Magnesium Supplements and Statin Medication

Subjects: Medicine, General & Internal

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Many investigations have discovered a connection between statins and magnesium supplements. On one hand, increasing research suggests that chronic hypomagnesemia may be an important factor in the etiology of some metabolic illnesses, including obesity and overweight, insulin resistance and type 2 diabetes mellitus, hypertension, alterations in lipid metabolism, and low-grade inflammation. Chronic metabolic problems seem to be prevented by a high Mg intake combined with diet and/or supplements.

Keywords: magnesium supplements ; metabolic syndrome ; lipoproteins ; statins ; MetS ; Dyslipidemia

1. Introduction

Dyslipidemia, an important factor in defining metabolic syndrome (MetS), represents a worldwide challenge, due to the increased risk of atherosclerosis and cardiovascular diseases (CVD) [1]. Dyslipidemia is characterized by elevated levels of total cholesterol and/or triglycerides, with decreased high-density lipoprotein (HDL) levels. Elevated levels of LDL (low-density lipoprotein) and VLDL (very low-density lipoprotein-density) can be also observed [1][2][3].

The progression to atherosclerosis depends on the vascular endothelial metabolism (Kruppel-like factor 2 expression) and LDL serum level (above 20–40 mg/dL) [4][5][6].

Statins are the main treatment for LDL cholesterol reduction because they demonstrably lower cardiovascular morbidity and mortality (according to International Guidelines for the Management of Dyslipidemia 2022), in cases of high-risk conditions, such as clinical atherosclerosis, abdominal aortic aneurysm, diabetes mellitus, chronic kidney disease (age ≥50 years), and patients with LDL-C ≥ 5.0 mmol/L. However, many studies highlight a series of adverse reactions and/or rather modest results in reducing the level of LDL cholesterol and indirectly reducing dyslipidemia, after statin administration [7][8].

There are several factors involved in abnormal lipid profiles such as genetic background, a Western-style diet, alcohol abuse, being overweight or obese, insulin resistance, or some chronic conditions, such as nephrotic syndrome [8][2][3][9][10]. Recent studies suggest that serum magnesium levels can be associated with lipid abnormalities. As epidemiological research is refined by the description of the biological and pathophysiological mechanisms, the goal of this research is to summarize the current understanding of the pathological relationships between dyslipidemia, statin use, and serum magnesium levels.

It is not just theoretically interesting to learn about the connections between dyslipidemia and serum magnesium levels. Magnesium, through its action on lecithin–cholesterol acyl transferase (LCAT), can improve the metabolism of lipoproteins, and implicitly dyslipidemia [11][12][13][14]. If correctly controlled, interventions like diet, exercise, and magnesium supplementation could be very beneficial and lessen the effect of dyslipidemia on CVD [14].

2. Magnesium and Dyslipidemia

2.1. Magnesium Deficiency

Magnesium, the most common intracellular divalent cation, participates in around 300 enzymatic processes, including the metabolism of lipoprotein lipase (LPL), HMG-CoA reductase, and lecithin-cholesterol acyl transferase (LCAT), as well as the attenuation of Na-K ATPase and the breakdown of glycogen [15].

Just 1% of the body's magnesium is found in circulation (0.3% in plasma/serum), while the majority of the body's magnesium is found in the bony tissue (60%) and intracellular (40%) compartments [16]. Magnesium is distributed differently inside each individual compartment. For instance, bone has two deposits of magnesium: one in the bone

network and the other present on the bone surface. Magnesium within cells is found in the cell membrane, intracellular components, and the nucleus in some amounts. The content of magnesium in red blood cells (RBC) is three times higher in blood than it is in plasma [16]. There are currently two recognized types of magnesium shortage: acute hypomagnesemia and chronic magnesium deficit. Extreme cramps, nystagmus, refractory hypokalemia, refractory hypocalcemia, eclampsia during pregnancy, and cardiac arrhythmias are only a few of the clinical signs and symptoms of extracellular acute hypomagnesemia [17]. In some instances, they respond quickly to intravenous magnesium. Although a chronic magnesium shortage is frequently coupled with normal magnesium levels in serum (0.75–0.95 mmol/L), which is mistakenly thought to eliminate the magnesium deficiency, it represents decreased levels of magnesium inside the cells and bone [16][17]. The overall amount of magnesium absorbed and eliminated through the kidneys, as well as factors such as food intake or supplementation and serum albumin level, can all affect the body's magnesium levels [18]. Magnesium insufficiency is also made worse by other concomitant conditions such as inflammatory bowel disease, unmanaged diabetes, or renal dysfunction [19][20]. The causes that produce magnesium deficiency are presented in **Table 1.**

Table 1. Causes of magnesium deficiency.

Causes of Magnesium Deficiency	
Insufficient intake **A diet low in Magnesium** [18][21] **Slimming cures** [18][22]	**Intensification of losses** **At the gastrointestinal level: vomiting; purgatives/laxatives; trailing diarrhea** [19][23][24] **By the renal route: nephropathies; diuretics; chronic alcoholism; diabetes** [20][25][26][27][28][29][30][31]
Decreased intestinal absorption **Conditions after intestinal resection** [19][32] **Diarrhea** [19][23][24] **Malabsorption** [19][23][24][33] **Chron's disease** [19][24][33] **Ulcerative colitis** [19][33] **Coeliac disease** [19][23]	**Stressing Factors** **Pregnancy** [18][34][35][36][37] **Lactation** [18][34][35][36][37] **The growing period** [18][38] **Sport performance** [18][39][40][41] **Old age** [19][23][25][37][42][43] **Convalescence** [18][44][45]
Endocrine disorders **Hyperthyroidism** [20][46][47] **Aldosteronism** [20][46][47] **Hyperparathyroidism** [20][46][47][48] **Poorly controlled diabetes** [20][25][49]	**Interference of absorption** **Increased calcium intake** [18][33][48] **Hyper protein diet** [18][24] **Lipid foods** [18][48][50][51] **Excessive alcohol consumption** [18][37][52]

However, numerous epidemiological, experimental, and clinical studies (not dependent on the type, design, measured indexes, size, and statistical approach of these studies) have demonstrated that chronic magnesium deficiency is connected with higher risk and prevalence of the pathologies listed in **Figure 1**.

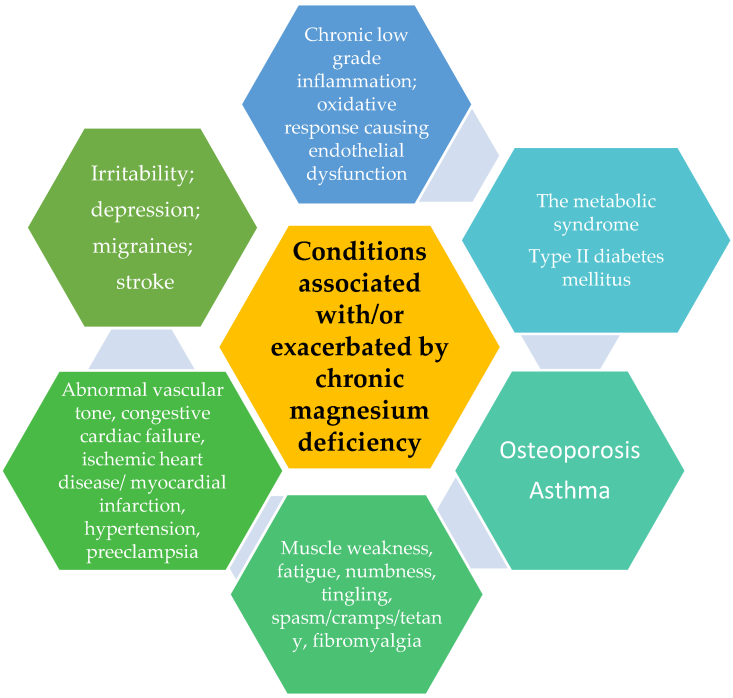

Figure 1. Pathologies connected to/or increased by chronic magnesium deficiency.

Also, it was discovered that a magnesium deficit could predict negative outcomes, and when supplementation or treatment was started, there was a decreased chance of pathology [17].

2.2. Magnesium and MetS

According to the World Health Organization (WHO), coronary heart disease (CHD) accounts for more than 7 million deaths each year and is the leading cause of mortality regardless the gender [53]. It is commonly recognized that type 2 diabetes (T2DM) is a significant risk factor for coronary heart disease (CHD). Patients with diabetes have twice the risk of developing coronary heart disease than people without the disease [20][54]. Several studies have demonstrated a link connecting CHD and metabolic syndrome (MetS), type 2 diabetes, and increased levels of oxidative and inflammatory stress biomarkers [55][56]. A complex biological process called oxidative stress is defined by an excessive creation of reactive oxygen species (ROS), which function as destabilizers of the body's REDOX balance and cause oxidative dysfunction. Oxidative stress impairs every process and even affects the equilibrium of nucleic acids. ROS interacts with proteins and phospholipids, which causes structural alterations in tissues and organs. Those who are predisposed to heart problems typically develop a constellation of cardiovascular risk factors (CVRFs). Oxidative stress is frequently linked to cardiovascular diseases (CVDs) such as coronary artery disease (CAD), cardiomyopathy, or heart failure (HF), which may occur in people with hypertension (HTN), diabetes mellitus (DM), obesity, and other disorders [57]. According to some studies, patients with CHD and T2DM had significantly lower levels of magnesium [12][38][58][59][60]. There is also strong evidence linking magnesium deficiency to metabolic syndrome [23][55][61][62]. The elements of MetS, such as hyperglycemia, hypertension, hypertriglyceridemia, and insulin resistance, have been linked to hypomagnesemia [12]. The components of MetS, such as insulin sensitivity, fasting blood glucose (FBG), triglyceride (TG) levels, high-density lipoprotein cholesterol (HDL-C), and high blood pressure (BP), is said to respond favorably to magnesium supplementation [58]. The aforementioned metabolic illnesses all share the common pathophysiological feature of chronic low-grade inflammation, and magnesium deficiency can both directly and indirectly cause inflammation by altering the gut flora [24]. In addition, a lack of magnesium worsens immunological function by priming phagocytes, promoting granulocyte oxidative burst, activating endothelial cells, and raising cytokine production levels [12]. Magnesium has anti-inflammatory, glucose, and insulin metabolism-improving, endothelium-dependent vasodilation-improving, and lipid profile-normalizing properties [63]. C-reactive protein (CRP), a measure of systemic inflammation and a predictor of future cardiovascular events in individuals with MetS, and serum magnesium levels are inversely correlated [20][64]. At the same time, changes in the metabolism of several micronutrients were observed in obese patients, such as decreased magnesium concentrations in the serum, plasma, and erythrocytes [21][65][66]. Magnesium supplementation has been shown to have positive effects on patients with metabolic disorders in terms of their metabolic profile [25]. For example, Asemi et al. demonstrated that magnesium supplementation in pregnant women with gestational diabetes (GDM), in the form of magnesium oxide at a dose of 250 mg per day, significantly improved glycemic control, lipoproteins, and the biomarkers of oxidative stress and inflammation [25]. Higher magnesium intakes were associated with lower fasting insulin levels in healthy women without diabetes [67]. The relationship between total dietary magnesium intake and insulin responses to an oral glucose tolerance test was inverse [23][39].

Recent evidence from some meta-analysis studies demonstrated the efficacy of oral magnesium supplementation in significantly decreasing various inflammatory markers, especially CRP, and increasing nitric oxide (NO) [68]. The reduction of fasting blood glucose was also observed, as well as a 3–4 mm Hg reduction in systolic blood pressure (SBP) and 2–3 mmHg in diastolic blood pressure (DBP), with a beneficial impact on the lipid profile [15][22]. The experimental data show that magnesium deficiency worsens atherosclerosis while magnesium supplementation slows atherogenesis [11][69][70]. In addition, randomized controlled trials have shown that magnesium supplementation improves endothelial function while lowering blood pressure [26][27][36][42], arterial stiffness [71], fasting hyperglycemia [27][72], insulin resistance [73], and postoperative arrhythmias [70][74].

2.3. Magnesium–Statin-like Effect

Magnesium is crucial for regulating the activity of several key enzymes involved in lipid metabolism, including 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase) [46][75], which controls cholesterol biosynthesis; lecithin–cholesterol acyltransferase (LCAT), which lowers plasma concentrations of LDL-c and VLDL-c [15][21]; desaturase (DS) [12][15]; and lipoprotein lipase (LPL) [47][76]. LPL, DS, and LCAT activity are suppressed by hypomagnesemia, and Mg supplementation can positively affect their expression [50][75]. On the other hand, Mg deficiency is associated with increased activity of HMG-CoA reductase [43]. The ratio of saturated to unsaturated fatty acids increases and the levels of TG, LDL, HDL, and VLDL decrease when the activity of this enzyme is impaired [77]. Modulation of the gene expression of LDLR (LDL receptor) and other transcription factors, such as sterol regulatory element-binding proteins SREBP-1a and SREBP-2, may also contribute to the hypercholesterolemic effect of an inadequate intake of Mg, although the increase in

LDL concentration is mediated by increased LDLR and SREBP expression [78]. According to a study in type 1 diabetes mellitus (T1DM) patients, the Mg levels and blood levels of oxidized low-density lipoprotein (ox-LDL) are linked [12]. Magnesium also seems to affect the expression of genes that regulate a number of processes, including adipogenesis, lipolysis, and inflammation, such as peroxisome proliferator-activated receptor gamma (PPARγ) [21][79]. Also, research has shown that a dietary magnesium deficiency causes a higher activity of the enzyme's serine palmitoyl CoA transferase 1 and 2, which, in turn, triggers the processes of atherogenesis, angiogenesis, and immunoreaction [12][21][80].

A 12-week randomized, double-blind, placebo-controlled clinical trial comparing the effects of magnesium oxide (250 mg/day) versus placebo on anthropometric indices, blood pressure, blood glucose, insulin, C-reactive protein, uric acid, and a lipid profile was performed on individuals with prediabetes (n = 86). Compared to the placebo group, subjects who took magnesium supplements had significantly increased levels of HDL cholesterol at the end of the study. However, magnesium supplementation at the dose and time mentioned above did not alter other cardiometabolic parameters [81].

Participants with moderate coronary artery disease (CAD) lowered their serum levels of LDL-C, SGOT, SGPT, and ox-LDL by taking 300 mg/day of MgSO4 for six months in a double-blind, randomized clinical investigation [66].

In addition, a recent meta-analysis of studies that included people with hypertriglyceridemia revealed an important decrease in triglyceride levels after magnesium supplementation, indicating a potential beneficial effect of magnesium supplementation on dyslipidemic diseases [15].

Clinical research using oral Mg supplementation provides the majority of the evidence for relationships between Mg and the blood lipid profile [28][29][46][76][77][82][83][84][85][86]. The authors of various meta-analyses describing this link stressed the inconsistency of the findings of this research [87][88]. The significant variety of groups examined, the numerous approaches to measuring blood serum Mg concentration, and the absence of stratification of the subgroups of patients compared have all contributed to the ambiguity of the results produced in this sector [12].

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