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Magnesium homeostasis in cardiorespiratory comorbidity: shared pathogenetic mechanisms and therapeutic potential in COPD and arterial hypertension

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Abstract

Chronic obstructive pulmonary disease (COPD) and arterial hypertension are characterised by a high level of comorbidity, based on systemic inflammation and oxidative stress. Magnesium deficiency significantly intensifies these pathological processes; however, traditional serum markers often do not reflect true tissue depletion.

Objective. To summarise the role of magnesium deficiency in the pathogenesis of COPD and essential hypertension, identify common molecular targets, and assess the clinical potential of systemic and local (nebulised) therapy.

Results. Magnesium deficiency acts as a powerful catalyst of mitochondrial and endothelial dysfunction, sustaining neutrophilic inflammation in the lungs and calcium-dependent constriction in the vessels. Despite the fundamental consistency of these effects, the practical use of oral magnesium supplementation remains controversial because of the diagnostic limitations of serum magnesium. At the same time, local delivery (nebulised magnesium

sulfate) demonstrates a favourable safety profile and a selective pulmonary effect without systemic hypotension.

Conclusions. Correction of magnesium metabolism is promising but requires improved diagnostic criteria and optimisation of routes of administration for patients with cardiorespiratory comorbidity.

Keywords: chronic obstructive pulmonary disease (COPD), arterial hypertension, magnesium homeostasis, oxidative stress, endothelial dysfunction, nebulised magnesium sulfate.

I. Introduction

Magnesium is the fourth most abundant cation in the human body and the second most common intracellular cation after potassium, with a total body content of 20–28 g distributed among bone, soft tissues and extracellular fluid [1]. In addition, magnesium is a cofactor in more than 600 enzymatic reactions, including all ATP-dependent processes [2]. Over 99% of total body magnesium is intracellular: 50–65% is stored in bone, 34–39% in muscle and soft tissues, whereas extracellular fluids and blood account for less than 1–2% [3]. Although serum magnesium is tightly regulated within the range 0.7–1.1 mmol/L (with hypomagnesaemia below 0.7–0.75 mmol/L), this parameter is an extremely insensitive biomarker. Due to the minimal extracellular fraction, routine laboratory tests are unable to reflect true tissue deficiency, so chronic depletion of the body often remains clinically hidden [4–6].

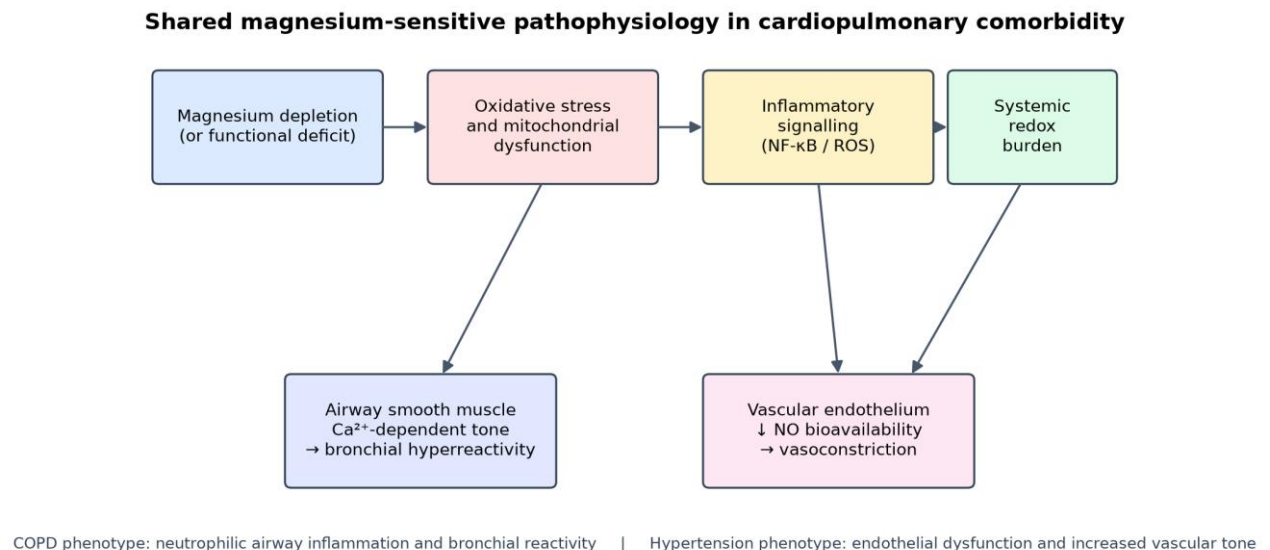


Figure 1. Shared magnesium-sensitive pathophysiology linking COPD and arterial hypertension.

Low magnesium levels are associated with arterial hypertension, arrhythmias, heart failure and cardiovascular mortality due to endothelial dysfunction and deregulation of ion channels [7-8]. Thus, magnesium deficiency complicates the course of chronic diseases by inducing oxidative stress, mitochondrial dysfunction and inflammatory signalling pathways, while the effectiveness of magnesium therapy remains limited by the absence of unified diagnostic criteria and the insensitivity of traditional serum biomarkers.

Since chronic obstructive pulmonary disease (COPD) and arterial hypertension are closely interrelated via shared redox processes and systemic inflammation, disruption of magnesium homeostasis acts as a powerful catalyst for mitochondrial dysfunction and endothelial pathology in both target organs, which justifies a careful analysis of its role in both pulmonary and vascular biology.

II. Main part

Magnesium influences the pathogenesis of COPD and essential hypertension through common key mechanisms. These include calcium antagonism in smooth muscle, regulation of neutrophilic inflammation, control of oxidative stress and maintenance of endothelial vasodilation involving nitric oxide.

Magnesium: intracellular content and regulation

Table 1. Principal magnesium-sensitive mechanisms relevant to cardiopulmonary disease.

Domain	Physiological role of magnesium	Potential consequence of depletion
Intracellular energetics	ATP-dependent enzymatic reactions and mitochondrial function	Reduced metabolic reserve and oxidative stress
Ion channels and transport	TRPM6, TRPM7, MAGT1, SLC41, MRS2 and CNNM proteins	Altered excitability and calcium handling
Inflammatory regulation	Control of redox-sensitive and innate immune signalling	Increased cytokine and ROS burden
Vascular function	Nitric oxide signalling and smooth-muscle relaxation	Endothelial dysfunction and vasoconstriction
Airway function	Calcium antagonism and cholinergic modulation	Bronchial hyperreactivity and bronchoconstriction

Intracellular magnesium refers to the element contained within cells and is divided into a large bound pool and a much smaller free ionised fraction, which directly participates in signalling, enzymatic reactions, ATP metabolism and membrane function [5, 4]. Regulation occurs at several levels: whole-body balance depends on the intensity of intestinal absorption, renal regulation and exchange with bone and muscle tissue [30], whereas at the cellular level homeostasis is controlled by transporters and ion channels (such as TRPM6, TRPM7, MAGT1, SLC41 proteins, MRS2 and CNNM), as well as local hormonal and metabolic factors [31]. In various tissues, low intracellular magnesium has repeatedly been associated with mitochondrial dysfunction, inflammation, insulin resistance, electrical instability and greater disease severity, but methods of measurement remain fragmented and often impractical outside research laboratories [5, 7, 32]. Intracellular magnesium content is regulated primarily by overall intake and retention of the element in the body [25]. At the cellular level transport proteins provide tissue specificity. TRPM6 is concentrated in the intestine and distal nephron, whereas TRPM7 is more widespread and has repeatedly been described as the principal regulator of intracellular

magnesium homeostasis in vascular cells, neurons, immune cells, hepatocytes and tumours [6, 20].

Methods are divided into approaches for measuring free and total magnesium. Phosphorus-31 magnetic resonance spectroscopy evaluates free cytosolic magnesium indirectly by ATP resonance shifts and can be applied in vivo in the brain and muscles [1, 25]. NMR spectroscopy can also quantitatively determine ionised magnesium in plasma with high analytical accuracy [33-34]. Fluorescent probes allow real-time intracellular visualisation, but selectivity for magnesium, affinity, calibration and loading into cells remain serious challenges [5-35].

An important and promising tool in practical application is the study of magnesium directly within the intraerythrocytic pool, although clinical data regarding it remain ambiguous. On the one hand, erythrocyte magnesium levels remained stable during postoperative inflammatory stress despite falls in serum indicators, suggesting its reliability as an intracellular marker in acute states [36]. On the other hand, erythrocyte magnesium content may change under the influence of factors unrelated to tissue status: for example, after massive transfusion donor erythrocytes demonstrated reduced magnesium levels despite an increase in the recipient's serum concentration [37].

Thus, the complex multi-level homeostasis of intracellular magnesium and its direct link to the severity of pathological states determine the critical need to improve and implement reliable tissue and cellular methods of its diagnosis, since traditional extracellular indicators are often uninformative.

Role of magnesium deficiency in the pathogenesis and clinical picture of COPD

COPD is characterised by pronounced oxidative stress driven by both exogenous oxidants and endogenous reactive oxygen species (ROS) from inflammatory cells, particularly neutrophils and macrophages [9-11]. Neutrophils are not merely markers but effectors of tissue damage, releasing reactive oxygen species, proteases, myeloperoxidase and inflammatory mediators that correlate with airway obstruction and the biology of exacerbations [10]. The influence of magnesium on inflammatory processes is far greater than its direct antioxidant action. Its deficiency stimulates phagocytes and granulocytes to develop an “oxidative burst” and secrete cytokines, whereas magnesium supplementation contributes to reductions in levels of C-reactive protein (CRP) and specific inflammatory mediators [4, 12]. In COPD, increased neutrophil counts and a high systemic immune-inflammation index act as a key link between magnesium deficiency and disease course. At the same time, oral magnesium intake in patients with COPD decreases the concentration of this inflammatory marker, although it is not accompanied by noticeable improvements in spirometric parameters or quality of life [13, 14].

Higher indices of magnesium depletion have independently been associated with a markedly greater prevalence of COPD [13], with odds ratios gradually increasing as deficiency deepened [15]. The proposed pathophysiology includes impairment of respiratory muscle function, enhanced airway hyperreactivity, bronchospasm and intensification of inflammatory reactions [13-14].

Magnesium sulfate relaxes airway smooth muscle mainly by limiting calcium influx and suppressing the cholinergic bronchoconstrictor mechanism through reduced acetylcholine release [14, 16]. Clinical benefit in COPD is most consistent in the form of adjunctive intravenous magnesium sulfate during exacerbations, where a meta-analysis [17] found improvement in peak expiratory flow at 45 minutes and a reduced risk of hospitalisation from

the emergency department, whereas some individual clinical trials found a negligible bronchodilatory effect or none when used as monotherapy [16].

Therefore, in COPD lower magnesium levels are associated with higher disease prevalence, a greater burden of exacerbations, airway hyperreactivity and worse lung function, whereas intravenous magnesium sulfate demonstrates an adjunct bronchodilator effect predominantly during acute exacerbations rather than as a consistently effective monotherapy [14, 16, 18].

Vascular effects and the role of magnesium in arterial hypertension

From the vascular perspective, low magnesium contributes to the formation of a pro-inflammatory endothelial phenotype. Reduced extracellular magnesium concentration enhances the generation of reactive oxygen species, activates signalling pathways associated with nuclear factor kappa B (NF- κ B), disrupts endothelial barrier integrity and shifts the vasoactive balance away from protective mediators [19-21].

In the context of arterial hypertension magnesium acts as a physiological calcium antagonist, stimulates endothelial nitric oxide (NO) signalling and inversely correlates with vascular tone, endothelial dysfunction and arterial stiffness, although results of interventional trials regarding vascular stiffness and blood pressure are more equivocal [1, 8].

Magnesium regulates vascular tone via direct effects on vascular smooth muscle and indirect endothelial effects. The direct pathway is calcium antagonism: lower intracellular magnesium or increased efflux promotes calcium-dependent constriction, whereas magnesium limits calcium entry, attenuates contraction and reduces peripheral resistance [8, 22].

Stimulation of endothelial nitric oxide synthase (eNOS) and increased prostacyclin levels ensure the predominance of vasodilatory influences over constrictor ones and explain the vascular protective properties of magnesium in cardiovascular disease [1, 8]. Magnesium deficiency shifts this system towards dysfunction, activating inducible nitric oxide synthase (iNOS) and related stress pathways in the endothelium, as well as enhancing accumulation of reactive oxygen species (ROS), release of inflammatory cytokines, vascular constriction, fibrosis and remodelling. The ion channel TRPM7 emerges as a key transporter-kinase in the homeostasis of endothelium and vascular smooth muscle [20, 23]. According to recent observational studies, higher indices of magnesium depletion have independently been associated with a higher augmentation index and carotid–femoral pulse wave velocity, but recent randomised trials using supplements still do not demonstrate a consistent reduction in arterial stiffness or blood pressure [24].

Magnesium homeostasis in the comorbid course of COPD and arterial hypertension: the problem of practical application

Considering COPD and arterial hypertension through the prism of cardiorespiratory comorbidity, their deep pathogenetic connection becomes evident. This provides a shared redox–endothelial axis in COPD and hypertension: systemic oxidative stress, leakage of inflammatory mediators into the systemic circulation and a reduced vasodilatory reserve [9].

The main strength of the existing evidence is their profound pathogenetic concordance: in both respiratory and vascular medicine magnesium consistently functions as a physiological

calcium antagonist that reduces smooth muscle tone whether in the bronchial wall or in the vascular bed. This universal mechanism explains why magnesium deficiency exacerbates airway hyperreactivity in COPD and vasoconstriction in hypertension. In COPD there is clear neutrophil-mediated tissue damage, and magnesium deficiency clearly correlates with systemic inflammatory activation and ROS biology, but disease-specific interventional evidence regarding neutrophils in the human lung remains limited [9, 11, 26].

Thus, in both systems magnesium deficiency has repeatedly been associated with oxidative stress and activation of inflammation, but direct clinical evidence that magnesium supplementation consistently neutralises all long-term consequences remains incomplete [12, 19, 25].

At the same time, practical application of magnesium preparations is the main limitation: intravenous magnesium sulfate in acute COPD exacerbations demonstrates moderate evidence for a short-term broncholytic effect and reduction in hospitalisations. Chronic oral supplementation in stable COPD, as well as for vascular protection, yields conflicting results in several clinical trials and requires further study [14, 17, 24]. This gap most likely reflects heterogeneity of baseline magnesium levels, route of administration, dose, disease phenotype, and also the fact that serum magnesium is an imperfect marker of intracellular depletion [1, 21, 27].

Alternative routes of administration: the role of nebulised magnesium sulfate

Table 3. Comparison of systemic and local magnesium-delivery routes.

Route	Potential indication	Advantages	Limitations
Oral	Documented or probable deficiency	Convenient for repletion	Variable absorption and gastrointestinal effects
Intravenous MgSO ₄	Selected acute exacerbations as adjunctive therapy	Rapid systemic availability	Hypotension and renal-safety concerns
Nebulised MgSO ₄	Local airway adjunct within a protocol	Potentially selective pulmonary effect	Heterogeneous evidence and delivery variability
Magnesium-containing mineral water	Experimental or supportive physiological intervention	Combined mineral and hydration context	Composition and evidence are variable

In the search for more effective therapeutic strategies, inhalational delivery of the drug emerges as a promising direction: nebulised magnesium sulfate delivers the preparation directly to the pulmonary vascular network and airways, providing local bronchodilation and vasodilation with minimal systemic absorption. Inhalational administration provides selective pulmonary vasodilation and improves oxygenation without the systemic hypotension observed with intravenous administration [28].

According to contemporary meta-analyses [29], inhalational administration of MgSO₄ as adjunctive therapy to standard bronchodilators contributes to an additional improvement in expiratory flow function 60 minutes after the start of inhalation (median difference [MD] 9.17%). Although the effect on overall need for hospitalisation remains variable, studies clearly indicate a statistically significant reduction in the need to transfer patients to intensive care units (risk ratio [RR] 0.52) due to local bronchodilator and relaxant effects.

The safety advantage of nebulised MgSO₄ is particularly relevant for patients with cardiorespiratory comorbidity, in whom avoidance of systemic hypotension is critical. However, reduced delivery efficiency and variable clinical effectiveness compared with intravenous routes indicate that nebulised MgSO₄ is best positioned as a safer alternative for specific vascular indications rather than as a universal replacement for systemic therapy.

III. Discussion

The obtained generalisations allow magnesium deficiency to be considered a common pathogenic denominator of cardiorespiratory comorbidity in COPD and arterial hypertension. Key unifying links are calcium-mediated effects on the tone of smooth muscle in bronchi and vessels, enhancement of oxidative stress, and impairment of NO-dependent endothelial vasodilation. These mechanisms explain why magnesium imbalance can simultaneously worsen bronchial reactivity and vascular tone, forming a common pathophysiological axis between two apparently different nosologies.

At the same time, an important contradiction has been revealed between laboratory diagnostics and true magnesium status of the body. Serum magnesium, despite tight physiological regulation, is an insensitive indicator of intracellular/tissue deficiency. This explains the conflicting results of clinical studies. Intravenous magnesium sulfate, by contrast, demonstrates a reproducible effect specifically in acute states — during COPD exacerbations, when rapid correction of calcium-dependent bronchoconstrictor mechanisms has the greatest pathogenetic significance.

The data obtained indicate the need for a differentiated approach: the effectiveness of magnesium therapy likely depends not only on the presence of deficiency, but also on the form of its correction, the clinical context and the accuracy of methods for diagnosing magnesium status. In this context the development of nebulised forms of magnesium delivery, which potentially combine local efficacy with

IV. Conclusions

A review of the literature indicates that magnesium deficiency is an important pathogenic factor that unites COPD and arterial hypertension through shared mechanisms: calcium antagonism, oxidative stress, neutrophilic inflammation and endothelial dysfunction. Despite clear fundamental logic, clinical application remains controversial because of limitations of routine diagnostic methods (serum magnesium) and heterogeneity of interventional protocols.

Traditional systemic therapy is often limited by the risk of adverse effects, whereas a promising alternative approach is local delivery (nebulised MgSO₄). Providing a selective pulmonary vasodilator effect with minimal systemic absorption, the nebulised form

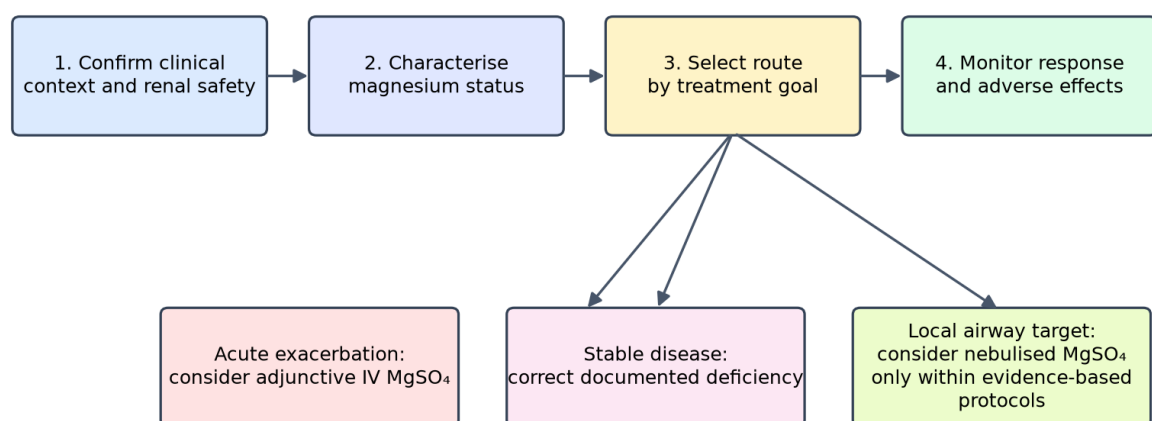
demonstrates a favourable safety profile in comorbid patients. However, due to technical delivery features and moderate efficacy in chronic conditions it should be considered not as a universal replacement for systemic supplementation but as a safe targeted tool for correction of pulmonary and vascular disturbances. Further research should focus on improving markers of tissue deficiency and optimising personalised treatment protocols.

Strengths and limitations

Common molecular mechanisms (calcium-mediated constriction, oxidative stress, endothelial dysfunction) that link the pathogenesis of COPD and arterial hypertension have been systematised into a single conceptual model. Methodological limitations of magnesium status diagnostics were separately analysed, which is valuable for interpreting conflicting clinical data. The practical aspect — comparison of systemic (oral, intravenous) and local (nebulised) routes of magnesium administration — was considered.

Limitations include: heterogeneity of the evidence base without formal meta-analytic synthesis, lack of unified criteria for magnesium deficiency. It should also be noted that data on nebulised magnesium sulfate in COPD and arterial hypertension are currently limited, which reduces the level of evidence of practical recommends.

Proposed evidence-informed decision pathway (conceptual)



This figure is a conceptual synthesis, not a clinical guideline or treatment prescription.

Figure 2. Conceptual evidence-informed pathway for magnesium assessment and route selection.

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Author contributions

O.S. Khukhlina: study concept, general supervision, analysis of results, writing—review and editing. T.I. Hormaniuk: physiological synthesis, writing—review and editing, literature curation, methodological review. All authors should confirm this statement before submission.

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No new clinical or experimental data were generated.

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Declaration of the use of generative artificial intelligence and AI-based technologies

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Conflict of Interest

The authors declare that they have no known financial conflicts of interest or personal relationships that could have influenced the work described in this article, subject to the separate editorial-board disclosure above.