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Editorial

Vitamin D and Pulmonary Arterial Hypertension

Vitamin D deficiency is highly prevalent worldwide.[1] In patients with pulmonary arterial hypertension (PAH) vitamin D deficiency is much higher – 95% in the Spanish[2] and Japanese,[3] 80% in the Iranian[4] and 54% in the Argentinian[5] cohorts – than in the general population. Likewise, secondary hyperparathyroidism, a consequence of severe vitamin D deficit, is also highly prevalent in PAH.[2,6]

Several studies have retrospectively analyzed the prognosis and clinical impact of vitamin D deficiency in PAH. Patients with total 25(OH)vitD plasma below the median in the Spanish cohort (7.2 ng/ml) had worse functional class, higher BNP/pro-BNP levels, lower 6-min walking distance (6MWD) and lower tricuspid annular plane systolic excursion (TAPSE).[2] Survival in patients with vitamin D levels above the median was markedly increased than in those below the median value (age-adjusted hazard ratio: 5.40 [CI95 2.88–10.12]). In the Argentinian cohort, there was higher prevalence of vitamin D deficiency in patients with worse functional class and a linear correlation between 6MWD and vitamin D levels.[5] In the Japanese cohort, vitamin D levels showed a significant correlation with cardiac output.[3] Moreover, low vitamin D levels are associated with a poor therapeutic response to PDE5 inhibitors.[7] In addition, vitamin D deficiency was also associated with group 3 pulmonary hypertension. In a recent retrospective study, vitamin

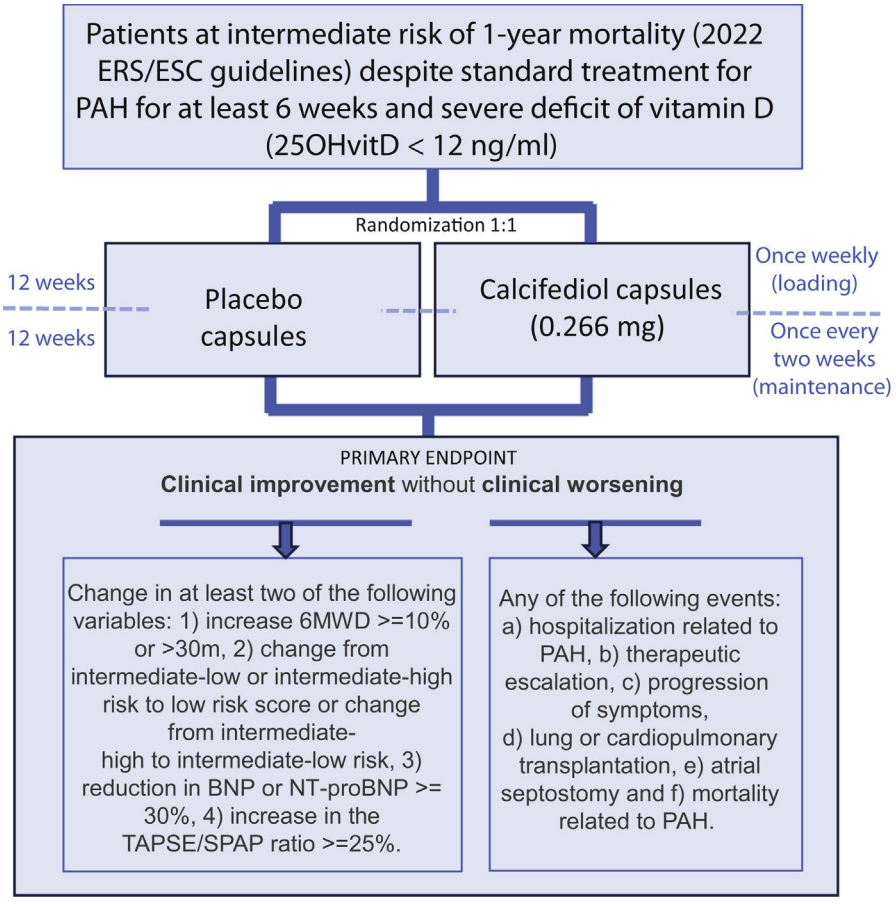

Fig. 1. Trial design and primary end-point of the REVIDAH study.

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D deficiency was present in 35% of controls, 57% of patients with COPD and 86% of patients with COPD plus pulmonary hypertension. Vitamin D was negatively correlated with pulmonary artery systolic blood pressure.[8]

At present, there is no clear evidence to support that there is a causal link, at least in humans, between vitamin D deficiency and PAH. Moreover, if present, the causal relationship might be in either direction: vitamin D causing/aggravating PAH or PAH inducing vitamin D deficiency. Nonetheless, data from preclinical and small uncontrolled trials suggest that low vitamin D aggravates PAH. In rats with PAH, induced by either hypoxia plus Su5416[9] or by monocrotaline,[10] vitamin D deficiency aggravated the increase in mean pulmonary arterial pressure (mPAP), right ventricular (RV) hypertrophy and other biomarkers of PAH. The combination of Bmpr2 loss of function mutation plus vitamin D free diet in rats induced additive or synergic right atrial enlargement, increased plasma BNP and cardiac calcification, i.e. three well-known risk factors of poor prognosis in PAH.[11] Interestingly, in PAH rats with vitamin D deficiency, restoration of vitamin D levels improved the in vitro response to the PDE5 inhibitor sildenafil, mimicking the different vitamin D-dependent responsiveness to PDE5 inhibitors in PAH patients.[7] In addition, there is a small ($n = 28$) prospective uncontrolled longitudinal trial in Iranian patients with pulmonary hypertension (mostly PAH) and vitamin D deficiency that were given 50,000 IU cholecalciferol weekly plus calcicare (200 mg magnesium + 8 mg zinc + 400 IU vit D) daily for 3 months.[4] The serum vitamin D level increased from 14 (SD 9) to 69 (31) ng/ml ($p < 0.001$), the mean 6MWD increased from 260 (SD 124) to 331 (139), $p < 0.001$, and the RV size significantly improved.

From a mechanistic point of view, the active form of vitamin D, calcitriol, activates the vitamin D receptor (VDR), a transcriptional factor that regulates the expression of specific target genes[12] relevant in key processes within the cardiovascular and respiratory systems, such as cell proliferation, differentiation and migration, control of vascular tone, immunomodulation and regulation of metabolism among others. Vitamin D has been reported to directly modulate the activity and expression of several targets involved in PAH. Notably, it regulates the TGF-β and BMPR2 pathway by interfering with its intracellular signalling molecule SMAD3. Thus, vitamin D analogues inhibit TGF-β effects in multiple tissues.[13] Vitamin D also regulates the BMPR2 ligands BMP4 and BMP6, the calcineurin-NFAT and the mTOR-S6 signalling pathways and modulates thrombospondin-1, survivin, interleukin-17, interleukin-6 and KCNK3 expression.[9]

There are some relevant questions that remain to be answered: (1) Does vitamin D deficiency trigger the development of PAH in predisposed subjects? (2) Does vitamin D deficiency aggravate symptoms and prognosis in PAH patients? and moreover, the key clinical question for PAH patients is: (3) Does restoration of vitamin D levels lead to clinical improvement and better prognosis in PAH patients?

Thus, we hypothesize that in patients with stable PAH and vitamin D deficiency, restoration of vitamin D status improves symptoms and prognosis. Accordingly, a multicentric placebo-controlled, randomized clinical trial, the REVIDAH study, has been launched to analyze whether a vitamin D supplement improves clinical outcomes in patients with PAH (Fig. 1).

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Conflict of interests

The authors declare no conflict of interest.

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