

## Vitamin D and acute myocardial infarction

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### Abstract

Vitamin D deficiency is a prevalent condition, cutting across all ethnicities and among all age groups, and occurring in about 30%-50% of the population. Besides vitamin D established role in calcium homeostasis, its deficiency is emerging as a new risk factor for coronary artery disease. Notably, clinical investigations have suggested that there is an association between

hypovitaminosis D and acute myocardial infarction (AMI). Not only has it been linked to incident AMI, but also to increased morbidity and mortality in this clinical setting. Moreover, vitamin D deficiency seems to predispose to recurrent adverse cardiovascular events, as it is associated with post-infarction complications and cardiac remodeling in patients with AMI. Several mechanisms underlying the association between vitamin D and AMI risk can be involved. Despite these observational and mechanistic data, interventional trials with supplementation of vitamin D are controversial. In this review, we will discuss the evidence on the association between vitamin D deficiency and AMI, in terms of prevalence and prognostic impact, and the possible mechanisms mediating it. Further research in this direction is warranted and it is likely to open up new avenues for reducing the risk of AMI.

**Key words:** Vitamin D; Acute myocardial infarction; Incidence; Prognosis

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**Core tip:** Vitamin D deficiency is a prevalent condition and it is emerging as a new risk factor for coronary artery disease. Notably, hypovitaminosis D has been reported to be common in patients with acute myocardial infarction, and preliminary studies indicate a possible association with short-term and long-term morbidity and mortality. Although these observational initial proofs, interventional trials with supplementation of vitamin D have yielded controversial results. We herein discuss the current evidence suggesting an association between acute myocardial infarction and vitamin D deficiency, in terms of prevalence and prognostic impact, and the possible underlying mechanisms.

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## INTRODUCTION

Cardiovascular disease, and specifically acute myocardial infarction (AMI), is the main cause of morbidity and mortality in western countries, despite current preventive and therapeutic strategies<sup>[1,2]</sup>.

Besides the traditional, most recognized risk factors for AMI development, new risk factors are emerging with potential relevant therapeutic implications. Among them, hypovitaminosis D has been the focus of recent interest. It is well known that vitamin D insufficiency, or deficiency, is highly prevalent in the general population<sup>[3-7]</sup>. Traditionally, the most characterized consequences of vitamin D depletion have involved bone metabolism and calcium homeostasis<sup>[8]</sup>. However, its close association with major cardiovascular risk factors, such as diabetes, hypertension, and chronic kidney disease, and the detection of nuclear vitamin D receptors (VDR) on vascular endothelial cells and cardiomyocytes have paved the way to studies investigating the intriguing link between hypovitaminosis D and cardiac disease<sup>[9-11]</sup>.

Deficiency of vitamin D was shown to be common in AMI, and preliminary studies indicate a possible association with their short-term and long-term prognosis<sup>[12-14]</sup>. Indeed, vitamin D deficiency seems to predispose to in-hospital and recurrent adverse cardiac events, since it is associated with the number of affected coronary arteries, AMI complications, and cardiac remodeling in patients with AMI<sup>[12-14]</sup>.

In this review, we provide an overview on the currently available evidence supporting the relationship between hypovitaminosis D and AMI, its prognostic relevance, and the possible underlying mechanisms. Finally, we will try to identify challenges and future investigative perspectives in this field.

### Vitamin D metabolism

There are two major forms of vitamin D: Vitamin D<sub>2</sub>, which is contained in plants and fortified foods, and vitamin D<sub>3</sub>, which is obtained from aliments or through the conversion of dehydrocholesterol in the skin<sup>[11,15]</sup>. Of note, the cutaneous synthesis of vitamin D<sub>3</sub> from sunlight exposure is the main source of vitamin D in humans. Vitamin D undergoes hydroxylation in the liver to 25-hydroxyvitamin D - its main circulating form in the blood - and then in the kidney to 1,25-dihydroxyvitamin D. The 1,25(OH) vitamin D<sub>3</sub> reaches the nucleus where, by binding to its receptors, it regulates the transcription and function of more than 200 genes<sup>[16,17]</sup>. The VDR, which are expressed in enterocytes, osteoblasts, parathyroid glands, distal renal tubule cells, regulate calcium homeostasis and bone metabolism. Recent investigations have also demonstrated their presence on endothelial cells, lymphocytes, macrophages,

**Table 1** Most relevant risk factors for vitamin D deficiency

Age
Increased distance from the equator
Winter season
Darkly pigmented skin
Institutionalized/housebound
Sunscreens and cover-up clothing
Air pollution
Smoking
Obesity
Physical inactivity
Malabsorption
Chronic kidney disease
Liver disease
Drugs (glucocorticoids, antirejection medications, human immunodeficiency virus medications, antiepileptic drugs, etc.)

smooth vascular muscle cells, beta-pancreatic cells and cardiomyocytes, through which vitamin D<sub>3</sub> mediates cardiovascular effects<sup>[18-20]</sup>.

There is no consensus on how to define vitamin D deficiency, and this introduces significant difficulties in conducting epidemiological studies in this field<sup>[21-24]</sup>. The most widely accepted definition for normal vitamin D serum levels, according to the United States Endocrine Society guideline recommendations, is  $\geq 30$  ng/mL. Vitamin D insufficiency is characterized by levels of 21-29 ng/mL, while its deficiency by levels  $\leq 20$  ng/mL<sup>[25]</sup>. Vitamin D deficiency is the most common nutritional deficiency worldwide in both children and adults<sup>[26]</sup>. In the United States and Europe,  $> 40\%$  of the adult population has low vitamin D levels<sup>[26]</sup>. The Third National Health and Examination Survey (NHANES III) reports a high prevalence of vitamin D deficiency and its rapid increase, going from 55% in the period 1988-1994 to 77% in the years 2001-2004<sup>[27,28]</sup>. The main causes of vitamin D deficiency are listed in Table 1.

### Rationale for the link between vitamin D and AMI

A growing amount of data has highlighted the potential link between vitamin D and cardiovascular disease. Firstly, VDR have been found in the myocardium, as well as in vascular cells<sup>[18,29,30]</sup>. Secondly, epidemiological studies demonstrated that the incidence of coronary artery disease, diabetes, hypertension, and hypovitaminosis D, increase in proportion to distance from the equator<sup>[31]</sup>. Cardiac death and prevalence of vitamin D deficiency have also been reported to be at their highest during periods of decreased sunlight exposure (*i.e.*, winter months)<sup>[32]</sup>. Thirdly, new evidence suggests that vitamin D deficiency has a role in the development of different cardiovascular risk factors, in particular hypertension<sup>[33,34]</sup>, metabolic syndrome<sup>[35]</sup>, and diabetes mellitus<sup>[36-38]</sup>. Finally, patients with conditions known to be associated with vitamin D deficiency, such as chronic kidney disease and primary hyperparathyroidism, die more frequently from cardiovascular causes than from those related to their underlying disease<sup>[39]</sup>.

Taken together, these findings strongly support the

notion that vitamin D is involved in cardiac risk factor development, finally leading to an increased burden in coronary artery disease and to a worse short-term and long-term outcome in AMI patients.

### Clinical studies on vitamin D in AMI

An initial Danish report in 1978 examined vitamin D levels in 75 patients with stable angina, in 53 patients with AMI, and in 409 healthy subjects, and it found that vitamin D levels were significantly lower in patients with angina or AMI than in controls<sup>[40]</sup>. In 1990, a case control study showed that AMI patients had lower vitamin D levels than controls, and this difference was more pronounced in the winter-spring period<sup>[41]</sup>. Of note, the relative risk of AMI decreased across increasing quartiles of vitamin D, suggesting an inverse correlation between vitamin D levels and AMI risk<sup>[41]</sup>. These figures have also been confirmed in more contemporary cohorts. Among 1739 Framingham Offspring Study healthy participants, the rates of major cardiovascular events were 50% and 80% higher in those with vitamin D insufficiency and deficiency, respectively<sup>[42]</sup>. In particular, subjects with no history of coronary artery disease and vitamin D levels < 10 ng/mL experienced a hazard ratio of 1.8 for developing a first cardiovascular event during a 5-year follow-up compared with subjects with levels > 15 ng/mL<sup>[43]</sup>. Finally, in 18225 men in the Health Professionals Follow-up Study, low vitamin D levels were associated with a higher risk of AMI, even after controlling for other cardiovascular risk factors and, at 10-year follow-up, subjects with normal vitamin D levels (> 30 ng/mL) had approximately half the risk of AMI<sup>[43]</sup>. These findings have been recently confirmed in a large meta-analysis that showed an adjusted pooled relative risk of 1.52 for total cardiovascular events when comparing the lowest to the highest categories of baseline circulating vitamin D concentration<sup>[44]</sup>. Thus, there is growing evidence suggesting that vitamin D deficiency represents a novel risk factor for AMI.

In agreement with these epidemiological data, prospective reports have found a high prevalence of vitamin D deficiency in patients hospitalized with AMI. A multicenter study performed in 239 acute coronary syndrome patients showed that 96% of them had vitamin D levels < 30 ng/mL at hospital presentation<sup>[45]</sup>. In line with this, Ng *et al*<sup>[13]</sup> demonstrated that 74% of AMI patients had low vitamin D levels and, of note, 36% of them had a severe deficiency. Correia *et al*<sup>[46]</sup> reported a median serum concentration of vitamin D of 18.5 ng/mL in a cohort of 206 AMI patients (7% with STEMI), and a severe deficiency in 10% of the sample analyzed. Similar findings were also observed by De Metrio *et al*<sup>[12]</sup> and Aleksova *et al*<sup>[14]</sup>, who reported a prevalence of hypovitaminosis D in AMI patients of 89% and 68%, respectively.

Low vitamin D levels seem to be not only a prevalent independent risk factor for AMI, but also to be associated with a worse outcome when it occurs (Table 2). Correia

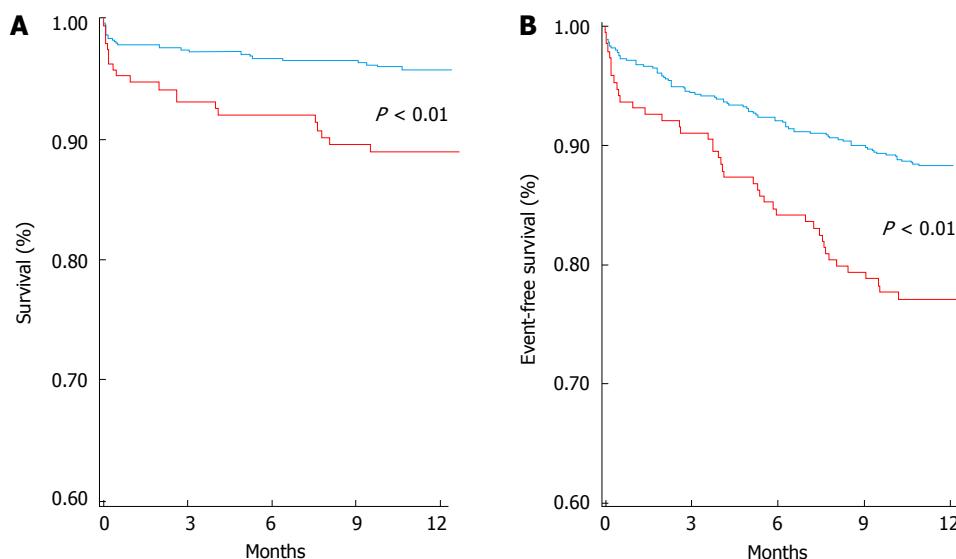
*et al*<sup>[46]</sup> provided the first evidence of the potential independent association between severe deficiency of vitamin D and in-hospital mortality in patients with acute coronary syndromes. Indeed, patients with vitamin D levels < 10 ng/mL had a 24% in-hospital cardiovascular mortality rate, significantly higher than that observed in the remaining patients (4.9%, with a relative risk 4.3). A possible association between hypovitaminosis D and higher in-hospital mortality was also reported by Khalili *et al*<sup>[47]</sup> in 139 STEMI patients. However, the study was underpowered to show statistically significant difference in in-hospital mortality between patients with normal and low vitamin D<sup>[48]</sup>. More robust data have been provided on the long-term clinical implications of low vitamin D levels in AMI. Thus far, the largest study assessing vitamin D and prognosis in 1259 acute coronary syndrome patients is that by Ng *et al*<sup>[13]</sup>. In their study, the lowest vitamin D quartile (< 7.3 ng/mL) was associated with long-term major adverse cardiovascular events. Notably, the association was predominantly with re-hospitalization for acute decompensated heart failure or for successive acute coronary syndrome<sup>[13]</sup>. In agreement with these findings, in our cohort of AMI patients, the lowest quartile of vitamin D was a strong predictor of 1-year mortality (Figure 1)<sup>[12]</sup>. Of note, vitamin D deficiency was again a borderline independent predictor of in-hospital mortality, possibly due to the relatively low in-hospital mortality rate of our population, and it was associated with the highest risk of several in-hospital major adverse cardiac events. Interestingly, the lowest vitamin D quartile was associated with a higher incidence of bleeding requiring transfusion, although similar baseline hemoglobin values<sup>[12]</sup>. This is a crucial issue in the setting of AMI, as potent antithrombotic therapy is the mainstay of treatment, and bleeding and transfusions have a detrimental role on outcomes. We also found an association between the lowest vitamin D quartile and acute respiratory insufficiency rate<sup>[12]</sup>. The higher occurrence of these threatening complications might have contributed to the higher in-hospital mortality risk found in AMI patients and low vitamin D levels.

The causal relationship between vitamin D status and outcomes in AMI remains to be elucidated. Indeed, in more than 3000 patients undergoing coronary angiography, a significant association between hypovitaminosis D and lower left ventricular function was shown<sup>[49]</sup>. Of note, in this report, vitamin D deficiency was associated with deaths due to heart failure and with sudden cardiac deaths<sup>[50]</sup>. This highlights the possible relevance of vitamin D contribution to several aspects of AMI, such as acute ventricular dysfunction, heart failure progression, post-AMI ventricular remodeling, inflammation, thrombotic/bleeding balance and arrhythmias, which should be more deeply investigated through well-designed studies. Taking together, these considerations, along with older age, higher incidence of well-known cardiovascular risk factors, and lower rate of

**Table 2** Main prospective studies on serum vitamin D levels in patients with acute myocardial infarction

Ref.	Study population (n)	Definitions of vitamin D levels (ng/ml)	Prevalence	End points considered	Major findings
Lee et al <sup>[45]</sup>	NSTEMI STEMI (n = 219)	Normal > 30 Insufficiency 21-29 Deficiency < 20	4% were normal 75% were insufficient 21% were deficient	Prevalence and vitamin D correlates	Vitamin D deficiency was more commonly observed in non-Caucasian patients, in diabetics patients, and in those with a higher body mass index
Khalili et al <sup>[47]</sup>	STEMI (n = 139)	Deficiency < 30	73% were deficient	In-hospital mortality correlation with MMP-9 levels at 72 h	Inverse correlation between vitamin D and MMP-9 levels
Correia et al <sup>[46]</sup>	UA NSTEMI STEMI (n = 206)	Severe deficiency < 10	10% were severely deficient	In-hospital mortality long-term mortality (mean FU 635 d)	A significant higher incidence of in-hospital and long-term mortality in patients with severe vitamin D deficiency
Ng et al <sup>[13]</sup>	NSTEMI STEMI (n = 1259)	Deficiency < 20	74% were deficient	long-term incidence of mortality and MACE (median FU 550 d)	A significant higher incidence of MACE in patients with deficient vitamin D levels
De Metrio et al <sup>[12]</sup>	NSTEMI STEMI (n = 814)	Normal > 30 Insufficiency 21-29 Deficiency < 20	11% were normal 19% were insufficient 70% were deficient	In-hospital mortality and in-hospital MACE 1-yr mortality and 1-yr re-admission for acute coronary syndrome and acute decompensated heart failure	A higher incidence of in-hospital mortality, mechanical ventilation, and major bleeding in patients with the lowest quartile of vitamin D levels A significant higher incidence of 1-yr mortality and re-hospitalization for acute decompensated heart failure in patients with the lowest quartile of vitamin D levels
Aleksova et al <sup>[14]</sup>	NSTEMI STEMI (n = 478)	Sufficient > 30 Insufficiency 21-30 Deficiency ≤ 20	10% were sufficient 22% were insufficient 68% were deficient	Independent predictors of vitamin D deficiency	Older age, female gender, higher body mass index, autumn/winter sampling, and lower GFR predicted vitamin D deficiency

HR: Hazard ratio; FU: Follow-up; GFR: Glomerular filtration rate; MACE: Major adverse cardiac event; MMP-9: Matrix metalloproteinase-9; NSTEMI: Non-ST-elevation myocardial infarction; STEMI: ST-elevation myocardial infarction; UA: Unstable angina.



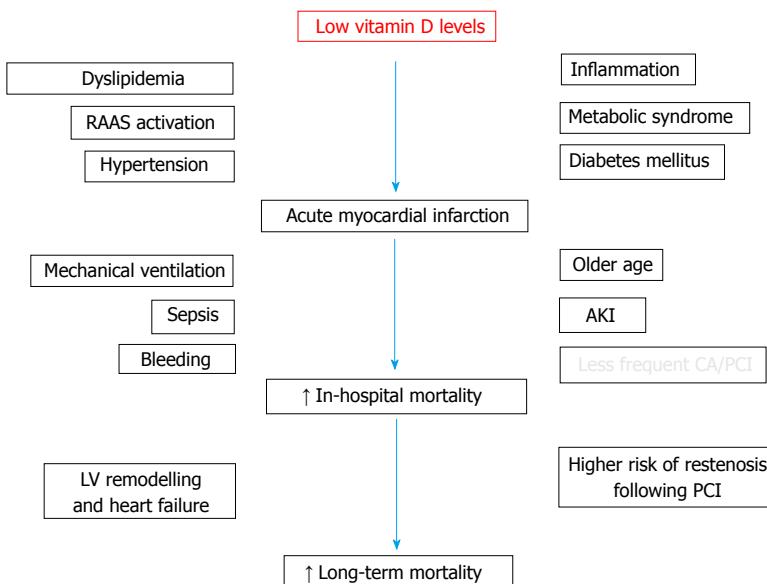
**Figure 1** Kaplan-Meier curve analysis stratified according to vitamin D levels. The lowest quartile (red line) vs the other three quartiles pooled together (blue line) for 1-year mortality (A), and for the combined end point<sup>1</sup> (B), in the whole study population. P value by Log rank test. Reproduced from De Metrio et al<sup>[12]</sup>.  
<sup>1</sup>Combined end point: death, major bleeding (requiring blood transfusion), acute pulmonary edema, cardiogenic shock, clinically significant tachyarrhythmias and bradycardias, and acute kidney injury.

reperfusion strategy, might explain the worse outcome of AMI patients presenting with low vitamin D levels (Figure 2). A similar prognostic relevance has also been reported in critically ill patients, in whom a low vitamin D status was significantly associated with disease severity and

mortality<sup>[50-52]</sup>.

#### Potential therapeutic implications

Although many studies suggest a higher cardiovascular risk associated with low vitamin D levels, the data



**Figure 2 Potential factors impacting on acute myocardial infarction occurrence and outcome associated with low vitamin D levels.** AKI: Acute kidney injury; CA/PCI: Coronary angiography/percutaneous coronary intervention; LV: Left ventricular; RAAS: Renin-angiotensin-aldosterone system.

regarding vitamin D supplementation are more sparse and controversial, in terms of primary prevention<sup>[53-57]</sup>. The potential benefit of vitamin D administration in the early phase of AMI has not been investigated yet. From a clinical point of view, vitamin D levels can be rapidly determined by blood testing and treated by supplementation. It has been demonstrated that a single oral ultra-high dose of vitamin D is able to restore normal levels in 2 d in critically ill patients, with no adverse effects, potentially providing an easy-to-administer dosing regimen for intervention trials in acute cardiovascular settings<sup>[58]</sup>. Although this evidence was not focused on AMI patients, it may pave the way for new investigations based on the use of a high oral loading dose regimen of vitamin D for restoration of adequate levels within few days. Notably, a dose-response association with cardiovascular risk and mortality has been demonstrated by Wang et al<sup>[44]</sup>, and this was particularly true when short-term outcomes were considered.

Data on vitamin D supplementation in the setting of secondary prevention of AMI are also lacking. Yet, it has been recently demonstrated that high-dose vitamin D supplementation for 1-year in patients with chronic heart failure due to left ventricular systolic dysfunction and vitamin D deficiency, on contemporary optimal medical therapy, resulted in a significant improvement in left ventricular structure and function<sup>[59]</sup>. Of note, in almost 60% of these patients, the etiology was ischemic heart disease, suggesting a possible beneficial effect on post-AMI ventricular dysfunction<sup>[59]</sup>.

Some studies have also proposed a possible association between low vitamin D and increased levels of cholesterol and of inflammatory markers, in particular C-reactive protein, in the setting of AMI<sup>[12,46]</sup>. Interestingly, 1-year atorvastatin treatment in patients with AMI determined a marked decrease in cholesterol and an unexpected increase in vitamin D levels, reinforcing the interplay among inflammation, low vitamin D and

dyslipidemia<sup>[60,61]</sup>.

#### Future perspectives and conclusions

Thus far, evidences in this field have been mainly driven by observational cohort studies, and these data are hypothesis-generating. Therefore, whether vitamin D is a risk factor or marker in this clinical setting cannot be inferred from the current literature. Larger studies are needed in order to shed lights on this issue. Because of their health status, frail patients with a high cardiovascular risk burden may spend mostly of their time indoors, which leads to low levels of vitamin D. This is also supported by the fact that such a similar observation has been found in patients with cancer, multiple sclerosis, and psychiatric diseases, potentially supporting the notion that hypovitaminosis D may be simply a marker of health<sup>[62]</sup>. However, even when adjusted for major confounders, vitamin D status still remains an independent risk factor, as it is significantly linked to incident AMI, worse short-term outcome, and recurrent major adverse cardiovascular events.

Whether vitamin D supplementation can counteract this increased risk in AMI patients is still an unanswered question, which should be investigated in large, well-designed, adequately powered interventional trials.

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