REVIEW

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Malnutrition in pulmonary arterial hypertension: a possible role for dietary intervention

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Purpose of review
The last decade's progress has been made in the pharmacological treatment of pulmonary arterial hypertension (PAH). The role of nutrition in relation to quality of life in this group of patients is not investigated yet. In addition to avoiding salt and high-fluid intake based on left heart failure diet, there is no evidence-based diet recommendation for PAH.

Recent findings
It was recently demonstrated that patients with PAH suffer from malnutrition resulting in iron and vitamin D deficiency and glucose/insulin resistance. Recent experimental studies suggest that besides reduced malabsorption of important nutrients, the microbiome of the gut is also less diverse in PAH. In this review, we summarize the current knowledge on malnutrition and dietary intake in PAH. We discuss the possible underlying mechanisms and discuss novel therapeutic interventions validated in patients with left heart failure.

Summary
Large-scaled studies on dietary interventions are needed in PAH.

Keywords
malabsorption, microbiome, nutrition, right heart failure

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a lung disease characterized by increased blood pressure (BP) in the pulmonary circulation ultimately causing right ventricular (RV) failure (RVF). Although in the last decades progress has been made in the pharmacological treatment of PAH, little attention has been paid on nutrition and lifestyle strategies. For this, the only recommendation in the most recent consensus article is the mentioning of avoiding salt and high-fluid intake [1]. Significantly, in patients with left heart failure (LHF) the important role of nutritional education and interventions has been well recognized and are an integral part of LHF management [2,3].

The current review will describe the known mechanisms of malnutrition in PAH, summarize studies exploring nutrition-related interventions in PAH and identify knowledge gaps.

MALNUTRITION

Intake, appetite and malabsorption

Malnutrition in patients with LHF has been extensively described and is a result from many different components, including appetite loss, bowel congestion due to hepatic or gastrointestinal dysfunction, metabolic disturbances, medication-related effects, fatigue, higher resting metabolic rate and increased work of breathing [4]. In patients with PAH, malnutrition has been less studied although venous congestion and lower BMI are typical features of severe right heart failure [5,6]. At this moment, there is no information available about appetite and metabolism rate in PAH [6,7]. Malabsorption as a consequence of gastrointestinal

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KEY POINTS

- Malnutrition and weight loss are frequent present in PAH patients.
- Venous congestion, low cardiac output and medication use are main contributors of altered bowel function.
- Vitamin D and intravenous iron suppletion should be recommended in patients who are iron and vitamin D deficient.

edema due to decreased RV function, alterations in the gut microbiome and impact of PAH medication on the bowel however will result in decreased nutrient uptake [6] (Fig. 1).

UNDERLYING MECHANISM

Medication and malabsorption

High-dose diuretics are used on a regular base in PAH to prevent fluid retention. Long-term use of furosemide in patients with LHF results in a thiamine deficiency, which is an important vitamin for energy and carbohydrate regulation [8]. Whether thiamine and proton pump inhibitor (PPI)-related vitamin deficiencies are relevant in PAH is currently unknown. A recent study among 343 geriatric patients, shows hypomagnesemia as a consequence of long-term use of PPI and other medications, such as vitamin K antagonists. The number of drugs used was inversely and linear related to the plasma level of magnesium. Hypomagnesemia is closely associated with cardiovascular disease and events. Whether hypomagnesemia is relevant in PAH is not investigated jet [9]. Symptoms of hypomagnesemia are: muscle cramps, palpitations and cardiovascular disease [10]. A frequent used drug in the treatment of PAH is prostacyclin and a common side effect is diarrhea. Prostacyclin activates adenylate cyclase, which increases cyclic adenosine monophosphate (cAMP). cAMP causes secretion of chlorine from interstitial tissue to the gut lumen along with sodium and water. Fluid and electrolyte proliferation in the intestinal lumen leads to diarrhea [11,12], which causes malabsorption. Selexipag, a prostacyclin analogue, gives identical side effects.

Gastrointestinal edema and fluid retention

PAH-patients suffer from fluid retention, due to RVF, which leads to venous congestion and a low cardiac output (CO) and has as a consequence a low systemic BP. To prevent fluid retention at the kidney level, diuretics are standard in the treatment of RVF. Although it is likely that a strict diet based on fluid and salt restriction has beneficial effects on the management of RVF, this has not been studied until now. Finally, high-glucose and insulin levels have been shown to increase salt and water retention and are closely associated with kidney dysfunction and PAH [13–19].

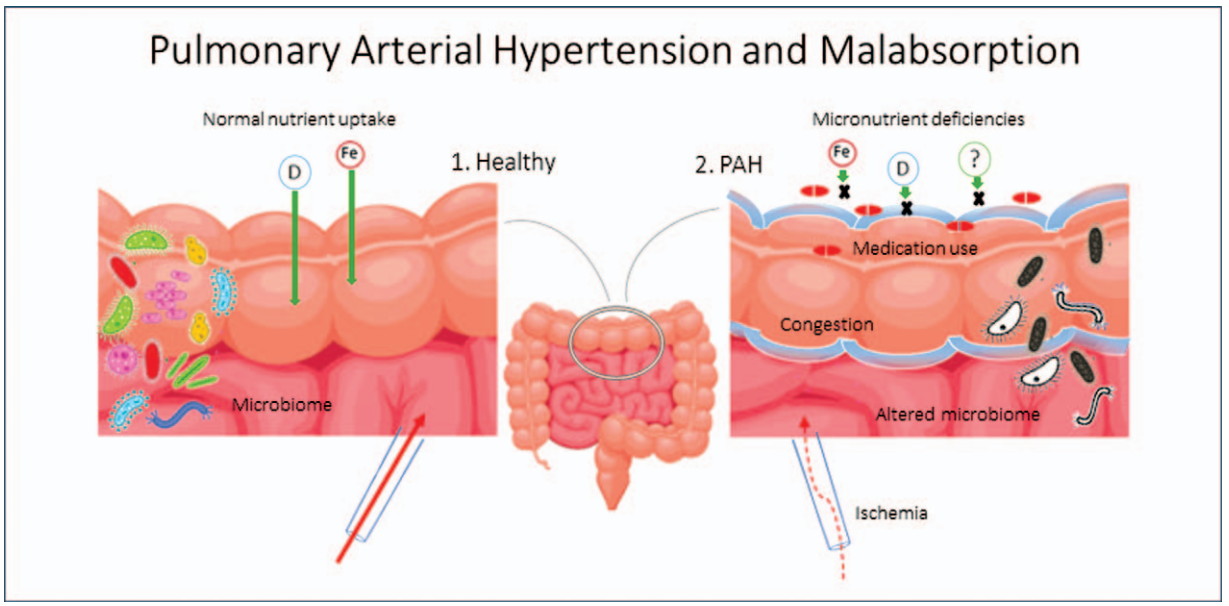

FIGURE 1. A comparison between healthy intestines (1) and those of pulmonary arterial hypertension patients (2). Possible explanations for this intestinal differences in pulmonary arterial hypertension are medication use, a changed microbiome, intestinal congestion and ischemia, and micronutrient deficiencies, for example, vitamin D and iron.

Glucose and insulin resistance

In recent years, more interest has developed in the role of insulin resistance and diabetes in pulmonary hypertension. Several reports showed increased glucose intolerance and resting expenditure with reduced insulin secretion in PAH patients, worse 6-min walking distance in patients with more insulin resistance, and even worse survival in patients with PAH and concomitant diabetes [20,21]. It is unclear whether insulin resistance play a role in the development of the disease or is just a marker of disease severity.

In addition, RV adaptation is crucial in PAH and might be influenced by diet. In a mouse model, a western diet-induced higher pulmonary artery pressure, RV diastolic dysfunction and RV steatosis. In mice where pulmonary hypertension was induced by pulmonary artery banding, a more pronounced effect was seen of the western (high fat) diet compared with healthy mice [22▪]. Metformin was able to prevent all these effects.

The microbiome

Many bacteria and other microorganisms colonize the human gut. The microbiome produces many metabolites that can exert biological effects and is responsible for maintaining the gut barrier function. Changes in the microbiome have been previously shown in several diseases such as LHF, diabetes, chronic kidney failure and obesity where a less diverse microbiome was found [23,24]. Adding probiotics or prebiotics have been shown to restore the microbiome and reduce BP in systemic hypertension [24,25].

In pulmonary hypertensive rats, the gut microbiome was less diverse compared with controls. There were more short-chain fatty acid (FA) producing bacteria and a trend toward more acetate producing bacteria [26▪]. These specific alterations in microbiome can lead to bacterial translocation, resulting in higher plasma bacterial lipopolysaccharide (LPS), which is the main ligand for Toll-like receptor four (TLR4). Strikingly, TLR4 alone is already associated with development of pH even without LPS [27,28]. An additional factor that favors bacterial translocation is intestinal edema, which also compromises the guts barrier function [26▪,27]. Whether the microbiome is changed in PAH and if a diet can restore these possible changes, needs to be explored in future.

Although little is known about the nutritional state of PAH patients, two deficiencies have been explored in more debt: iron and vitamin D.

Iron deficiency

Iron deficiency is common in PAH patients and is associated with reduced exercise capacity, higher New York Heart Association Classification functional class and worse survival, irrespective of the presence of anemia [29–32]. Iron deficiency in PAH patients most likely develops due to a combination of lower intake and absorption of iron, increased iron loss, and iron utilization due to increased erythropoiesis [32–34]. Disturbed iron handling due to high hepcidin levels, however, is probably the most important contributor to iron deficiency development in PAH, as hepcidin reduces intracellular iron release into the bloodstream [31,35]. Although hepcidin is increased by inflammatory marker IL-6, which is generally increased in PAH patients, no direct relation between IL-6 and hepcidin was found in iron deficient PAH cohorts [31,35]. Other factors that influence hepcidin in PAH are BMPR2 mutations, resulting in BMP-6 stimulated hepcidin expression, increased erythroid precursor growth differentiation factor-15 and mutations in GATA-4 [31,36]. Supplying intravenous iron resulted in improved 6-min walking tests, exercise endurance time and aerobic capacity, and quality of life. Increased quadriceps muscle oxygen handling could be the cause of the improvement since RVF remained unaltered [35,37].

Vitamin D

Tanaka *et al.* [38] showed that 61% of 41 patients with PAH and chronic thromboembolic pulmonary hypertension, was vitamin D deficient. A lower 25(OH)D levels was associated with a poor hemodynamic phenotype [38] Mirdamadi *et al.* prescribed supplemental vitamin D to PAH patients and showed improved 6-min walking distance after treatment. However, only 22 patients were included with all different kinds of pulmonary hypertension and these results should therefore be interpreted with caution [39]. A few studies investigated whether vitamin D plays a pathophysiological role in PAH [38,40]. In an in-vitro setup, adding a precursor of vitamin D to rat pulmonary artery endothelial cells, led to a reversal of hypoxia-induced activation of pathways of inflammation, fibrosis and proliferation. This was represented by reduced expression of transforming growth factor-beta1, alpha smooth muscle actin and Smad7 with induced expression of microRNA-204, p21 and Smad2, which have been reported to be involved in the development of pH [40]. Similar biomarker results were then found in vivo in pH rats were vitamin D was given intraperitoneal [40]. In another pH rat model, supplementation of dietary vitamin D improved survival and inhibited RV remodeling although hemodynamic parameters were not different. Also medial wall thickness of pulmonary

arteries was unaltered by supplemental vitamin D [38]. For this, further research is required to explore the impact of screening on vitamin D deficiency and the impact of suppletion.

WHAT CAN WE LEARN FROM NUTRITION STUDIES IN PATIENTS WITH LEFT HEART FAILURE

Although mechanisms of disease are different in LHF and PAH patients, the impact of heart failure on the body share almost similar characteristics leading to malnutrition and muscle wasting. Since no studies exploring the impact of dietarian interventions in PAH so far, it is worthwhile to take lessons from LHF. Several diets have been tested in LHF which could give some information about possible benefit in PAH. A 6-week high-calorie high-protein diet in patients with LHF resulted in increased edema-free body weight, body composition and quality of life. Increased serum lipoproteins and reduced serum TNFα levels were found [41]. A Mediterranean diet, characterized by intake of FAs such as olive oil and fish, vegetables, grains, nuts and red wine, was associated with improved cardiac function, less cardiac remodeling and cardiovascular events, and a reduction of LHF risk and LHF-related mortality [42–46]. Furthermore, the Dietary Approach to Stop Hypertension (DASH) diet, characterized by low-salt, red meat, saturated fat, sugar-intake and low-fat dairy products, with high magnesium, potassium, calcium, amino-acids, fiber, fruit, vegetables and whole grains, was associated with improved cardiac function, exercise capacity and quality of life [47–50].

CONCLUSION

Although malnutrition and waste loss are frequently found in PAH, little is known on the effectiveness of nutrition and lifestyle interventions in PAH-patients. Mechanisms underlying malnutrition and food deficiencies include low CO state, intestinal edema, inflammation, abnormal kidney function, changes in microbiome and side effects of PAH-specific medication and diuretics. Common deficiencies include iron and vitamin D. Although small studies showed the beneficial impact of iron and vitamin D, large-scaled studies on dietary interventions are lacking in PAH. Further research in this area in PAH should focus on a systematic analysis of nutritional state in PAH, development of a validated and disease-specific score for malnutrition in PAH and dietarian intervention studies.

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Conflicts of interest

There are no conflicts of interest.

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