Hypomagnesemia in Cardiac Arrhythmias

Subjects: Cardiac & Cardiovascular Systems

Contributor: Alina Gabriela Negru, Anda Pastorcici, Simina Crisan, Gabriel Cismaru, Florina Georgeta Popescu, Constantin Tudor Luca

The importance of magnesium (Mg^{2+}), a micronutrient implicated in maintaining and establishing a normal heart rhythm, is still controversial. It is known that magnesium is the cofactor of 600 and the activator of another 200 enzymatic reactions in the human organism. Hypomagnesemia can be linked to many factors, causing disturbances in energy metabolism, ion channel exchanges, action potential alteration and myocardial cell instability, all mostly leading to ventricular arrhythmia.

Keywords: hypomagnesemia ; supraventricular arrhythmia ; torsade de pointes ; ventricular arrhythmia ; ventricular tachycardia

1. Introduction

Magnesium is a micronutrient, an alkaline earth metal occurring as a free cation (Mg^{2+}). It is the second intracellular and the fourth extracellular electrolyte in concentration in humans. The adult human organism contains approximately 25 g of magnesium [1]. Up to 60% of the total Mg^{2+} is stored in the bone system, about 38–40% intracellular in the soft tissue and between 0.3 to 2% can be found in the blood serum [2]. Hypomagnesemia is defined as a total serum (Mg^{2+}) < 0.65 mmol/L, is determined by measuring the total serum concentration by different methods and is often symptomatic [3]. The lower cut-off limit of normal magnesemia is set differently by various studies. However, a recently standardised agreed normal value of serum magnesium is 0.85–2.3 mg/dL [4]. There is an important limitation of these methods linked to the ability of Mg^{2+} to keep serum concentration within normal limits due to and at the cost of intracellular depletion [5]. There are currently no rapid and effective tests to assess the concentration of intracellular Mg^{2+}, which specifically plays an essential role in both the heart and the whole body. However, there is a method that indirectly assesses the intracellular concentration of magnesium based on a reduction in excretion below 80% within 24 h after a loading dose [6].

Costello et al and later Rosanoff et al, described updated serum magnesium concentrations necessary for classification of magnesium status using adapted current reference intervals to describe symptomatic hypomagnesemia (<1.22 mg/dL), asymptomatic hypomagnesemia (1.22–1.82 mg/dL), chronic latent deficiency (1.82–2.06 mg/dL), normal range (2.06–2.33 mg/dL), asymptomatic hypermagnesemia (2.33–4.86 mg/dL) and symptomatic hypermagnesemia (>4.86 mg/dL). This classification introduces two new subclasses (asymptomatic hypomagnesemia and chronic latent deficiency). The new subclasses increase the accuracy of establishing magnesium status and correcting hypomagnesemia from early stages as it is known to date that chronic latent magnesium deficiency increases susceptibility to disease [4][7].

2. Causes of Hypomagnesaemia

Hypomagnesaemia can be a consequence of insufficient intake, redistribution from the extracellular to intracellular space and increased loss through the renal or gastrointestinal system [8][9].

Reduced magnesium intake can result from insufficient dietary consumption, alcohol dependence or parenteral nutrition that uses products with a poor magnesium content. Malnutrition, especially age-related, is most often associated with deficiency of macro-elements such as Mg^{2+}, whose scarcity can lead to multiple implications, including a decline in physical performance and cardiovascular health issues represented mainly by hypertension and arrhythmias [10][11]. Redistribution of Mg^{2+} from the extracellular to the intracellular compartment can occur after surgical treatment of hyperparathyroidism (hungry bone syndrome) during the treatment of diabetic ketoacidosis, in refeeding syndrome, and during sympathetic stimulation (such as in alcohol withdrawal), in acute pancreatitis or other critical illnesses or postoperative states.

Magnesium renal loss due to tubulopathies is associated with hereditary conditions such as Gitelman syndrome, familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC), Bartter syndrome, hypomagnesemia with secondary hypocalcemia (HSH), isolated recessive hypomagnesemia (IRH) with normocalcemia, isolated dominant hypomagnesemia (IDH) with hypocalciuria, and autosomal-dominant hypocalcemia with hypercalciuria (ADHH) [12].

Acquired causes include medications (loop and thiazide diuretics, aminoglycoside antibiotics, amphotericin B, immunosuppressive regimens: tacrolimus, cyclosporine, and chemotherapeutic agents such as cetuximab, panitumumab and cisplatin), and other pathologies: primary aldosteronism, chronic alcohol abuse (reversible tubular dysfunction), polyuria after urinary tract obstruction, or during acute tubular necrosis, hypercalcemia and hypophosphatemia [13].

Gastrointestinal losses can occur with vomiting, diarrhea, fistulas and nasogastric suction. Chronic malabsorption syndromes usually involve the small intestine and chronic use of protein pump inhibitors reduce the gastrointestinal absorption of magnesium [14], resulting in hypomagnesaemia.

It is worth mentioning that intracellular magnesium depletion can be associated with normal plasma values [15]. Yet, most patients with hypomagnesaemia will present with reduced total serum magnesium as well. More accurate measurements of Mg^{2+} can be obtained from lymphocytes and erythrocytes that have been correlated to intramyocardial muscle magnesium levels. Samples from buccal tissues can also be used to measure magnesium levels, though only available in the USA; however, such testing is reserved for research [16][17].

3. Cardiovascular Importance of Magnesium

The clinical implications of hypomagnesemia in the appropriate functioning of the cardiovascular system have been demonstrated over time. At the level of the vessels, the deficit of Mg^{2+} can promote increased vulnerability to oxygen-derived free radicals, altering the endothelial function and contributing to the genesis of atherosclerotic plaque formation [18]. An animal model study showed a reduction in infarct size associated with early reperfusion and magnesium administration. Furthermore, additional animal research highlights that Mg^{2+} supplementation decreases the myocardial infarct size when administered early, before reperfusion therapy, which is rather due to a direct cellular effect than to the regional myocardial blood reflow [19]. Although some small randomised clinical trials demonstrated a remarkable reduction in mortality when magnesium was administered to high-risk patients with acute myocardial infarction, three other large-scale randomised clinical trials (LIMIT 2, ISIS-4 and MAGIC trials) failed to show any benefit of the administration of intravenous magnesium over placebo. LIMIT 2 and ISIS-4 described different results, casting a shadow of doubt on the importance of magnesium in acute myocardial infarction; while in LIMIT 2 magnesium sulphate administration showed benefits both in patients who underwent thrombolysis and in those who did not, in ISIS-4 meta-analysis the evidence of magnesium supplementation benefit was absent in both groups [20][21][22]. The MAGIC trial assessed the influence of magnesium therapy on mortality in high-risk patients with acute myocardial infarction. Magnesium supplementation in the MAGIC trial aimed to prevent reperfusion injury; however, it did not demonstrate any benefit on 30-day mortality [21].

Besides ion disturbance and a large variety of arrhythmias, low Mg^{2+} is associated with increased vascular tone aggravating arterial hypertension [23], and apparently can affect valves and the course of heart failure (**Table 1**).

Table 1. Clinical manifestations of hypomagnesemia potentially influencing the cardiovascular system [24].

Hypomagnesemia	Clinical Manifestation
VESSELS	**Atherosclerosis**
	Impairment on endothelial function
	Coronary artery disease
	Arterial hypertension
	Increases mortality and morbidity after acute myocardial infarction
	Increases vascular tone and resistance
ARRHYTHMIAS	**Torsades de pointes**
	Other ventricular tachycardias
	Atrial fibrillation
	PACs
	PVCs
	Supraventricular tachycardias
	Sinus tachycardia

Hypomagnesemia	Clinical Manifestation
VALVES	Mitral valve prolapse
HEART FAILURE	Increased morbidity and mortality in patients with heart failure
ION DISTURBANCE	Hypokalaemia
	Hypocalcemia

Magnesium strongly affects the myocyte's homeostasis and maintains a normal action potential. Its use as an adjunctive therapy has demonstrated its importance in electrolyte balance in clinical practice. Recent data confirm a degree of interdependence between hypomagnesemia and cardiac arrhythmias.

Changes in the surface electrocardiograms (ECG) associated with hypomagnesemia have been described over time, dependent and varying according to magnesium levels: ST segment depression, peaked and tall or flattened T waves, shortening of the PR interval and QTc, lowering of the QRS voltage, increasing in the QRS duration and the presence of U waves. In a study by Yang et al., isolated hypomagnesemia was found to be associated with increased dispersion of ventricular repolarization evaluated by Tpe /QT ratio (T peak-to-end interval (Tpe), QT-peak interval standard measurement from the beginning of the QRS complex to the peak of the T-wave (QTp)) [25].

Cardiac arrhythmias have various causes and can be associated with a macroscopic structurally normal heart. Frequent examples of these types of causes are inherited conditions, as in the case of the accessory pathway-mediated tachycardias or the normal variant of nodal conduction duality characterized by the presence of a fast and a slow pathway with modified electrophysiologic properties predisposing to atrioventricular nodal reentrant tachycardia. The rest of the known arrhythmias are associated mostly with changes in the heart's structure found in many pathological conditions and are represented mainly by atrial fibrillation, premature atrial contractions, premature ventricular contractions, ventricular tachycardia and ventricular fibrillation.

Hypomagnesemia has many causes and seems to be linked to disturbances in energy metabolism, ion channel exchanges, action potential alteration and myocardial cell electrical instability, all leading to different types of arrhythmia.

The implication of hypomagnesemia in the genesis or potentiation of cardiac arrhythmias has several mechanisms (**Table 2**). The first described mechanism is the inadequate effect of low-concentration magnesium against calcium in the atrioventricular node (AV node), as magnesium is known to be the natural Ca2+ antagonist.

Table 2. Hypomagnesemia-induced arrhythmogenic mechanisms.

Hypomagnesemia-Dependent Arrhythmogenic Mechanisms
• inadequate effect of low Mg^{2+} concentrations against calcium in the AV node and ventricular myocardium
• low magnesium causes malfunction of Na+/K+-ATPase, consequently creating a less negative resting membrane potential by decreasing the concentration of intracellular K+ and increasing intracellular Na+
• hypomagnesemia-dependent hypokalaemia and hypocalcemia
• direct effect of magnesium on preventing calcium overload in the myocite
• PAF- related inflammatory cardiac response linked to arrhythmias
• disturbance of the action-potential

Another aspect of arrhythmogenesis refers to different types of Mg^{2+} dependent K+ currents playing an essential role against the excessive prolongation of myocardial action potential and having a protecting role against arrhythmia [26]. The mechanisms behind hypomagnesemia-associated hypokalaemia seem to be linked to the alteration of Na-K-ATPase responsible for a decrease in the cellular uptake of K+ and increased renal K+ excretion due to the inhibition of the

Na+/K+-ATPase. Low magnesium causes impairment of the function of Na+/K+-ATPase, which is Mg^{2+} regulated and increases intracellular sodium and reduces intracellular potassium levels, creating a less negative resting membrane potential. Magnesium deficiency can also lead to hypokalaemia and hypocalcemia, making the role of establishing the link between pure hypomagnesemia and cardiac arrhythmias somehow difficult. There is a strong relationship between Mg^{2+} and K+; both cations are integral for decreasing cell excitability and stabilizing membrane potentials. Half of the significant hypokalemias seem to be associated with magnesium deficiency; the co-administration of magnesium thus is essential in correcting serum potassium (K+) concentrations [27]. Enhanced gastrointestinal and renal excretion of K+ can also lead to hypokalaemia; however, it was shown that in patients with both hypomagnesemia and hypokalaemia, the repletion of Mg^{2+} alone also increased the serum K+ level [4][28].

The cellular mechanism behind the reduction of K+ excretion induced by Mg^{2+} repletion is linked to the effect on the ROMK. This inward-rectifying K+ current helps flow the potassium ion inside the cells of the apical membrane of the distal tubule. Intracellular magnesium binding to the channel's pore causes a temporary block for efflux of K+. On the other hand, the influx of K+ displaces the channel-bent magnesium ion and the maximal needed quantity of K+ enters the cell. As a result, the arrhythmia precipitated by K depletion requires both K+ and Mg^{2+} repletion for termination [29].

Other hypomagnesemia-dependent effects are the induction of hypokalemia and hypocalcemia and the loss of the direct effect of the normal concentration of magnesium on preventing calcium overload in the myocardial cell. Hypomagnesemia also induces the elaboration of platelet activated factor (PAF), which raises the production of pro-inflammatory cytokines, thrombin and vasoactive mediators, creating and maintaining the inflammation of cardiac tissue that predisposes to arrhythmias [30].

A series of relationships implicating Mg^{2+} dependent energy metabolism have been described. Mitochondrial Mg^{2+} regulates reactions in mitochondrial energy metabolism, tricarboxylic acid (TCA) cycle, adenosine diphosphate (ADP)/adenosine triphosphate (ATP) translocation and the electron transport chain [31].

Cardiac function is heavily influenced by (Mg^{2+}) and its various effects on vascular tone, peripheral vascular resistance, myocardial metabolism and Ca2+ homeostasis. Magnesium ions affect the myocyte's 'electrical properties by influencing the ion channels' activity implicated in generating the cell's action potential, particularly in phases 2 and 3. In phase 2, intracellular Ca2+ overload and therefore cell toxicity are prevented by (Mg^{2+})-dependent inhibition of the L-type Ca2+ channel. In phase 3, high (Mg^{2+}) concentration seems to block the slow activating component of the rectifier K+ current and the inward rectifier K+ channel. Magnesium ion is a cofactor of the Na+/K+ ATPase pump, which is active in phase 4 of the action potential and necessary for resuming an appropriate resting membrane potential. Magnesium depletion can reduce the activity of the pump, resulting in partial depolarization [32]. In addition, (Mg^{2+}) plays a role in myocardial excitation-contraction coupling by influencing the intracellular Ca2+ movement [33]. Magnesium binds calmodulin and troponin C and interacts with Ca2+ -transporting proteins such as the Na+/Ca2+ exchanger (NCX) and Ca2+-ATPase (SERCA). Concerning cardiac and vasculature function, Mg^{2+} has a role in vasodilation [34]. Furthermore, normal serum levels of Mg+2 reduce oxidative stress in endothelial cells and, consequently, endothelial inflammation [35][36].

A meta-analysis of six studies including 1550 patients admitted to intensive care units (ICU), showed that hypomagnesemia was associated with higher mortality [37]. On the other hand, recent data assessing the effect of Mg^{2+} on the mortality rate of 20,438 hospitalised patients suggested that both hypo- and hypermagnesemia were associated with increased mortality and, moreover, that hypermagnesemia should be considered a critical laboratory biomarker for mortality [38]. In-hospital acquired ionized hypomagnesemia is quite common, affecting up to 25% of hospitalised patients, and seems to be associated with a worse prognosis and an increase in in-hospital mortality [39]. One recent study evaluating changes in Mg^{2+} concentrations in patients with severe COVID-19 illness revealed that patients with in-hospital hypermagnesemia had a higher incidence of vasopressor-requiring cardiogenic shock and respiratory failure with the need for ventilation and acute kidney failure necessitating haemodialysis and increased mortality [40][41]. In addition, hypomagnesemia might be associated with severe arrhythmias in patients with septic shock and systemic inflammatory response syndrome. At the same time, high normal serum magnesium and hypermagnesemia seem to both be independent predictors of mortality in patients admitted to ICU for acute myocardial infarction [42][43]. Arrhythmia is the primary mechanism of death associated with hypomagnesemia.

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