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Magnesium to counteract elastin degradation and vascular calcification in chronic obstructive pulmonary disease

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A B S T R A C T

Accelerated elastin degradation is an important pathogenic mechanism in chronic obstructive pulmonary disease (COPD) leading to irreversible lung function loss and cardiovascular comorbidities. The rate of elastin breakdown is a predictor of mortality in patients with COPD. Decelerating elastinolysis might be an attractive therapeutic target in this debilitating condition.

Vascular calcification starts in the elastin network of the arterial wall and is enhanced in patients with COPD. Elastin calcification is accompanied by an upregulation of matrix metalloproteinase gene expression and consequently a shift in the elastase/anti-elastase balance towards degradation. Magnesium can be regarded as a natural calcium antagonist and has the proven ability to ameliorate vascular calcification. Furthermore, an animal study has suggested that magnesium deficiency promotes elastin degradation. I hypothesize that inhibiting elastin calcification by means of magnesium supplementation might counteract both vascular calcification and elastin degradation in COPD. This could potentially have a favorable impact on cardiovascular and respiratory related morbidity/mortality in patients with COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is a clinical heterogeneous disease in which a plethora of pathogenic mechanisms are implicated [1]. I will focus here on the enhanced degradation and calcification of elastic fibers in respectively the pulmonary and vascular extracellular matrix.

Magnesium, especially in comparison to calcium, can be regarded – unfairly, in my opinion – as a neglected mineral. I hypothesize that magnesium supplementation could play a role in COPD management by mitigating both elastin degradation and vascular calcification.

Elastin degradation

Elastin is a unique protein providing deformability and resilience to lungs and arteries [2]. It is essential to both respiration and circulation [2]. Accelerated elastin degradation, due to elastase/anti-elastase imbalance, is one of the hallmarks of COPD [3]. Desmosine and isodesmosine (DES) are covalent crosslinks between elastin fibers [4,5]. Since these amino acids are only found in crosslinked elastin fibers, the rate of elastin degradation can be quantified by measuring DES in body fluids [3]. Plasma DES levels reflect systemic elastin degradation and are on average higher in patients with COPD compared to age- and smoking-matched controls [6–8]. Elastin degradation in COPD patients is not only accelerated in lungs but also in other dynamic tissues, such as arteries [9]. Increasing age is related to higher plasma DES levels both in subjects with and without COPD [10]. However, this age-related DES increment is enhanced in COPD patients [10]. Furthermore, plasma DES levels were shown to be associated with mortality in a large observational study assessing the natural course of COPD during three-year follow-up [8]. Decelerating the rate of elastin degradation might be a novel target of therapy in COPD.

Vascular calcification

Vascular calcification starts at the level of the elastin network in arterial walls [11], due to elastin's high affinity for calcium [12]. Enzymatic degradation of elastin fibers enhances their polarity which further increases their attraction for calcium (Fig. 1A) [13]. The stimulating effect of elastin degradation on elastin calcification is probably responsible for the positive association found between plasma DES levels and coronary artery calcium (CAC) scores in COPD patients [8]. The burden of CAC is a strong cardiovascular risk factor independent from classic risk factors, such as hypertension and hyperlipidemia [14]. Cardiovascular diseases are prevalent co-morbidities of COPD [1], which corroborates with the elevated CAC scores found in patients with

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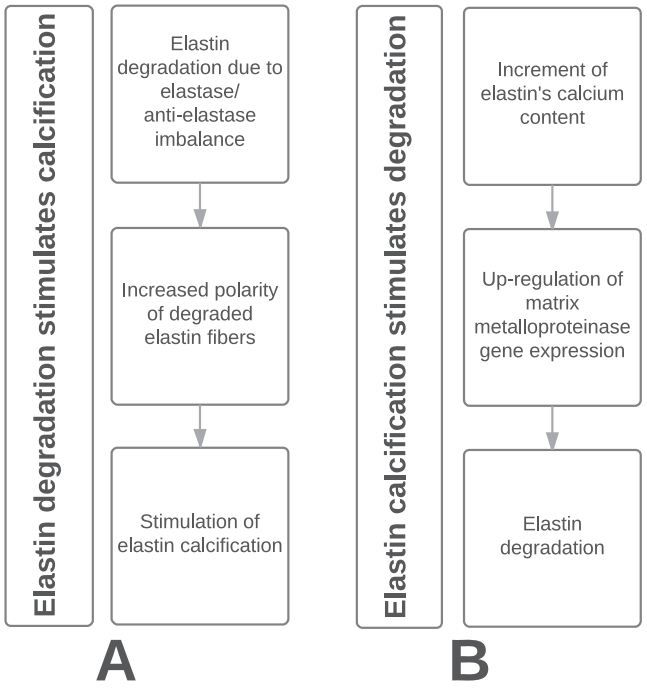

Fig. 1. The interrelationship between elastin calcification and degradation. A: Elastinolysis is the result of an imbalance between elastase and anti-elastase activity. Degraded elastin has an increased polarity, which accelerates elastin calcification. B: An increase in elastin's calcium content causes an up-regulation of matrix metalloproteinase gene expression leading to increased elastase activity and elastin degradation.

COPD compared to controls [15]. Interventions that decelerate elastin degradation via the inhibition of elastin calcification could theoretically be helpful to reduce both lung function decline and the incidence of cardiovascular diseases in COPD.

Hypothesis

Here, I propose that magnesium supplementation is an intervention with the potential to inhibit both elastin degradation and vascular calcification in patients with COPD.

Magnesium to inhibit elastin degradation and vascular calcification?

Magnesium can be regarded as a natural calcium antagonist. Both animal and human studies suggest that magnesium plays a role in the protection of arteries from calcification. In the famous Framingham heart study, for example, self-reported magnesium intake was inversely associated with arterial calcification [16]. Subjects with the highest magnesium intake had 58% lower odds of having CAC than those with the lowest [16]. Animal models corroborate these human data [17], however, the exact mechanism by which magnesium seems to prevent vascular calcification remains largely elusive. It has been suggested that magnesium counteracts elastin mineralization by increasing the solubility of calcium and phosphate thereby decreasing their tendency to precipitate on elastin fibers (Figs. 2 and 3) [18]. Another mechanism by which magnesium might protect elastin from calcification is by competing with calcium for mineral-binding sites thereby reducing the burden of calcium ion-elastin interactions [19]. Although much weaker than calcium, magnesium does indeed bind to elastin [19]. Elastocalcinosis is defined as the deposition of both calcium and phosphate along elastin laminae in the medial arterial wall [20]. Interestingly with respect to my current hypothesis, elastocalcinosis is also accompanied by a decrease of DES crosslinks in the involved blood vessels probably due to the accelerating effect of elastin mineralization on elastin

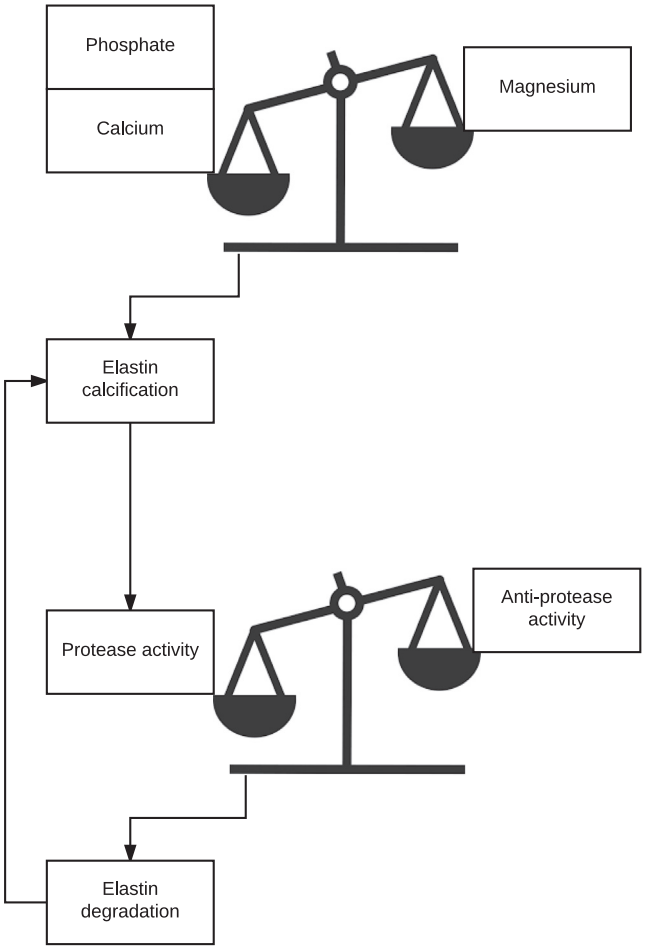

Fig. 2. I propose that the mechanisms depicted above are responsible for the elastinolysis/elastocalcinosis stimulating effect of magnesium deficiency and the elastinolysis/elastocalcinosis damping effect of magnesium supplementation. The rate of elastin calcification depends on the balance between calcium/phosphate (stimulating effect on elastin calcification) and magnesium (inhibiting effect on elastin calcification). Elastin calcification stimulates protease activity leading to elastin degradation. Elastin degradation is the result of the protective effects of anti-proteases and the destructive ones of proteases. Finally, elastin degradation stimulates elastin calcification leading to a self-perpetuating vicious circle.

degradation [21]. Gene expression of the elastases matrix metalloproteinase (MMP)-2 and MMP-9 increases in parallel to elastin calcification leading to degradation of elastin fibers and release of DES (Fig. 1B) [22]. Furthermore, there is evidence from an animal model suggesting an inhibiting effect of magnesium on elastin degradation [17]. Dietary-induced magnesium shortfall increased calcium and decreased elastin content in rats' aortas suggesting an unfavorable effect of magnesium deficiency on both elastin calcification and degradation [17].

Analogy between chronic kidney disease and COPD

In terms of elastin mineralization and degradation, there seems to be a significant analogy between chronic kidney disease (CKD) and COPD. CKD is characterized by a gradual deterioration of kidney function over time and is associated with very high cardiovascular risk [23]. CKD-mineral bone disease (MBD) occurs when the kidneys fail to maintain the proper levels of calcium, phosphate, vitamin D and parathyroid hormone (PTH) [24]. This dysregulated mineral metabolism has a huge unfavorable impact on the vascular health of CKD patients [25].

Hyperphosphatemia is a direct stimulus to vascular calcification and a well-established risk factor for mortality in patients with CKD [26].