



## Pulmonary hypertension and deficiency of vitamin D

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### Abstract

Pulmonary hypertension has been observed to be elevated among end-stage renal disease and patients who are on dialysis. Several investigations, have demonstrated that, pulmonary hypertension in end-stage kidney failure patients is related to expressively enhanced mortality and morbidity. Pulmonary hypertension represents a group of comparatively erratic illnesses that causes different pulmonary vascular alterations including vasoconstriction, endothelial and smooth muscle cell proliferation, thrombosis and inflammation cause sustained high pulmonary vascular resistance and pulmonary arterial pressure. Hyperparathyroidism secondary to vitamin D deficiency may has a role in higher pulmonary arterial pressure and might be a relationship between pulmonary hypertension and vitamin D deficiency.

**Keywords:** Vitamin D, Pulmonary hypertension, Parathyroid hormone, Hyperparathyroidism, 25-hydroxyvitamin D, Endothelial dysfunction, Parathormone

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### Introduction

The role of vitamin D is known in the regulation of musculoskeletal health and homeostatic stability of the body (1). Recently role of vitamin D has attracted the attention of many researchers that found its role in pathogenesis of many chronic diseases, such as diabetes, hypertension, infections, and cancer (2). Vitamin D receptors are discovered to be expressed in a different tissues, such as cardiomyocytes, vascular smooth muscle cells and endothelial cells (2). Deficiency of vitamin D activates the renin-angiotensin-aldosterone system and can provide susceptibility to hypertension (3). Furthermore, parathyroid hormone and vitamin D have been associated with blood pressure control (4). Vitamin D deficiency leads to an enhanced in parathyroid hormone secretion (3). Pulmonary hypertension (PH) represents a group of comparatively erratic illnesses that causes different pulmonary vascular alterations including vasoconstriction, endothelial and smooth muscle cell proliferation, thrombosis and inflammation cause sustained high pulmonary vascular resistance and pulmonary arterial pressure (5).

One study proposes that hyperparathyroidism secondary to vitamin D deficiency may has a role in higher pulmonary arterial pressure and might be a relationship between PH and vitamin D deficiency (6). Activation of renin-angiotensin-aldosterone system is associated with PH (2). The mechanism of parathyroid hormone that induced hypertension is thought to be through increasing intracellular  $Ca^{++}$ (4). This study also proposed, the effect of vitamin D on hypertension may also be through parathyroid hormone and metabolism of calcium (7). Deficiency

of vitamin D causes an increase in parathyroid hormone secretion that in the beginning, relax the vasculature and will finally tighten it, thus leading to hypertension. It will occur due to an increase of intracellular calcium levels and causing endothelial and vascular growth dysfunction (7).

### Materials and Methods

For this mini-review, we used a diversity of sources by searching through PubMed/Medline, Scopus, EMBASE, EBSCO and directory of open access journals (DOAJ). The search was conducted, using combination of the following key words and or their equivalents; vitamin D, Pulmonary hypertension, parathyroid hormone, hyperparathyroidism, 25-hydroxyvitamin D, endothelial dysfunction and parathormone. Titles and abstracts of articles were investigated of review article, clinical trials, cohort studies, case-control studies, and report that relevance to the intended topic.

### Pulmonary hypertension, parathyroid hormone and vitamin D

Various studies have established that vitamin D may play a role in several chronic lung diseases, including asthma, chronic obstructive pulmonary disease (COPD), respiratory infections and pulmonary arterial hypertension (6,8,9).

A recent study that conducted on bone mineral density and secondary hyperparathyroidism in PH, remarkably, found a mainly noticeable increase of the mean parathormone (PTH) serum levels in patients with PH (5). An enhanced PTH was observed in more than 50% of all PH

### ■ Implication for health policy/practice/research/medical education

High level of parathormone as a consequence of low vitamin D levels was related to higher pulmonary artery pressure, particularly in hemodialysis and pre-dialysis patient.

patients (5).

Furthermore, in this study, patients with left heart failure were evaluated as controls. Seventy percent of PH patients were cured with loop diuretics. They noticed, no variation in mean PTH serum levels between loop diuretic-treated and not treated patients in the two study groups and additionally not related with impaired renal function. Therefore, it seems that neither enhanced creatinine nor diuretics responsible for elevated PTH levels, and factors except renal failure or diuretics, probably deficiency of vitamin D, endothelial dysfunction or changed hemodynamics, seems to be responsible for secondary hyperparathyroidism in PH. In pulmonary hypertensive patients, enhanced PTH associated negatively with serum 25-hydroxyvitamin D levels too (5).

### Pulmonary hypertension in patient with renal failure

Pulmonary hypertension has been observed to be elevated among end-stage renal disease and patients who are on dialysis (10). Several investigations, have demonstrated that, PH in end-stage kidney failure patients is related to expressively enhanced mortality and morbidity (10,11). The pathogenesis of PH in hemodialysis patients is not clearly recognized (11).

A study, investigated a group of hemodialysis patients with end-stage renal disease via arteriovenous fistula that was created on the hand, and with acetate basis dialysate and polysulfone membranes (12). This study showed a significant association of pulmonary artery systolic pressure with serum PTH in hemodialysis patients, positively (12). Other study showed 35.9% prevalence for PH in patients with proteinuria stage 1–4 chronic kidney disease(13). Additionally, PTH status were significantly elevated in patients with PH compared with individuals with normal pulmonary artery pressure. PTH levels were positively associated with pulmonary artery pressure (13). Moreover, PH induced via enhanced PTH levels, is related to pulmonary vascular calcification, a finding that also has been detected in an experimental dog model of chronic kidney disease (14).

Secondary hyperparathyroidism is proposed to be a risk factor for PH in patients with chronic kidney disease (13). Chronic kidney disease is a disorder with reduced active vitamin D levels as a result of diminished 1 alpha-hydroxylation of vitamin D in the kidneys, which causes enhanced PTH levels (13). Recently a study stated that hyperparathyroidism as a consequence of low vitamin D levels was related with higher pulmonary artery pressure (6). The investigator suggested that enhanced pulmonary artery pressure may be caused by activation of the renin–

angiotensin–aldosterone system as a result of vitamin D deficiency (13). Endothelial dysfunction that is a current outcome in renal failure patients as established by reduced nitric oxide and endothelin-1 levels, has been suggested to impact on PHT development (15), though these results were found in a small study population that they propose the role of end-stage renal disease in the pathogenesis of PH. In fact, these findings clearly are helping to suggest renal transplantation for patients with higher pulmonary artery pressure (15).

Likewise, a recent study described the prevalence, determinants and consequences of PH among patients on hemodialysis (16). Some of the main results of this study was the higher prevalence of PH among end-stage renal disease who were on hemodialysis. Study showed that, the independent factors of PH are increased left atrial diameter, low urea decrease ratio and no vitamin D receptor activator use (16). Vitamin D receptor activators improve diastolic function and are consequently possible to decrease afterload for the right ventricle (17). Importantly, this study does not confirm, the relation of serum calcium, phosphorus or parathyroid hormone with PH (16). Demir et al compared systolic pulmonary artery pressure between patients with vitamin D deficiency and control groups (6). They found significant association between pulmonary artery pressure and vitamin D (6). In patients, enhanced pulmonary artery pressure associated positively with PTH and negatively with 25-hydroxyvitamin D levels. In this study, systolic pulmonary artery pressure level of the patients was significantly elevated than the systolic pulmonary artery pressure levels of the control group. Additionally, the PTH levels of patients groups were significantly higher than the PTH levels of the control persons. These observations demonstrated that deficiency vitamin D may be associated with PHT. This result proposes that hyperparathyroidism secondary to vitamin D deficiency may have a role in elevated pulmonary artery pressure (6).

### Hypertension in dialysis patients

Low 25-hydroxyvitamin D levels and high parathyroid hormone have been related to hypertension (18). Our previous study assessed the influence of serum PTH on the severity of hypertension in end-stage renal disease patients on regular hemodialysis (19). In this study, the main outcome was a positive association between serum PTH and level of hypertension. Positive association significantly was similarly observed between stages of hypertension (19). Secondary hyperparathyroidism and hypertension are two components involved in enhanced atherosclerosis in hemodialysis patients resulting in enhanced mortality (19). The pathogenesis of hypertension in patients undergoing maintenance hemodialysis treatment is multifactorial for example sodium and water loading as a consequence of the impaired excretory capacity of the kidneys, extremely enhanced activity of the renin-angiotensin-aldosterone system and sympathetic nervous system, and also enhanced levels of the vasoconstrictor endothelin-1, accumulation of endogenous inhibitors of nitric oxide

synthesis and decreased formation of vasodepressor factors (20,21).

Hypertension is one of the major risk factors for cardiovascular morbidity and mortality in the population that are more common in dialysis patients than the non-uremic individuals (19). Cardiovascular diseases establish a main cause of mortality in hemodialysis patients (19). While hypertension and secondary hyperparathyroidism are common characters of the uremic syndrome, it has been proposed that they may have a role in the pathogenesis of hypertension in patients with end-stage renal disease (22).

Functions of parathyroid hormone to keep calcium levels in the blood and release of calcium is stimulated via decreased calcium levels in the blood (19). PTH causes vitamin D activation, enhanced calcium absorption during intestine, enhanced bone resorption, enhanced calcium reabsorption in the kidney and enhanced phosphate excretion in the urine. The clear consequence of PTH activity is an enhanced in blood calcium level without a raise in the level of phosphate (19). Hypertension could be caused via an enhanced in total peripheral resistance or an enhanced in blood volume. PTH can aggravate hypertension by enhancing of these factors (19).

### Conclusion

Several causes have been suggested to have a role in the pathogenesis of PH in patients with pre-dialysis chronic kidney disease and patients on hemodialysis, such as some clinical, hemodynamic and metabolic abnormalities (13,23).

According to numerous studies high levels of PTH as a consequence of low vitamin D levels were related to higher pulmonary artery pressure, particularly in hemodialysis and pre-dialysis patients. More investigations are needed to conduct the impact of PTH and vitamin D levels on hypertension and PH in patients with kidney disease.

### Authors' contribution

SB and HN wrote the manuscript equally.

### Conflicts of interest

The authors declared no competing interests.

### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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