine. Intracellular potassium levels had also risen, while intracellular calcium and sodium concentrations had decreased. In a meta-analysis, evaluating 1220 individuals from 20 randomized clinical trials, significant dose-dependent blood pressure reductions were reported after magnesium supplementation [50]. Other studies similarly showed significant blood pressure-lowering effects of oral and/or intravenous magnesium administration [75, 76]. But, other trials have failed to demonstrate blood pressure-lowering effects of magnesium supplementation [77, 78]. This also holds true for the Trial of Hypertension Prevention Study (TOHP) in which no benefit of magnesium therapy was found in 698 patients who had been followed up for a 6-month period [79]. A review by the Cochrane Collaboration in 2009, investigating magnesium supplementation for the management of primary hypertension in 12 randomized-controlled trials with 545 participants found no reduction in systolic blood pressure, but a small, albeit statistically significant, reduction in diastolic blood pressure [80]. A recent comprehensive analytical review (meta-analysis) of 44 studies of oral magnesium therapy in hypertension came to the conclusion that magnesium supplementation may enhance the blood pressure-lowering effect of anti-hypertensive medications [81]. The inconsistency of the study results might be explained by the different types and dosages of magnesium salts, which were given in the various trials as well as by the heterogeneity of the study populations. Numerous epidemiological and clinical investigations support the hypothesis that increased magnesium intake contributes to the prevention of hypertension and cardiovascular disease [59, 82–86]. However, magnesium administration decreased blood pressure levels in several [48, 87–90] but not all clinical trials [50, 80, 81, 91–94]. Thus, before making definitive therapeutic recommendations, further controlled interventional long-term trials, including carefully characterized hypertensive patients, are needed [95].

- A correlation between magnesium status and blood pressure exists.
- Most patients with high blood pressure also suffered from hypomagnesaemia.
- Magnesium administration decreased blood pressure levels in several, but not all clinical trials.
- Subgroups of hypertensive patients appear to benefit from magnesium supplementation.

Atherosclerosis

Atherosclerosis is a well-known risk factor for cardiovascular disease, potentially triggering myocardial infarction and stroke. The pathogenesis of atherosclerosis, however, is complex and like endothelial dysfunction and hyperlipidaemia, hypomagnesaemia has been identified as a major risk factor [96]. Thus, magnesium deficiency may alter lipid metabolism and change the rate of the atherosclerotic process [97].

Animal data have revealed that dietary magnesium deficiency exacerbates atherosclerosis and vascular damage [98, 99]. Experimental magnesium deficiency induced an inflammatory syndrome in animal models, characterized by macrophage and white blood cell activation, release of

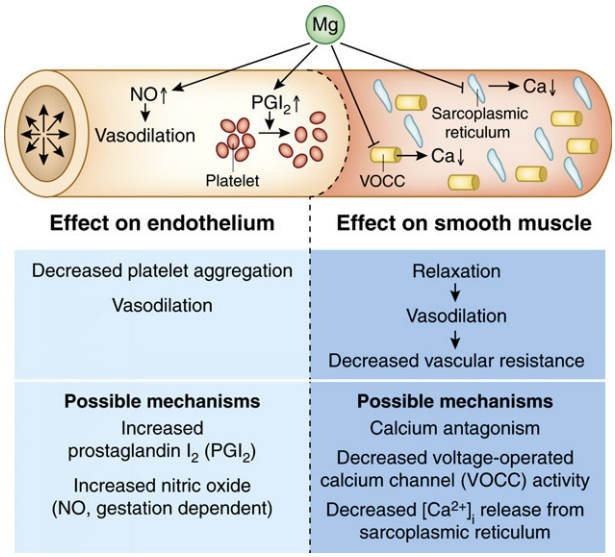

Fig. 4. Vascular effects of magnesium sulphate [66]. Magnesium is a potent vasodilator of uterine and mesenteric arteries as well as the aorta, but has little effect on cerebral arteries. In vascular smooth muscle, magnesium competes with calcium for binding sites, in this case for voltage-operated calcium channels (VOCC). Decreased calcium channel activity lowers intracellular calcium, resulting in relaxation and vasodilation. In the endothelium, magnesium increases production of prostaglandin I_2 which in turn decreases platelet aggregation. Magnesium also increases NO production causing vasodilation. From Euser and Cipolla [66], with permission, adapted.

proinflammatory cytokines, activation of the acute-phase response and excessive production of oxygen-free radicals [100–102].

According to the follow-up of the ARIC study, patients with the lowest serum magnesium level had the highest risk for coronary artery disease (CAD). ARIC included 13 922 healthy individuals at baseline [103]. The National Health and Nutrition Examination Survey Epidemiologic Follow-up Study also showed an inverse relationship of serum magnesium and mortality from CAD [104]. Another study, based on a cohort of 12 708 participants of the ARIC study, showed that the average thickness of the carotid wall in women increased with each 0.1 mmol decline in serum magnesium levels ($P = 0.006$). The association in men was, however, not significant (multivariate analysis) [54]. Results from an observational study conducted in the general Japanese population ($n = 728$) demonstrated similar findings: lower serum magnesium levels were significantly and independently associated with a greater average intima–media thickness ($P = 0.004$) and the risk of at least two carotid plaques ($P = 0.03$) [105]. Furthermore, Ascherio *et al.* [106] found a negative association between dietary magnesium intake and risk of stroke in a prospective study including 43 738 individuals (for detailed description about magnesium and vascular calcification, see Massy and Drüeke [107] in this supplement).

Possible underlying mechanisms. Even at the beginning of the 20th century after the discovery of magnesium as an essential nutrient, magnesium deficiency was linked to inflammation [102]. Treatment effects in preventing cardiovascular disease were thought to be attributed to the reduction of the inflammatory response. Magnesium also reduces vulnerability to oxygen-derived free radicals, improves endothelial function and inhibits platelet aggregation and adhesion [108] and thus its properties resemble the effects exerted by certain drugs such as clopidogrel [108]. Recent epidemiological evidence supports the hypothesis that magnesium intake is inversely associated with C-reactive protein concentration [102]. It is also possible that magnesium deficiency contributes to inflammation via changes in proatherogenic lipoprotein concentrations, i.e. accumulation of triglyceride-rich lipoproteins accompanied by elevated plasma apolipoprotein B levels and a decline in HDLs [102].

Therapeutic considerations. Dietary magnesium consumption appears to play a crucial modulatory role in controlling lipid metabolism [37]. Although the mechanisms are poorly understood, studies demonstrated that increased intake of dietary magnesium can lower blood triglyceride and increase HDL-C levels [109]. It was reported that oral supplementation with magnesium chloride (up to 26.3 mmol/day) resulted in a significant increase in the HDL-C fraction [96]. In addition, magnesium intake was inversely associated with markers of systemic inflammation and endothelial dysfunction in women [110] and also postmenopausal women [111].

- Dietary magnesium deficiency might aggravate atherosclerosis and vascular damage.
- In epidemiological studies, low serum magnesium level was associated with a higher risk of coronary artery disease and a higher risk of stroke.
- Magnesium supplementation might lead to an increase in the HDL-C fraction.

Acute myocardial infarction

Magnesium deficiency has been associated with induction of severe vascular damage in the heart, acceleration of the development of atherosclerosis, vasoconstriction of the coronary arteries, increase in blood pressure and enhanced platelet aggregation [99]. Hypomagnesaemia seems to be involved in the pathogenesis of ischaemic heart disease by altering lipoprotein composition, predisposing individuals to atherosclerosis [112]. In animal models of myocardial infarction, magnesium administration prior to reperfusion led to a reduction in infarct size [113].

Possible underlying mechanisms. The results of autopsy studies reveal that patients who had died from ischaemic heart disease had lower magnesium levels in myocardium and muscle compared with those who had died from non-cardiac causes [114]. It was observed that during myocardial ischaemia, total intracellular magnesium decreases while free ionized intracellular magnesium increases [115]. In addition, ischaemia leads to intracellular calcium overload—which is even more pronounced in the reperfusion phase—compromising myocardial function. It was speculated that magnesium administration reduces calcium overload because there was evidence that these two elements compete with one another for the same binding sites. Magnesium might be considered a natural 'calcium antagonist' [65] and is able to attenuate phosphate-induced apoptosis in vascular smooth muscle cells [116]. Calcium channel blockers are effective in treating certain cardiovascular disorders, particularly angina, and because

magnesium mimics the effect of these drugs [117], it might protect cells during ischaemia and so limit infarct size [113]. In addition, the effects of magnesium on vascular tone, its anticoagulant properties, its ability to improve endothelial dependent vasodilation, possibly through improvement of NO release [118], theoretically may all exert a beneficial effect in acute myocardial infarction. Based on these different observations, investigators started to study magnesium replacement as an adjunctive pharmacotherapy within the setting of acute myocardial infarction.

Therapeutic considerations. Magnesium therapy has been extensively studied in the context of acute myocardial infarction in various clinical trials. The Second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2), included 2316 patients who were randomized to receive intravenous magnesium sulphate or matching placebo. Patients received placebo or magnesium for 5 min before initiation of thrombolytic therapy, followed by an infusion for the next 24 h. This study showed a 24% reduction in 28-day mortality, a 25% reduced incidence of left ventricular failure and an improvement in long-term survival in terms of reduction of long-term mortality from ischaemic heart disease (average follow-up period of 2.7 years) [119, 120]. The authors concluded that early intravenous magnesium sulphate is a simple, safe and useful addition to standard procedures in acute myocardial infarction. Furthermore, its efficacy in reducing early mortality does not affect thrombolytic or antiplatelet therapy [119]. Intravenous magnesium therapy in a placebo-controlled randomized trial enrolling 194 high-risk patients not eligible for thrombolysis significantly reduced incidence of arrhythmias and in-hospital mortality in the verum group [121]. In contrast, the ISIS-4 trial (Fourth International Study of Infarct Survival), in which a large group of 58 050 patients with suspected acute myocardial infarction was included, did not demonstrate a beneficial effect of magnesium therapy in the acute myocardial infarction setting. The routine use of magnesium had little or no effect on mortality rates—though it did not do any harm—in patients with acute myocardial infarction [122]. The difference to the result of the LIMIT-2 trial and to the results of an earlier meta-analysis [123] have been attributed to variations in the study designs (early versus late administration of magnesium). It is noteworthy that in the ISIS-4 study, magnesium was given after reperfusion (iatrogenic or spontaneous), and this difference in timing might explain the negative result of the trial [124, 125]. In addition, it has been suggested that magnesium therapy is beneficial only in those patients not receiving, or not suitable for, thrombolytic treatment. It was also hypothesized that magnesium therapy is less beneficial in low-risk patients and more advantageous in high-risk patients [113]. But further studies confirmed the negative results of the ISIS-4 study. An Italian study, involving 150 patients with acute myocardial infarction demonstrated that intravenous magnesium given prior, during and after reperfusion, neither minimized myocardial damage nor improved short-term clinical outcome [126].

These results were again confirmed in another larger clinical trial. The MAGIC trial included 6213 high-risk patients with ST-elevation myocardial infarction. After intravenous $MgSO_4$ bolus administration, no improvement of short-term mortality was found as compared to patients who were randomly assigned to placebo. At 30 days, an equal proportion of patients had died in both groups (15.3 versus 15.2%). No benefit or harm from magnesium administration was observed, which was also the case for patients not eligible for thrombolysis [127]. Even though there is no real explanation for the discrepancies, it was discussed whether magnesium's proposed cardioprotective mechanisms might be interfering with the effects of standard medical regimens including aspirin, β-blockers and angiotensin-converting enzyme inhibitors not routinely used in earlier trials. Thus, the conclusion after these last clinical trials was that magnesium sulphate cannot be generally recommended for the routine administration in acute myocardial infarction [127].

- Early studies showed a protective role of magnesium administration on mortality after acute myocardial infarction.
- More recent studies could not confirm these results.
- Given the last large trial results—ISIS-4 and MAGIC—there is no indication for routine administration of magnesium in acute myocardial infarction.

Arrhythmia

Hypomagnesaemia is a possible cause of arrhythmia—both of atrial and ventricular origin—which has been discussed in the literature [128]. Certainly, it is difficult to establish a direct link between magnesium deficiency and arrhythmia because the correlation of serum and cardiac magnesium concentration is poor. Little clinical evidence exists that isolated hypomagnesaemia induces arrhythmias. To complicate matters further, hypomagnesaemia is closely related to hypokalaemia, which itself is arrhythmogenic. In addition, magnesium deficiency exacerbates potassium-mediated arrhythmia, in particular in the presence of digoxin intoxication [128, 129]. Nonetheless, the therapeutic role of magnesium in this indication has been thoroughly studied, and most investigations revealed a favourable effect when keeping magnesium concentrations within the physiological range, an effect which was enhanced when both magnesium and potassium concentrations were adjusted [58].

Possible underlying mechanisms. Anti-arrhythmogenic properties of magnesium may involve changes in the activity of calcium and potassium channels [130]. Both extracellular and cytosolic magnesium has significant effects on cardiac ion channels, which in turn may have important consequences on the duration of action potential, cell excitability and contractility [130]. Magnesium blocks calcium influx [65], reducing sinus node rate firing, prolonging AV conductance and increasing atrio-ventricular (AV) node refractoriness [58].

Therapeutic considerations. A randomized, double-blind, placebo-controlled study called Magnesium in Cardiac Arrhythmias (MAGICA), demonstrated that patients with frequent ventricular arrhythmia ($n = 232$) benefitted from increasing dietary magnesium and potassium

intake in terms of a moderate but significant antiarrhythmic effect [131]. Intravenous magnesium infusions decreased the frequency of ventricular arrhythmias after acute myocardial infarction [132–135] and reduced QT-dispersion [133]. The LIMIT-2 trial [119], however, did not reveal such an effect, and even though the frequency of ventricular fibrillation was slightly reduced in the ISIS-4 trial, there was no benefit regarding survival [122]. As a consequence, there are currently no firm recommendations for the use of magnesium in the treatment of patients with arrhythmia after myocardial infarction [136].

According to guidelines [136] in patients with ventricular arrhythmia, any electrolyte imbalance should always be corrected but the administration of magnesium as an active treatment is only recommended for certain types of arrhythmia [136, 137]. These include ventricular arrhythmia-associated torsade de pointes, where magnesium has a well-established role under certain circumstances [137–143]. It is thus recommended to treat patients who present with long QT syndrome, polymorphic ventricular tachycardia and few episodes of torsade de pointes with intravenous magnesium sulphate [136, 137, 144]. These patients can be treated with magnesium sulphate intravenously as a first-line agent to terminate torsade de pointes, irrespective of serum magnesium level. Magnesium is not likely to be effective in patients with normal QT intervals [136]. The same guidelines also recommended magnesium sulphate for resuscitation of patients with pulseless ventricular fibrillation and ventricular tachycardia in cases when epinephrine, lidocaine or amiodarone prove ineffective.

Digoxin-induced arrhythmia is facilitated by hypomagnesaemia and can be terminated by magnesium administration [145, 146]. Cardiac glycosides such as digoxin are used for treatment of patients with atrial fibrillation, but digoxin is also arrhythmogenic itself in overdose [147, 148]. The American Heart Association states that magnesium is reasonable for patients who take digitalis and present with sustained ventricular arrhythmias, advanced AV block and/or asystole [136]. In fact, magnesium has been used since the 1930s for digitalis intoxication [149].

Although it has been established that there is a significant relationship between low magnesium levels and an increased incidence of atrial fibrillation [150], the role of magnesium therapy and prophylaxis of atrial fibrillation remains unclear. Even though numerous studies have investigated the role of magnesium administration in relapse prevention of atrial fibrillation [129, 151], the results are still controversial. Several publications demonstrated beneficial effects of magnesium when added to standard treatment, while others failed to do so [150–153]. This is the reason why some investigators suggest that magnesium treatment should be limited to those patients for whom other drugs are contraindicated or have been shown to be ineffective [58]. However, magnesium was successfully administered in neonates and infants to prevent post-operative arrhythmias in the setting of arterial switch operation [154].

- Electrolyte imbalances including hypomagnesaemia, often caused by the use of diuretics, should be corrected in patients suffering from arrhythmias, irrespective of the form and/or underlying cause.
- Magnesium therapy should be given to patients with ventricular arrhythmia associated with torsade de pointes who present with long QT syndrome as well as for the treatment of patients with digoxin intoxication-induced arrhythmias.
- The role of magnesium therapy in the prevention of atrial fibrillation needs to be further elucidated.

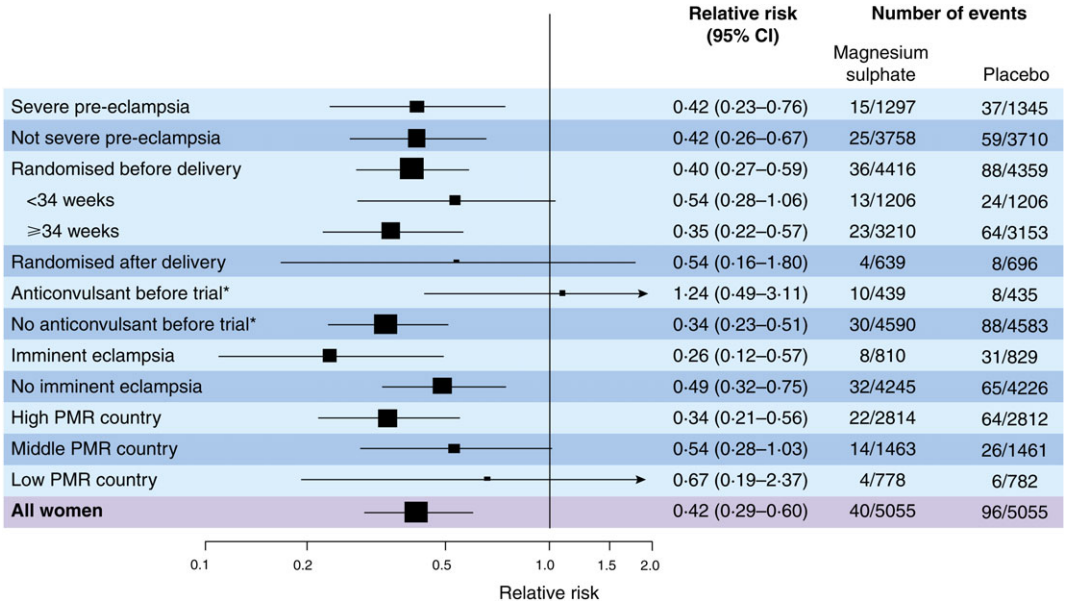

Fig. 5. Treatment effects of magnesium administration in patients with (pre-)eclampsia [169]. Magnesium led to consistent effects regardless of severity of pre-eclampsia, stage of gestation and anticonvulsant therapy. Reprinted from Altman *et al.* [169], Copyright (2002), with permission from Elsevier. PMR, perinatal mortality rate; *Unknown whether prior anticonvulsant treatment was given to 26 women allocated to the magnesium sulphate and 37 allocated to the placebo groups.

Magnesium and pre-eclampsia/eclampsia

For centuries, doctors have feared the occurrence of convulsions during pregnancy as they have been associated with poor prognoses for the mother and the unborn child. At first, eclampsia—associated with a 50% maternal mortality rate in earlier days—was thought to be a simple convulsive disorder. During the 19th century, eclampsia was then noted to be associated with albuminuria and hypertension, which led to an earlier diagnosis of the condition in the last century [155, 156]. Seizures in eclampsia were distinguished from other types of seizures primarily by the absence of previous history of seizures before pregnancy [156].

Pre-eclampsia is defined as a condition with hypertension, proteinuria [157], often accompanied by pathological oedema, occurring in about 6–8% of all gestations over 20 weeks [155]. It is seen more often in nulliparous women [155]. Pre-eclampsia usually regresses rapidly postpartum [155]. This complex disorder is characterized by haemoconcentration, vasoconstriction with increased peripheral resistance and reductions in cardiac output, plasma volume [158–160] and prostacyclin synthesis [161]. Prostacyclin is a potent vasodilator and inhibitor of platelet aggregation, and thus the shift in balance of the thromboxane/prostacyclin ratio might end-up favouring vasoconstriction and platelet aggregation [155]. The observed proteinuria is associated with glomerular lesions typical for pre-eclamptic women. Circulating angiogenic factors, such as soluble vascular endothelial growth factor Type 1 receptor (also known as soluble Fms-like tyrosine kinase 1, sFlt1) are suggested to contribute to the development of the disease [162].

The hypothesis that magnesium deficiency plays a role in pre-eclampsia and the importance of serum magnesium levels as marker of severity of pre-eclampsia has been proposed and investigated in several studies with controversial results [163–166]. While Standley *et al.* [163] observed that serum magnesium levels decrease earlier in women with pre-eclampsia, others, however, could not demonstrate significant differences when comparing pre-eclamptic to uncomplicated pregnancies [164–166].

Treatment. Since the early 1900s, pre-eclampsia has been treated with magnesium. Up until the present day, magnesium sulphate has remained the most frequently used agent in the management of pre-eclampsia and eclampsia [167]. Magnesium is the drug of choice to prevent convulsions in eclampsia [168]. This is not surprising because the placebo-controlled Magnesium Sulphate for Prevention of Eclampsia trial (MAGPIE) showed that magnesium sulphate decreased the risk of eclampsia significantly (by half) in pre-eclamptic women. The study included 10 141 women with pre-eclampsia in 175 hospitals in 33 countries and its data clearly demonstrated that magnesium sulphate has an important role in preventing and controlling eclampsia. Its effect on eclampsia was consistent regardless of severity of pre-eclampsia, stage of gestation and anticonvulsant therapy (Figure 5) [169].

Magnesium sulphate is also more effective than other anticonvulsants in the treatment of eclampsia. Data from a study with 2138 hypertensive pregnant women demonstrated that magnesium sulphate was superior to phenytoin when given prophylactically to prevent seizures [167]. This large clinical trial also showed a considerable reduction in the development of eclampsia [167]. The Collaborative Eclampsia Trial investigated which anticonvulsant would be the best for women with eclampsia and provided Level I evidence for magnesium sulphate in this setting [170]. Magnesium sulphate therapy resulted in a 52% lower risk of recurrent convulsions compared with diazepam and a 67% lower risk of recurrent convulsions compared with phenytoin. The effect was consistent regardless of severity of pre-eclampsia, stage of gestation and whether or not other anticonvulsants had been taken [170].

Although the use of magnesium sulphate for pre-eclampsia is well substantiated, there is little evidence

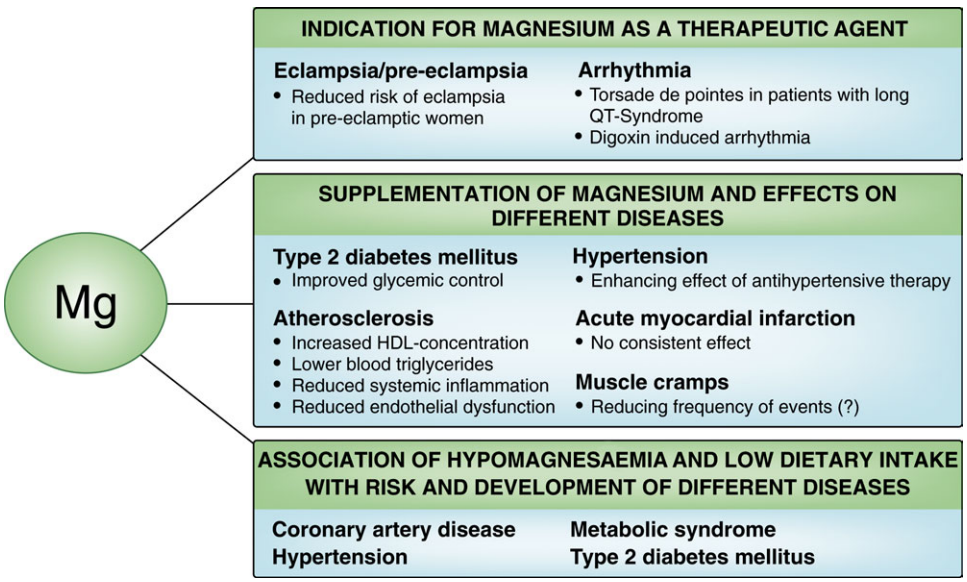

Fig. 6. Associations between low serum magnesium levels and low dietary magnesium intake and an increased risk for diseases such as the metabolic syndrome, T2DM and hypertension and atherosclerosis have been shown in various epidemiological studies. In addition, a beneficial effect of magnesium supplementation has been observed for most of these diseases. However, an indication for the administration of magnesium as a therapeutic could only be confirmed for pre-eclampsia and specific forms of arrhythmias.

supporting its routine use in gestational hypertension. Shear *et al.* [157] mentioned that in their clinic, magnesium sulphate is often used in women with severe pre-eclampsia and in those who are at risk for becoming pre-eclamptic. In patients with proteinuria or with mild pre-eclampsia, magnesium sulphate should be given according to the specific clinical needs of the individual patient [58].

Possible underlying mechanisms. Magnesium appears to trigger the release of prostacyclin, a potent vasodilator and inhibitor of platelet aggregation [171, 172], which is synthesized by the endothelium of vessels [171, 172]. In pre-eclampsia, acute magnesium sulphate administration improved endothelial function [171] and a rapid fall in systemic vascular resistance followed. Subsequently, blood pressure decreased transiently and cardiac index increased [173].

- Magnesium sulphate has been successfully used for decades in the management of pre-eclampsia and eclampsia to prevent eclamptic seizures.
- Magnesium sulphate reduces the risk of eclampsia by half compared with placebo.
- Magnesium is preferred over diazepam or phenytoin for the treatment of eclampsia.

Summary

Associations between low serum magnesium levels and low dietary magnesium intake and an increased risk for diseases such as the metabolic syndrome, T2DM and hypertension and atherosclerosis have been shown in various epidemiological studies. However, an indication for the administration of magnesium as a therapeutic agent could only be confirmed for pre-eclampsia and specific forms of arrhythmias (Fig. 6).

Conflict of interest statement. H.G. received speakers' or consultancy honoraria from and participated in clinical trials with Abbott, Amgen, Genzyme, Fresenius and Shire. C.W. has received speakers' honoraria from Abbott, Fresenius, Genzyme, Mitsubishi and Shire.

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