Magnesium physiology and pathogenic mechanisms that contribute to the development of the metabolic syndrome

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Abstract. The clinical and public health impact of the metabolic syndrome (MetS) has increased substantially in recent years. MetS is defined by a constellation of cardiovascular disease risk factors including: insulin resistance, elevated blood pressure, impaired glucose tolerance, central obesity, and atherogenic dyslipidemia as well as impaired clotting, increased inflammatory burden, and oxidative stress. Recently, there has been burgeoning experimental, clinical, and epidemiological data that provides strong evidence that dietary magnesium intake and supplementation are inversely associated with the risk for MetS and its components. In this review, we describe and discuss the myriad of integrated physiological mechanisms through which magnesium deficiency and the resultant altered magnesium status may lead to the development of the MetS and each of its components.

Key words: metabolic syndrome, magnesium, insulin resistance

Metabolic syndrome

Epidemiology

The metabolic syndrome (MetS) is a growing global epidemic whose prevalence in diverse populations is approximately 20% [1, 2]. Currently, an estimated 55 million individuals have the MetS in the United States [3, 4]. Moreover, it is predicted that, due to the growing obesity and diabetes epidemics the clinical and public health burden of the MetS will continue to rise in the future [1, 3, 5, 6]. Despite its highly prevalent global occurrence, MetS, as we currently understand it, is a relatively new phenomenon. Hanefeld and Leonhardt first introduced the term MetS as the joint occurrence of type II diabetes mellitus, hyperinsulinemia, obesity, hypertension, hyperlipidemia, gout, and thrombophilia in the early 1980s [7]. Although clinical definitions of MetS vary [8-10], MetS is defined by at least three of the following:

i) obesity (waist circumference: > 88 cm (female), > 102 (male)); ii) serum triglycerides ≥ 150 mg/dL; iii) HDL-cholesterol (< 50 mg/dL (female); < 40 mg/dL (male)); iv) blood pressure ≥ 130/85, and v) fasting plasma glucose ≥ 100 mg/dL [10]. MetS may also be marked by a state of increased thrombosis, augmented inflammatory burden, as well as increased oxidative stress/reduced endogenous antioxidant capacity [1, 11]. Agreement on how best to define the MetS remains controversial due in part to the constellation of clinical metabolic disorders which may occur in those individuals afflicted with the syndrome [12]. Alternatively, the simultaneous clustering of several metabolic disorders has also been referred to as the deadly quartet, syndrome X, and insulin resistance syndrome [13-15]. Once manifest, MetS is causally predictive of future risk for several clinical outcomes including: diabetes, cardiovascular disease, cerebrovascular disease, renal disease, as well as cardiovascular-related and all-cause
mortality [16-20]. MetS has also been linked to several other clinical events including: cancer, nonalcoholic fatty liver diseases, sleep apnea, essential hypertension, and polycystic ovary disease secondary to hyperandrogenemia [21-25]. Several lifestyle factors are associated with a substantially increased risk for incident and prevalent MetS including: low physical activity and cardiorespiratory fitness, increased body mass index (BMI), increased dietary intake of carbohydrates and saturated fat, and reduced fiber intake [26-29]. Additionally, advancing age irrespective of gender or ethnicity is associated with an increased risk for the MetS [30]. Furthermore, ethnic differences exist in the risk for MetS with Mexican Americans displaying the greatest MetS prevalence followed by Non-hispanic whites and African-Americans [4, 30].

**Genetics and the MetS**

Given the heritability of the MetS, considerable ethnic differences in MetS prevalence and incidence, and differences in concordance rates between monozygotic twins it is highly likely that a genetic susceptibility component to MetS is involved with its pathogenesis [31]. To date, studies have indicated that candidate genes involved in insulin signaling, glucose homeostasis, lipid metabolism, adipogenesis, inflammation, endothelial function, and coagulation are altered in patients with MetS [32]. For example, loss of function mutations in the transcription factor PPAR-γ have been associated with hypertension, diabetes mellitus, insulin resistance, dyslipidemia, and hepatic steatosis [33]. Researchers have found that the Pro12Ala polymorphism in the PPAR-γ gene is associated with lower BMI, improved insulin sensitivity, and consequently a reduced risk for diabetes mellitus type II [34, 35]. Also, recent studies have shown an interesting interaction between PPAR-γ polymorphisms, nutrient status, and risk for MetS. Luan et al. found that as the polyunsaturated:saturated fatty acid intake increases there is an inverse relation for BMI and insulin concentrations in the Ala carriers, but not the Pro homozygotes [36]. Importantly, the Pro allele is associated with a greater risk of MetS components and it is possible that individuals with this allele are not sensitive to the composition of fat in the diet. Lastly, in a Caucasian kindred of 129 individuals, Wilson et al. reported that a clustering of metabolic factors; namely elevated systolic and diastolic blood pressure, increased cholesterol, in parallel with hypomagnesemia was linked to a homoplasmic mutation in which cytidine was substituted for uridine immediately 5’ to the mitochondrial transfer RNA anticodon [37].

**Nutrition and the MetS**

Despite the plethora of data indicating that genetic makeup is a key determinant of an individual’s future risk for MetS, strategies aimed at preventing and controlling risk factors for MetS are primarily aimed at lifestyle modification and involve increased physical activity, weight loss, and dietary changes [38]. Specifically, antithromogenic diets low in saturated and trans-fat, high in unsaturated fat (e.g. ω-3 fatty acids), balanced carbohydrate intake (rich in dietary fiber, grains, fruits, and vegetables), and low-fat dairy have been suggested to prevent development of the MetS and its components [11, 39, 40]. Importantly, such diets tend to contain high amounts of several micronutrients such as calcium, potassium, and magnesium which may act to control MetS pathogenesis. [11, 41] Indeed, magnesium (Mg²⁺) is emerging as a key player in MetS pathogenesis as evidenced by the numerous experimental, clinical, and epidemiologic studies delineating a convincing link between Mg²⁺ status, MetS pathogenesis, and individual MetS components. For example, recently, it has been suggested that consumption of diets high in fructose along with low Mg²⁺ status result in the MetS, perhaps due to an augmented inflammatory burden [42-44]. Indeed, studies in experimental models have shown an interesting interplay between Mg²⁺ deficiency, fructose hyperconsumption, and pathogenesis of the MetS. When given to Mg²⁺ deficient animals, fructose promotes impaired insulin sensitivity and signaling and increased serum lipids [45, 46]. Apparently, the effects are brought about, in part, by increased inflammation and oxidative stress in these models of Mg²⁺ deficiency and fructose overload [46].

Data from several epidemiological studies have delineated a causal link between Mg²⁺ status and the MetS. A cross-sectional analysis demonstrated that a strong relation exists between low serum Mg²⁺ levels and prevalence of MetS and each of its components [47]. Furthermore, an inverse association between dietary Mg²⁺ intake and MetS prevalence was recently reported in over 11,000 middle-aged women within the Women’s Health Study [48]. Similar observations have been made in a smaller Italian study sample [49]. Recently, a small clinical trial consisting of 290 patients, revealed a strong correlation between serum [Mg²⁺], high plasma triglycerides, waist circumference, and microalbuminuria in
patients with type II diabetes mellitus [50]. In a longitudinal analysis of 4,637 young adults within the Coronary Artery Risk Development in Young Adults (CARDIA) study, we found that Mg\(^{2+}\) intake was inversely related to incident MetS, each of its components, and fasting insulin levels [51]. The focus of this review is to provide an integrated analysis and discussion of the molecular and cellular mechanisms by which reduced Mg\(^{2+}\) intake and/or impaired Mg\(^{2+}\) status and consequent decrease in serum [Mg\(^{2+}\)] and/or cellular [Mg\(^{2+}\)] translates into pathogenesis of the MetS and its components.

**Magnesium**

**Molecular and cellular physiology**

Mg\(^{2+}\) is the 2\(^{nd}\) most abundant intracellular cation and is an essential cofactor in well over 300 enzymatic reactions [52]. In particular, Mg\(^{2+}\) plays salient roles in such biologic processes as: energy metabolism and production, synthesis of nucleic acids and proteins, cytoskeletal function, cell cycle progression, maintenance of membrane integrity and stability, and ion homeostasis [53]. Mg\(^{2+}\) is also required by all enzymes involved in phosphoryl group transfer, Mg\(^{2+}\) is involved in energy metabolism and production, synthesis of nucleic acids and proteins, cytoskeletal function, cell cycle progression, maintenance of membrane integrity and stability, and ion homeostasis [53]. Mg\(^{2+}\) is also required by all enzymes involved in phosphoryl group transfer such as protein kinases and phosphatases (e.g. ATPases) [52, 53]. In this capacity, Mg\(^{2+}\) occupies a central role in the control of intracellular signaling and protein phosphorylation. Furthermore, Mg\(^{2+}\) is intricately involved in modulating intracellular calcium (Ca\(^{2+}\)) homeostasis and decreases in intracellular Mg\(^{2+}\) are, in turn, met by increases in Ca\(^{2+}\) levels [54]. Specifically, Mg\(^{2+}\) promotes Ca\(^{2+}\) uptake into the sarcoplasmic or endoplasmic reticulum by stimulating a membrane-localized ATP dependent transport pump within these organelles [55]. Additionally, Mg\(^{2+}\) modulates Ca\(^{2+}\) efflux from the cytoplasm by stimulating the sodium-calcium exchanger [55]. Mg\(^{2+}\) also blunts Ca\(^{2+}\) influx through L-type Ca\(^{2+}\) channels and, at the sarcoplasmic reticulum, blocks Ca\(^{2+}\) release by interfering with the ryanodine receptor [55-57]. Lastly, by competing for Ca\(^{2+}\) binding sites on the regulatory troponin C molecule, Mg\(^{2+}\) also regulates contractile protein activation and dynamics [58].

**Mg\(^{2+}\) homeostasis**

In the body, Mg\(^{2+}\) status is principally determined by absorption through the gastrointestinal tract, requirements of the tissues (e.g. cardiac, skeletal, and smooth muscle uptake and usage), and renal excretion. Mg\(^{2+}\) is localized to three compartments: bone (65%), intracellular (34%), and extracellular (1%) [59, 60]. Plasma [Mg\(^{2+}\)] is tightly controlled at 0.9-1.0 mM [61]. In the serum, approximately 70-80% of the Mg\(^{2+}\) exists in the biologically active ionized (free) form, while the remainder is bound to circulating proteins (e.g. albumin) (20-30%) or complexed to anions (e.g. phosphate, citrate, bicarbonate) (1-2%) [53, 62]. Studies using sensitive fluorescent indicators (e.g. Furaptra), microelectrodes, and \(^{31}\)P-nuclear magnetic resonance have shown that, in various cell types, free intracellular [Mg\(^{2+}\)] is between 0.5-1.0 mM [59].

By far, the kidney exerts the most predominant impact in controlling body Mg\(^{2+}\) status [63]. Absorption across the renal epithelial cell is accomplished via passive paracellular transport mediated, in part, by paracellin-1, a pore-building paracellular protein [64, 65]. Transcellular absorption is accomplished by secondary active mechanisms involving apical uptake through Mg\(^{2+}\) channels and basolateral export by the sodium-magnesium exchanger [63, 65]. Renal Mg\(^{2+}\) handling is tightly in sync with body Mg\(^{2+}\) status, as Mg\(^{2+}\) deficiency increases renal Mg\(^{2+}\) reabsorption across all nephron segments [65]. Renal Mg\(^{2+}\) handling is also modified by loop diuretics such as furosemide and bumetanide, which disfavor Mg\(^{2+}\) reabsorption [66].

Both cellular and serum Mg\(^{2+}\) balance are regulated by hormones commonly altered in patients with MetS. Several studies have shown that insulin and glucose promote Mg\(^{2+}\) uptake into smooth muscle cells, erythrocytes, and platelets [67-69]. It has also been reported that \(\alpha\) (phenylephrine) and \(\beta\) (norepinephrine, isoproteranol) adrenergic agonists prompt Mg\(^{2+}\) efflux from isolated hepatocytes [70]. Corica and coworkers have shown that subsequent to oral glucose loading plasma Mg\(^{2+}\) declines while erythrocyte and platelet Mg\(^{2+}\) increase in normotensive and hypertensive subjects [71]. In vascular smooth muscle cells from hypertensive animals, angiotensin II (AngII) and vasopressin were found to elicit increases in intracellular Mg\(^{2+}\), secondary to activation of the sodium-magnesium exchanger (NME) [72]. The NME removes one Mg\(^{2+}\) coupled to the secondary active uptake of 2 Na\(^{+}\) [73] In an animal model of AngII dependent hypertension, interference with NME activity attenuated increases in systolic blood pressure [74]. Thus, it may be that alterations in cellular and tissue Mg\(^{2+}\) status commonly found in subjects with the MetS arise secondary to altered NME activity due to increased insulin and/or AngII signaling.
Deficiency

The recommended daily allowance (RDA) of Mg2+ in the United States is 420 mg/day for men and 320 mg/day for women [53]. Recent dietary survey data suggest that the average intake in western countries has been declining during the last century and is often below the RDA [53]. Hypomagnesemia is clinically defined as serum [Mg2+] below 0.5 mM and usually arises from Mg2+ deficiency [53]. Two types of Mg2+ deficiency exist: primary and secondary. Primary Mg2+ deficiency is related to reduced Mg2+ intake and/or depletion due to decreased intestinal absorption, increased urinary excretion (reduced renal reabsorption), blunted bone uptake and release, hyperadrenoglucocorticosis, and insulin resistance [52]. Secondary Mg2+ deficiency arises due to various pathologies (e.g. diabetes mellitus type II, alcoholism, HIV/AIDS, acute myocardial infarction) and treatments (e.g. hypermagnesuric diuretics, digitalis, cardiopulmonary bypass) [75]. Furthermore, chronic Mg2+ depletion (hypomagnesemia), secondary to reduced dietary intake, decreased intestinal absorption, and/or increased renal losses, has been linked to increased risk of numerous preclinical and clinical events associated with the development of and/or presence of MetS including: stroke, atherosclerosis, myocardial infarction, hypertension, glucose intolerance, insulin resistance, diabetes mellitus, endothelial dysfunction, vascular wall remodeling, alterations in lipid metabolism and homeostasis, ventricular dysfunction, ventricular arrhythmias, atheroma formation, platelet aggregation/abnormal thrombosis, inflammation, oxidative stress, and cardiovascular mortality [75-85].

Magnesium and blood pressure

Several ecological studies during the 1970s provided the first epidemiologic data delineating a plausible link between water hardness and blood pressure; importantly, these works implied that Mg2+ may be the key agent responsible for the blood pressure lowering [86, 87]. More recent experimental, clinical, and epidemiologic work has demonstrated a clear role for Mg2+ in the modulation of blood pressure and development of hypertension. Decreased serum and tissue [Mg2+] has been reported in ventricular myocytes, skeletal fibers, smooth muscle cells, and circulating erythrocytes, lymphocytes, and platelets obtained from several animal models of experimental hypertension including the spontaneously hypertensive rat (SHR), deoxycorticosterone acetate (DOCA)-salt prone SHR models [88-103]. Similarly, in human hypertension, several studies have indicated that Mg2+ is depleted in numerous tissues (e.g. heart, lungs, kidney, bone, skeletal muscle, and blood vessels) and cell types (e.g. vascular smooth muscle cells, fibroblasts, erythrocytes, platelets, and lymphocytes) [71, 104-113]. Mechanisms for Mg2+ depletion in experimental and human hypertension have been postulated to include impaired gastrointestinal absorption, increased urinary losses of Mg2+, and compromised cellular Mg2+ handling [114, 115]. At the cellular level, reduced Mg2+ content in hypertension may be due to dysfunction of the NME [116]. Indeed, investigators have shown that NME activity is increased in erythrocytes of essential hypertensive patients, in lymphocytes of patients with hyperaldosteronism, and in vascular smooth muscle cells from hypertensive rats where it has been suggested to promote Mg2+ efflux [116, 117]. Moreover, inhibition of the NME decreases blood pressure in AngII overloaded animals through mechanisms that most likely involve several renal and vascular nitrogen activated protein kinases [118].

Alternatively, it may be that chronic deficiencies in Mg2+ by way of reduced intake promote the development of hypertension. Studies from the Dietary Approaches to Stop Hypertension (DASH) study demonstrate that a diet rich in fruit, vegetables, low-fat dairy products, fiber and minerals (calcium, magnesium, potassium, and potassium) produces a potent antihypertensive effect [119]. A comprehensive review of 29 observational studies indicated that Mg2+ intake is inversely related to systolic and diastolic blood pressure and incident hypertension [120]. Recent prospective cohort data paint a convincing picture of insufficient intake of Mg2+ increasing the risk for increased systolic and diastolic blood pressure and incident hypertension [121]. Joffres et al. reported that, of several nutrients, increased Mg2+ intake was the most strongly associated with blood pressure reduction in a large cohort of Japanese men within the Honolulu Heart Study [121]. These findings have also been paralleled in over 15,000 participants where lower Mg2+ intake and serum levels were associated with increased systolic and diastolic blood pressure and incident hypertension in the large, biracial Atherosclerosis Risk in Communities (ARIC) cohort [122, 123]. In the Women’s Health Study, subjects in the highest quintile of dietary Mg2+ intake displayed the lowest risk of developing incident hypertension [124]. Additionally, data from the Dietary Intervention Study in Children has shown that dietary intake of Mg2+ was strongly and inversely correlated with...
systolic and diastolic blood pressure in children between 8 and 11 years old [125]. Finally, the Belgian Interuniversity Research on Nutrition and Health Study indicates that Mg²⁺ intake is inversely related to systolic blood pressure in women [126].

Much evidence regarding the biological and functional impact of chronic dietary Mg²⁺ deficiency has been gleaned from work in animal models. These studies have shown that dietary restriction of Mg²⁺ results in: elevated blood pressure and development of hypertension, reduced arterial distensibility (increased stiffness), endothelial dysfunction, vascular remodeling (smooth muscle hypertrophy, increased intima-media thickness), increased sympathetic nervous system activity, and augmented responses to vasoconstrictor molecules (e.g. endothelin, AngII, phenylepine, nor epinephrine, and Ca²⁺) [102, 127-132]. In contrast, increases in Mg²⁺ status through supplementation in healthy animals, elicits vasodilation, increased blood flow, decreased vascular resistance, reduced arterial stiffness, increased capacitance of peripheral, coronary, renal, and cerebral arteries, and blunted agonist-elicited vasoconstriction [109, 133, 134].

Thus, while it appears that sufficient dietary intake of Mg²⁺ may lower blood pressure and prevent the development of hypertension through one of several mechanisms, data from interventional studies also illustrate that oral Mg²⁺ pharmacotherapy lowers blood pressure in subjects with and without established hypertension. In humans, oral Mg²⁺ pharmacotherapy was first shown to reduced blood pressure in patients with essential hypertension as early as 1925 [135]. Over the years, several clinical studies have shown that Mg²⁺ treatment reduces blood pressure in patients with established hypertension [136-139]. Mg²⁺ has also been used to treat pre-eclampsia, defined as hypertension in pregnant women after 20 weeks of gestation along with proteinuria and edema [140]. Taken together, although results from some clinical trials are slightly conflicting [141], a meta-analysis of 20 studies including over 1200 patients clearly indicates that Mg²⁺ supplementation does indeed elicit a dose-dependent decline in blood pressure in normal and hypertensive subjects [142].

The benefits of sufficient Mg²⁺ intake and/or oral Mg²⁺ pharmacotherapy are likely to lie, at least somewhat, in the normalization of Mg²⁺ levels in serum, erythrocytes, smooth muscle cells, and endothelial cells. In smooth muscle, a decline in [Mg²⁺] elicits a reciprocal increase in [Ca²⁺] which, in turn, prompts smooth muscle contraction, increased vessel tone and augmented blood pressure [143-147]. In the endothelial cell, the decline in [Mg²⁺] alters production of several vasoactive compounds including nitric oxide, prostaglandins, and endothelin-1 [131, 148-150]. In vitro studies indicate that Mg²⁺ deficiency results in decreased production of nitric oxide (NO) from endothelial cells along with a decreased vasodilatory response to acetylcholine and adenosine diphosphate, which could be restored by increasing [Mg²⁺] in the bathing solution [151]. Apparently, high [Mg²⁺] triggers production of NO by upregulating expression of endothelial nitric oxide synthase [131, 152]. NO is a potent vasodilator and not surprisingly a decline in its production has profound effects on arteriolar caliber, resistance, and blood pressure [153]. Mg²⁺ has also been shown to promote synthesis and release of endothelial and smooth muscle cell derived prostacyclin (prostaglandin I₂; PGI₂) which induces smooth muscle cell hyperpolarization by opening potassium channels, and thus, decreases smooth muscle cell contraction, arteriolar resistance, and, consequently, blood pressure [154-156]. In support of this tenet, Laurant et al., showed that, in the hypertensive DOCA-salt sensitive rat, increased Mg²⁺ intake results in decreased blood pressure as well as increased aortic concentration of PGI₂ [157]. Furthermore, Mg²⁺ deficiency elicits profound effects on endothelin-1 homeostasis. Endothelin-1 is a potent vasoconstrictor peptide synthesized in and released from endothelial cells [158]. In experimental models of hypertension, Mg²⁺ supplementation decreased endothelin-1 expression, production, and vasoconstrictor effects, whereas Mg²⁺ depletion resulted in increases in endothelin-1 production and release [93, 97, 129, 159, 160].

There is now substantial evidence that Mg²⁺ controls activation of both the renin-angiotensin-aldosterone system (RAAS) in health and disease. Aberrant activation of the RAAS has been associated with hypertension, insulin resistance, diabetes mellitus, along with increased oxidative stress, reduced NO bioavailability, and increased synthesis of pro-inflammatory cytokines; several common MetS phenomena [161]. Serum and cellular [Mg²⁺] has been reported to relate inversely to renin, aldosterone, epinephrine, and norepinephrine in patients with hypertension [113, 162]. For example, in hypertensive subjects with high plasma renin activity, serum [Mg²⁺] was much lower than that in normotensive patients [163]. Additionally, others indicate that, at the adrenal cortex, Mg²⁺ supplementation decreases AngII stimulated production and release of aldosterone from zona glomerulosa cells of normotensive subjects [164]. In Mg²⁺ deficient animals, others have
reported increased plasma renin activity and circulating levels of corticosterone and aldosterone [128, 165]. Finally, in vitro studies in isolated umbilical arteries revealed that exclusion of Mg2+ from the bathing medium results in increased contractile response to AngII, serotonin, and prostaglandin F2α [166]. Mg2+ also controls activity of the sympathetic nervous system. Shimosawa and coworkers noted that high [Mg2+] interferes with the release of norepinephrine in perfused mesenteric arteries by blocking N-type Ca2+ channels at nerve endings, which counteracts increases in blood pressure [167]. Rats fed a Mg2+ deficient diet manifest increases in catecholamine excretion and renal sympathetic activity coincident with increases in blood pressure [132]. In chronically hypertensive animals, Mg2+ supplementation has also been shown to attenuate anti-diuretic hormone and norepinephrine induced vasoconstriction of vascular smooth muscle along with vascular remodeling [129]. In vitro studies have shown that increasing Mg2+ in the bathing solution promotes relaxation of norepinephrine-precontracted aorta isolated from hypertensive rats [98]. Finally, in cultured mesenteric and aortic smooth muscle cells isolated from hypertensive rats, Touyz et al. illustrated that Mg2+-blunted vasopressor dependent increases in smooth muscle Ca2+ and consequent contraction [168].

Recent studies have expanded our understanding of the precise molecular details involved in Mg2+-dependent control of endothelial cell function, smooth muscle cell contractility, and blood pressure. In work with experimental models of hypertension, Northcott and Watts found that a decline in Mg2+ triggered activation of phosphatidylinositol-3-kinase (PI3-K), which increased both smooth muscle contraction and the contractile response to the vasoconstrictor phenylephrine, all of which were ablated by PI3-K inhibition [101]. Other studies, in cultured carotid and cerebral smooth muscle cells, revealed that Mg2+ deficiency induces smooth muscle contraction through activation of PI3-K as well as protein kinase C (PKC) α and βII [144-147]. Of note, inhibitors of both PI3-K and PKC decreased contraction of smooth muscle cells [147]. Investigators went on to illustrate that chronic Mg2+ depletion of aortic and cerebral smooth muscle cells activates transcription of early response genes (c-fos, c-jun), increases DNA synthesis, and increases protein expression of NF-κB; responses which were ablated by nonspecific PKC inhibition [90]. NF-κB is a multifunctional transcription factor of various genes linked to inflammation [169]. Finally, low Mg2+ has also been shown to promote smooth muscle cell contraction through activation of mitogen activated protein kinases and tyrosine kinases [144-146]. In summary, there is considerable experimental, clinical, and epidemiologic data that chronically reduced Mg2+ status causes endothelial dysfunction, enhanced smooth muscle contractility, increased responsiveness to vasoconstrictor agonists, and, as result, high blood pressure.

**Magnesium, glucose intolerance, insulin resistance and diabetes mellitus**

Data derived from numerous epidemiologic studies, including the Nurses’ Health Study, Women’s Health Study, and ARIC Study, has consistently illustrated an inverse relation between Mg2+ consumption/status and risk for incident insulin dependent and non-insulin dependent diabetes mellitus in diverse populations [48, 51, 122, 170-175]. Furthermore, various researchers have shown that plasma and cellular [Mg2+] are reduced in patients with insulin resistance, impaired glucose tolerance, and full-blown diabetes mellitus [50, 59, 173, 176-180]. Additionally, myocardial Mg2+ content is also depressed in diabetic subjects [181]. The reduced Mg2+ status may arise secondary to: reduced intake and/or urinary losses. Indeed, recent population based studies suggest that patients with either diabetes mellitus type I or type II consume inadequate amounts of Mg2+ [182]. Alternatively, reduced Mg2+ status in diabetics may be explained by urinary losses. For example, hypermagnesuria is a rather common finding in diabetic subjects [182, 183]. Of note, improved metabolic control of diabetics reduces Mg2+ losses in the urine [180]. It may be that hyperinsulinemia is the root cause of the hypermagnesuria as an intravenous infusion of insulin has been shown to cause an increase in urinary excretion of Mg2+ without changes in other cations [182].

Clinical trials have delineated a convincing benefit of oral Mg2+ pharmacotherapy in improving insulin sensitivity (indexed by HOMA-IR analysis), glucose homeostasis (fasting glucose, glucose uptake, oxidative glucose metabolism), and hemoglobin A1c levels in patients suffering with diabetes mellitus [184, 185]. Moreover, a recent meta-analysis of 9 randomized double-blind controlled studies of 370 patients indicated that oral Mg2+ supplementation for a period of 12 weeks significantly lowered fasting serum glucose levels in type II diabetic patients [186]. These salutary effects appear to be due, in part, to improved insulin elicited glucose uptake as Mg2+ is essential
for optimal coupling and signaling through the insulin receptor. Indeed, glycolytic flux is strongly determined and dependent upon cellular Mg$^{2+}$ status [187]. For example, in animal models, Mg$^{2+}$ deficiency results in increased serum glucose, decreased glucose utilization, blunted glucose-elicited β-cell insulin release, reduced insulin sensitivity, decreased phosphorylation of the β-subunit of the insulin receptor, concomitant with decreased tyrosine kinase activity [188, 189]. In vitro studies utilizing myocardial purified insulin receptors have shown that Mg$^{2+}$ stimulates the insulin receptor tyrosine kinase in both insulin-dependent and independent fashions [190]. Moreover, there is lucid evidence that prolonged increases in cellular [Ca$^{2+}$], arising secondary to a decline in [Mg$^{2+}$], blunt insulin sensitivity. Specifically, it appears that increased [Ca$^{2+}$] causes a decline in the ability of insulin to activate phosphoserine phosphatase-1, which promotes insulin-triggered glucose influx and storage by removing phosphates from GLUT-4, glycogen phosphorylase, and glycogen synthase [191]. Others postulate that enhanced cellular Ca$^{2+}$ activates protein kinase C isozymes, which increase protein phosphorylation and decrease insulin sensitivity [192]. In addition to modulating insulin sensitivity and responsiveness in skeletal muscle and adipose tissue, there is some evidence that Mg$^{2+}$ may also regulate pancreatic β-cell function [193, 194]. Taken together decreased Mg$^{2+}$ status results in: decreased tyrosine kinase activity, increased intracellular [Ca$^{2+}$], decreased activation of phosphoserine phosphatase-1, and increased protein kinase C activity, all of which conspire to decrease insulin sensitivity, glucose uptake and utilization, and glycolytic flux.

Magnesium, atherogenic dyslipidemia and ischemic cardiomyopathy

Atherosclerosis is regarded as an inflammatory disease marked by endothelial dysfunction, fatty streak formation, foam cell infiltration, and ultimately plaque development and rupture [195]. Reduced Mg$^{2+}$ balance is emerging as a key component in the pathogenesis of atherosclerosis and ischemic heart disease [196]. Moreover, Mazur et al. have provided strong evidence that Mg$^{2+}$ depletion may beget atherosclerosis by promoting a hyperinflammatory state [42]. Indeed, myocardial and aortic Mg$^{2+}$ contents are reduced in patients who died due to aortic aneurysm, acute myocardial infarction, and ischemic cardiomyopathy [197-200]. The decline in myocardial Mg$^{2+}$ has been suggested to result secondarily from hypomagnesemia [201]. Low Mg$^{2+}$ intake and, consequently, reduced serum Mg$^{2+}$ levels have been associated with an increased risk for coronary heart disease in the multi-ethnic ARIC cohort and in the Honolulu Heart Program [202, 203]. Moreover, in interventional studies, oral Mg$^{2+}$ supplementation has been shown to reduce serum triglycerides, apolipoprotein B, LDL-cholesterol, total cholesterol, and increase HDL-cholesterol in high risk patients with ischemic heart disease [204-206]. In genetic (ApoE and LDL-receptor deficient) and dietary (hypercholesteremic diet) murine models of atherosclerosis, Mg$^{2+}$ supplementation and resultant increases in serum [Mg$^{2+}$] cause a decline in total cholesterol, aortic deposited cholesterol, plaque area, lipid peroxidation, LDL oxidation, and extent of atherosclerosis [207-211]. Similarly, in rabbit models of coronary artery disease, Mg$^{2+}$ supplementation reduced serum cholesterol, triglycerides, atheroma formation, atherosclerotic lesions, and decreased intima-media thickness [212, 213]. In addition to established coronary artery disease, Mg$^{2+}$ balance has also been linked to increased burden of subclinical measures of arteriosclerosis (e.g. intimal media thickness, cross-sectional compliance, cross-sectional distensibility, increased elastic modulus) [214, 215].

The antiatherogenic effects of Mg$^{2+}$ appear to involve, at least partially, modification of several enzymes intricately linked with lipid metabolism and turnover including: lipoprotein lipase, HMG-CoA reductase, and lecithin acyltransferase. Lipo protein lipase is an enzyme normally docked on endothelial cells which hydrolyzes lipids in lipoproteins, like those found in chylomicrons and very low density lipoproteins (VLDL), into three fatty acids and one glycerol molecule [216]. Rodents fed a Mg$^{2+}$-deficient diet display increased serum triglycerides and reduced HDL-cholesterol secondary to reduced serum activity of lipoprotein lipase [217]. Mg$^{2+}$ is also an essential short-term modulator of HMG-CoA reductase, which catalyzes the rate-limiting step in cholesterol synthesis. Indeed, in in vitro studies, increasing the [Mg$^{2+}$] in the bathing solution attenuates HMG-CoA reductase activity [218]. In this capacity, Mg$^{2+}$ functions as a “physiological statin”. Lecithin acyltransferase (LCAT) is involved in reverse cholesterol uptake and, in so doing, facilitates cholesterol uptake from tissues into HDL-cholesterol [219]. LCAT activity is markedly reduced in patients with an acute MI and coronary artery disease co-incident with increased LDL-cholesterol, triglycerides, and reduced HDL-cholesterol [219]. LCAT activity also has been reported to be altered by changes in
Mg\(^{2+}\) homeostasis [220, 221]. Nozue et al. suggest that there is a direct relationship between ionized Mg\(^{2+}\), serum LCAT activity, and HDL-cholesterol levels in children [222]. Furthermore, in Mg\(^{2+}\) deficient rats, other investigators observed decreased LCAT activity along with reduced HDL-cholesterol and hyperlipidemia [84, 220]. Similarly, Δ-6 desaturase activity and expression was found to be decreased in hepatic microsomes isolated from Mg\(^{2+}\) deficient animals [223]. Δ-6 desaturase is an enzyme important in the conversion of essential ω-3 and ω-6 fatty acids to prostaglandins, which execute vasodilatory, antiplatelet aggregating, and antiatherogenic effects [223, 224]. Besides modulating catalytic activity of multiple enzymes involved in lipid metabolism, Mg\(^{2+}\) also regulates LDL-cholesterol uptake and oxidation. In animal models of Mg\(^{2+}\) depletion, LDL-cholesterol particles were more susceptible to oxidative damage [225, 226]. At the cellular level, exposure of endothelial and smooth muscle cells to low Mg\(^{2+}\) results in increased LDL transport and uptake, increased LDL oxidation, along with smooth muscle cell proliferation and intimal invasion; all of which are key features of the atherogenic process [210, 226-229]. Low Mg\(^{2+}\) increases IL-1 and IL-6 along with vascular cell adhesion molecule (VCAM) which is important for binding of leukocytes to the vascular endothelium and formation of atherosclerotic lesions [230]. Mg\(^{2+}\) deficiency has also been associated with structural changes in the vascular wall such as thinner aorta, altered expression of collagen and elastin, and changes in protein levels of matrix metalloproteinases 2 and 9 and thereby contribute to vascular smooth muscle remodeling and coronary artery disease [231]. Mechanistically, it appears that Mg\(^{2+}\) decreases matrix metalloproteinase production and secretion via tyrosine kinase dependent pathways in vascular smooth muscle and cardiac fibroblasts [232]. Taken together, reduced Mg\(^{2+}\) status promotes dyslipidemia and coronary artery disease by: i) altering the catalytic activity of several enzymes involved in lipid metabolism (namely HMG-CoA reductase, LCAT, Δ-6 desaturase); ii) promoting oxidation of serum lipids; iii) eliciting alterations in vascular wall biology; and iv) promoting increased inflammation and oxidative stress.

**Magnesium and obesity**

Central adiposity is another major hallmark of MetS and is often associated with a state of insulin resistance and impaired glucose tolerance [233]. There is emerging data that Mg\(^{2+}\) homeostasis may help sustain normal bodyweight. Specifically, it has been suggested that Mg\(^{2+}\) can form insoluble soaps with fatty acids in the intestine and in so doing prevent absorption of dietary fat [234]. Others have also indicated that obese adults and children are chronically deficient in Mg\(^{2+}\), which may help explain the insulin resistance observed in these patients [235-237]. In a Spanish population study, others have showed that obese subjects had decreased Mg\(^{2+}\) intake and serum levels [238]. In a cross-sectional study in which body fat was measured by bioelectric impedance in over 800 Indian men, it has been reported that individuals with higher body fat manifest lower serum Mg\(^{2+}\) and heightened oxidative stress [239]. Finally, in an animal model of obesity, Mazur et al. reported that obese animals had reduced erythrocytes and plasma Mg\(^{2+}\). Feeding the animals a high fiber diet reduced body weight, improved insulin sensitivity, normalized serum lipids, and corrected plasma Mg\(^{2+}\) content [240]. Apparently, Mg\(^{2+}\) modulates adipocyte function by stimulating adenylyl cyclase activity and increasing production of cyclic AMP [241]. Importantly, such changes in adipocyte function may be involved in energy metabolism, storage, and control of glucose homeostasis [242]. Indeed, rat epididymal adipocytes cultured in Mg\(^{2+}\)-deficient media manifested a reduction in insulin-promoted glucose oxidation and CO\(_2\) generation [243]. Future studies are needed to tease out the specific molecular and cellular mechanisms through which Mg\(^{2+}\) modulates adipocyte biochemistry and physiology and how such events may potentiate fat storage in those with or at risk for MetS.

**Magnesium and thrombosis**

Although not regarded as an essential component for defining the MetS, altered blood coagulation (hypercoagulability) is a commonly observed clinical feature in many MetS sufferers [1, 3, 11]. The prothrombotic state in MetS patients is characterized by high levels of plasminogen activator inhibitor-1 (PAI-1), fibrinogen, and other coagulation factors along with platelet abnormalities [244, 245]. Indeed, others have suggested that low platelet [Mg\(^{2+}\)] in those with excess adiposity, insulin resistance, diabetes mellitus type I and II, and hypertension accounts for the hypercoagulability in these patients [71, 105, 162, 176, 246-248]. In support of this notion, reduced Mg\(^{2+}\) status in human platelets results in decreased NO-elicited soluble guanylyl cyclase activity, decreased in [cGMP] levels in platelets, and presumed increases in platelet aggregation. Further-
more, in animal models of stent thrombosis, Mg2+ exhibits potent antithrombotic effects [105]. Importantly, atherosclerosis is a key feature of atherosclerosis, myocardial infarctions, and strokes; all of which are common clinical outcomes of the MetS.

A meta-analysis of randomized clinical trials which enrolled 1266 patients illustrated a salutary effect of Mg2+ in lowering the risk of ischemic events [249]. The second Leicester Intravenous Magnesium Intervention Trial (LIMIT-2) was the first clinical trial to illustrate a beneficial effect of oral MgSO4 supplementation in improving long-term survival, and reducing cardiovascular, and all-cause mortality along with reducing left ventricular failure in patients with an acute myocardial infarction, when given before any thrombolytic therapies [250]. Mechanistically, Mg2+ may prove beneficial in high-risk patients with an acute myocardial infarction by reducing: platelet aggregation, coronary artery resistance, myocardial O2 demand, and/or oxidative stress.

There now is compelling basic and clinical science data that Mg2+ supplementation, either oral or intravenous, decreases abnormal blood clotting in at-risk populations. Shechter et al. observed a correlation between intra-lymphocyte Mg2+, platelet-dependent thrombosis, and platelet P-selectin expression in patients with coronary artery disease [85]. Additionally, Mg2+ supplementation has been documented to improve flow mediated brachial vasodilation (endothelial function index), as well as, reduce platelet aggregation, fibrinogen binding with the glycoprotein IIb/IIa complex, and platelet expression of P-selectin, in patients with symptomatic coronary heart disease [85, 251-253]. The decline in expression of the glycoprotein P-selectin would be expected to interfere with platelet-leukocyte adhesion. Mg2+ has also been found to extend bleeding time in patients undergoing successful coronary revascularization with cardiopulmonary bypass, via mechanisms that involve blunted ADP and collagen-dependent platelet aggregation, platelet P-selectin expression and fibrinogen binding to platelet glycoprotein IIb/IIa receptor [254]. Sheu et al. reported that Mg2+ blocks phosphoinositide breakdown, collagen-elicited Ca2+ mobilization and thromboxane A2 formation, in parallel with a decline in phosphorylation of a 47Kda protein [255]. In healthy volunteers, others observed that Mg2+ decreased platelet synthesis of thromboxane and β-thromboglobulin independent of acetyl-salicylic acid [256]. Also, Itoh et al. reported that Mg2+ prevents PKC activation, phosphoinositide breakdown, and Ca2+ mobilization secondary to decreased sodium-hydrogen exchanger activity in thrombin-stimulated platelets [257]. It may that Mg2+ decreases platelet aggregation by inducing prostacyclin synthesis and release from endothelial cells, or, alternatively, by interfering with platelet stimulating factors (i.e. thromboxane A2) [156, 247, 252, 255, 256, 258, 259].

**Magnesium, inflammation, and oxidative stress**

**Inflammation**

An increased inflammatory burden, as indexed by serum levels of acute-phase proteins such as C-reactive protein (CRP), fibrinogen, plasminogen activator inhibitor-1 (PAI-1), interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), has been identified as a strong risk factor for incident insulin resistance, impaired glucose tolerance, and diabetes mellitus type II, atherosclerosis and coronary heart disease, cerebrovascular disease and stroke, and hypertension [244, 260-267]. Additionally, CRP levels have also been directly related to measures of fibrinolysis, such as PAI-1; indicating a direct functional link between inflammation and impaired coagulation; an increasingly common feature of the MetS [268]. Now, there is considerable data that obesity, abdominal adiposity, and BMI, known risk factors for MetS, are associated with increased adipocyte production of pro-inflammatory cytokines (e.g. TNF-α, IL-6) and decreased production of anti-inflammatory cytokines (e.g. adiponectin) [269]. Studies in murine models of obesity have shown that TNF-α expression in adipocytes is upregulated and elicits impaired insulin resistance and reduced glucose and lipid handling [270]. In humans, several studies have correlated plasma TNF-α and TNF-α receptor concentrations with the degree of obesity and have shown that levels of this pro-inflammatory cytokine decline with weight loss [271, 272]. Adiponectin is an anti-inflammatory cytokine produced purely by adipocytes that augments insulin sensitivity, improves glucose transport, flux, and utilization, and decreases many pro-inflammatory processes [273]. Also, patients with MetS or one of its components display reduced serum levels of adiponectin [274-277].

Using National Health and Nutrition Examination Survey (NHANES) data, Ford et al. illustrated that in children and adolescents, serum CRP was related to prevalence of the MetS [278]. Other studies have also reported associations between CRP and prevalent MetS [279-282]. Cross-sectional findings from the Framingham Heart Study have shown that CRP is related to the prevalence of MetS and is a useful risk
predictor of incident cardiovascular disease events in subjects with the MetS [19]. Several large-scale prospective cohort studies, including the Women’s Health Study and the West of Scotland Coronary Prevention Study, revealed that high-sensitivity CRP levels are independently associated with the risk for incident MetS [262, 283, 284]. Data from the Women’s Health Study, has shown that Mg²⁺ intake was inversely related with systemic inflammation, gauged by serum CRP levels, and prevalence of MetS in women over the age of 45 [48]. Similar findings have also been reported using NHANES data [285]. In a cross-sectional study of 280 men from the Health Professions Follow-Up study, higher Mg²⁺ intake was associated with higher adiponectin levels [286]. Numerous other researchers have also shown an inverse relation between Mg²⁺ intake, serum Mg²⁺, and TNF-α, IL-6, and CRP levels in healthy children and adults [82, 285, 287-289]. In cross-sectional studies, researchers observed that higher TNF-α levels were correlated with lower serum Mg²⁺ in obese individuals (BMI ≥ 30kg/m²) [289]. Moreover, in multi-variate analysis, those with the lowest serum Mg²⁺ were 80% more likely to have higher TNF-α levels [288]. Interestingly, pharmacologic treatment with a soluble TNF-α receptor (etanercept) reduced CRP, IL-6, and fibrinogen levels in patients with the MetS [290]. In animals, several studies have shown that Mg²⁺ deficiency causes marked elevation of several pro-inflammatory molecules including: TNF-α, IL-1β, IL-6, VCAM, and PAI-1 [131, 291-296], increased circulating inflammatory cells [297], and increased hepatic production and release of acute phase proteins (e.g. α2-macroglobulin, α1-antichymotrypsin, complement, haptoglobin, fibrinogen) [292, 297-299]. A direct mechanism link has been provided by in vitro studies which illustrated that low Mg²⁺ results in increased production and secretion of TNF-α and IL-1β in cultured adipocytes and alveolar macrophages [300, 301].

**Oxidative stress and antioxidant defense**

Oxidative stress and compromised antioxidant defense mechanisms are commonly associated with the MetS [42, 82]. Serum γ-glutamyl transferase (GGT), a marker of oxidative stress and precipitant of inflammatory molecules, was independently associated with an increased prevalence of high body mass index, blood pressure, LDL-cholesterol, triglycerides, blood glucose, and incident MetS [302]. Guerrero-Romero et al. reported that, in a small case-control study, hypomagnesemia (defined as serum [Mg²⁺] < 1.8 mg/dL) was positively associated with increased risk for incident MetS in parallel with increased serum CRP and malondialdehyde (oxidative stress biomarker) levels [82]. In Italian subjects, low Mg²⁺ intake was positively associated with increased CRP, uric acid, and GGT levels and reduced levels of vitamin C and E in subjects with prevalent MetS [49]. Oxidative stress may contribute to the etiopathology of the MetS by promoting insulin resistance, β-cell dysfunction, and diabetes [303, 304]. Interventional studies have shown that treatment with antioxidant therapies (e.g. vitamin C, E, and glutathione) improves insulin sensitivity in diabetic subjects [304-307]. Of note, some studies imply that improvement in endogenous antioxidant capacity (cellular GSH: GSSG ratio) and blunting of oxidative stress (decreased GSH, GSSG, increased lipohydroperoxides, increased thiobarbituric acid-reactive substances (TBARS), and decreased TEAC-rolox equivalent antioxidant capacity) are associated with improved whole body glucose disposal, which involves cellular Mg²⁺ homeostasis in important ways [305, 307].

In humans and animal models, Mg²⁺ deficiency has been linked with increased oxidative stress and decreased antioxidant defense, due, in part to increased inflammation [42, 296, 308, 309]. Previous studies have shown convincingly that Mg²⁺ deficiency in vitro or in vivo results in: increased production of oxygen-derived free radicals in various tissues, increased free-radical elicited oxidative tissue damage, increased production of superoxide anion by inflammatory cells, decreased antioxidant enzyme expression and activity (e.g. glutathione peroxidase, Cu/Zn superoxide dismutase, catalase), decreased cellular and tissue antioxidant levels (glutathione, ascorbate, selenium, vitamin E), and increased H₂O₂ production [42, 46, 127, 225, 227, 293, 295, 300-310]. In support of this notion, there is data to suggest that Mg²⁺, when present in sufficient amounts, prevents oxygen radical formation by scavenging free radicals and inhibiting xanthine oxidase and NADPH oxidase [320]. Moreover, Calviello et al. found that Mg²⁺ deficiency in rats causes decreases in hepatic glutathione, superoxide dismutase, and vitamin E along with increased lipid peroxidation and malondialdehyde levels secondary to upregulated NADPH oxidase activity [321]. Several interventional studies in animal models of Mg²⁺ deficiency have provided convincing evidence of the link between Mg²⁺ inflammation, oxidative stress, and components of the MetS. Treatment of Mg²⁺ deficient rats with an anti-inflammatory agent (chloroquine) preserves erythrocyte glutathione content,
lowers the rise in plasma TBARS levels in parallel with a decline in TNF-α, IL-1, and IL-6 levels [318]. In stroke-prone spontaneously hypertensive rats, Mg2+ deficiency results in marked increases in systolic blood pressure, blunted endothelial dysfunction, superoxide accumulation, and MAPK activation, all of which were attenuated with a superoxide dismutase mimetic (tempol) [322]. In experimental diabetes, researchers have observed decreases in serum and erythrocyte Mg2+ levels and increased urinary excretion of Mg2+ in parallel with increased plasma malondialdehyde, decreased plasma and liver vitamin C and E levels, decreased expression of hepatic superoxide dismutase and glutathione S-transferase; all of which were corrected by Mg2+ supplementation [311]. Taken together, Mg2+ deficiency results in enhanced oxidative stress and reduced antioxidant defense, which promotes inflammation, lipid oxidation, insulin resistance, pancreatic β-cell dysfunction, vascular remodeling, and atherosclerosis [311, 319, 323-325].

Conclusion

In this review, we have presented a comprehensive discussion of the myriad of molecular and cellular mechanisms by which reduced Mg2+ status can elicit hypertension (endothelial dysfunction; smooth muscle contraction and remodeling), insulin resistance, impaired glucose tolerance, dyslipidemia, atheroma development, ischemic cardiomyopathy, increased adiposity, enhanced thrombosis, inflammation, and oxidative stress (summarized in Figure 1). The causal mechanisms linking altered Mg2+ homeostasis and the metabolic syndrome clearly translate into clinical outcomes, increased incidence, as well as growing prevalence of the metabolic syndrome epidemic. While not impossible, pharmacologic prevention and management of the metabolic syndrome is difficult to attain, as numerous pharmacologic agents must be employed to control the bevy of cardiovascular disease and diabetes risk factors. Furthermore, given its pleiotropic impact on all
components of the metabolic syndrome, Mg\(^{2+}\) seems like an ideal candidate to use in strategies aimed at preventing and controlling the syndrome. Future studies that elucidate, with great clarity, the large-scale impact of Mg\(^{2+}\) supplementation on the pathogenesis of the metabolic syndrome or its components are urgently needed. Consequently, clinical trials should be conducted to unequivocally confirm that Mg\(^{2+}\) therapy can prevent the development of the metabolic syndrome and its components in diverse at risk populations.

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