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Editorial

Vitamin D and left ventricular adverse remodeling: Does association imply causation?☆

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Left ventricular adverse remodeling (LVAR) is defined as the dynamic process of maladaptive myocardial functional and structural changes in response to hemodynamic conditions of chronic pressure or volume overload and/or cardiac injury, predominantly acute myocardial infarction (AMI) [1]. AMI is associated with an irreversible loss of viable myocardium and an increased hemodynamic wall stress on border and remote non-infarcted myocardium, amplified by an exuberant individual inflammatory and neuro-hormonal activation, promoting a vicious cycle of LV enlargement and resulting in a progressive ventricular dysfunction and potentially overt heart failure (HF) [1,2]. Despite the widespread use of primary percutaneous coronary intervention (PCI) and the optimization of medical therapy for AMI, about 30% of patients with AMI still experience LVAR, with relevant negative prognostic implications [3].

The most significant and well-investigated predictors of LVAR following AMI are the infarct area, the infarct-related artery patency ('no-reflow phenomenon') and the ventricular loading conditions, because associated with a greater myocardial dysfunction, hemodynamic wall stress and the consequently greater inflammatory and neuro-hormonal activation [1]. Therefore, the therapeutic interventions implemented to prevent LVAR following AMI are aimed to guarantee a prompt reperfusion, a wall stress reduction and an inhibition of the deleterious exuberant neuro-hormonal and inflammatory activation [1]. While great results were obtained by optimizing percutaneous and medical reperfusion strategies along with the neuro-hormonal blockade, the role of the inflammatory and metabolic modulation to prevent and/or reverse myocardial remodeling and improve outcomes, represents an intriguing target needing further investigations [4].

In the recent issue of *International Journal of Cardiology*, Padoan et al. [5] reported the impact of baseline vitamin D levels on LVAR in a prospective cohort of 253 patients with AMI, the majority of whom with ST segment elevation AMI treated with PCI. In line with previous studies, they showed that 32% of patients after AMI developed LVAR, consequently associated with an increased risk of combined HF and mortality, after a median follow-up of 4.1 months [5]. They found no differences among patients with vs without LVAR in terms of age, sex, risk factors, timing and mode of revascularization, cardiac function, cardiology history and cardiovascular medications. However, they reported that patients with LVAR had lower vitamin D levels at the time of the acute event, and, at multivariable analysis, lower vitamin D levels independently predict LVAR and adverse events [5].

Vitamin D plays a pivotal role on calcium/bone homeostasis, however may also exert several cardiovascular functions. The majority of patients with ischemic heart disease and HF have low vitamin D levels especially due to intestinal malabsorption and disease-related sedentary lifestyle. Of note, a growing amount of epidemiological data have highlighted the association between low vitamin D levels and the increased risk of cardiovascular diseases and mortality although reverse causality and/or confounding factors should be taken into account [6,7]. It is unresolved if vitamin D deficiency play a biological causative role in cardiovascular diseases or is just a marker of a poor healthy condition and/or comorbidities. Currently there are no data convincingly support the benefit of vitamin D supplementation as strategy for cardiovascular protection [6,7]. Conversely, both in vitro and animal studies showed that vitamin D supplementation attenuates LV hypertrophy, reduces extracellular fibrosis and improves systolic and diastolic function, giving optimistic therapeutic perspectives [6–8].

Different pathophysiological mechanisms exerted by vitamin D may explain a *potential* causative role of vitamin D in the pathogenesis of LVAR (Fig. 1). Vitamin D metabolism is cross-linked with several mechanisms implicated in LVAR, including the increased hemodynamic wall stress and, neuro-hormonal, inflammatory and immunological activation [6–8]. Vitamin D regulates the renin-angiotensin system playing as a strong endocrine suppressor of renin biosynthesis at the level of the juxtaglomerular cells, independently from the secondary increase in parathyroid hormone that further contribute to upregulate of renin and aldosterone secretion, sympathetic activity, inflammation and myocardial hypertrophy, resulting in increased hemodynamic wall

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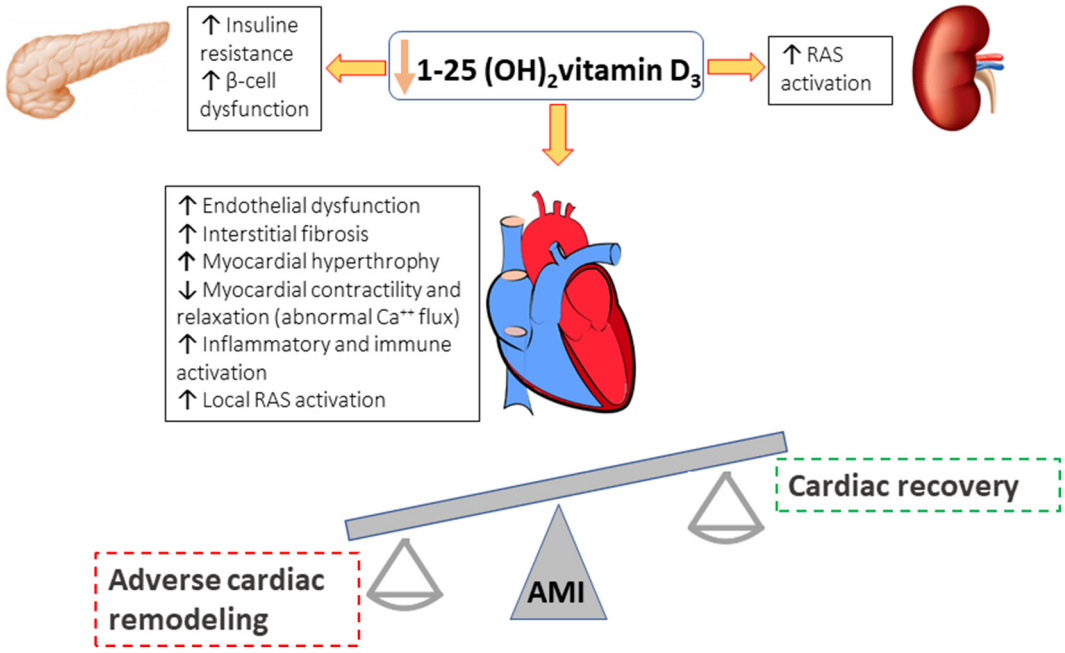

Fig. 1. Extra-skeletal effects of low vitamin D levels on cardiovascular system and their *potential* role in left ventricular adverse remodeling following AMI. Abbreviations: RAS: renin–angiotensin system; AMI: acute myocardial infarction.

stress and increased myocardial oxygen demand [7,8]. Vitamin D deficiency may also be causally linked to diabetes mellitus, that is associated with LVAR and HF, by promoting adiposity, inflammation, β-cell dysfunction and insulin resistance [7,8]. In addition, Vitamin D exerts direct myocardial effects because of the wide distribution of vitamin D receptors on cardiac myocytes, endothelial and fibroblast cells, transducing cardioprotective, anti-inflammatory and antifibrotic signaling pathways [7,8]. Finally, the most intriguing cross-relation between vitamin D and cardiovascular diseases lies on the modulation of inflammatory and immune system. Vitamin D shows a positive profile on the modulation of the inflammatory milieu by reducing tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6) cytokine levels and oxidative stress markers, there are critical mediators implicated in the persistent inflammatory activation that promote and independently predict LVAR and HF after an AMI [4,8]. The findings by Padoan et al. further reinforce this interplay. Patients with LVAR had lower vitamin D levels and showed higher C-reactive protein (CRP) levels (a surrogate of the inflammatory response). Larger studies may help in understanding if the impact of vitamin D levels on LVAR were mediated by inflammation [5].

Randomized controlled trials [6,7] tried to assess the impact of vitamin D supplementation on cardiovascular diseases but failed to show any cardiovascular benefits. However, they were limited by the small simple size, the low cardiovascular patient risk profile, the heterogenous inclusion criteria (including patients with no or borderline vitamin D deficiency), the different modalities and dosing of supplementation strategies, and the short trials duration. Encouraging results arise from the VINDICATE trial [9], in which vitamin D supplementation in patients with chronic HF and vitamin D deficiency was associated with a significant improvement in LV ejection fraction and reversal of LV remodeling [9].

Further well-powered interventional studies are needed to elucidate this controversial and unresolved issue and to delineate the timing and potential benefits, if any, of vitamin D supplementation in patients with AMI and vitamin D deficiency, especially for those patients with lower vitamin D levels and higher cardiovascular risk profile, with the purpose to prevent LVAR and improve cardiovascular outcomes.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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