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RESEARCH ARTICLE

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Nutritional status in pulmonary arterial hypertension

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Abstract

Nutritional deficiencies have been described in patients with pulmonary arterial hypertension (PAH), such as in iron and vitamin D. However, an extensive description of vitamin and mineral status is lacking and until now there is no data on dietary intake in PAH patients. We analyzed blood samples and determined nutritional intake using a food frequency questionnaire (HELIUS) in a cohort of prevalent PAH patients at a single center in Amsterdam, the Netherlands. Quality of life (QoL) was assessed by the SF-36 questionnaire. In total, 37 patients were included (6 males, 31 females; 48 ± 16 years). The dietary intake of sugar was above 25 g in 87% of the patients and fluid intake was above 1500 ml in 78% of the patients. Sodium intake was below 1800 mg in the majority (56%) of the patients. Sugar and fluid intake were linear related. We confirm previously observed deficiencies of iron and vitamin D in our study population. In addition, we observed a functional vitamin B12 deficiency in 29% of patients, which coincided with an increased expression of methylmalonic acid. 60% of patients had a low vitamin K1 status (<0.8 nmol/L). Finally, 40% of patients had selenium levels below <100 μg/L and low selenium levels associated with reduced vitality in these patients. Besides the known deficiencies in iron and vitamin D levels, we observed in a subset of patients signs of vitamin B12, vitamin K1 and selenium deficiencies. There is room for improving dietary intake. Future research aims to demonstrate the clinical importance and reveal the effect of nutritional interventions.

KEYWORDS
deficiencies, diet, nutrition, pulmonary hypertension

INTRODUCTION

Pulmonary Arterial Hypertension (PAH) is a lethal disease, caused by progressive remodeling of the pulmonary arterioles and subsequent development of right heart failure (RHF).[1] End-stage disease is characterized by weight loss and cardiac cachexia. Several factors may contribute to malnutrition in PAH, such as changes in food intake with progression of disease, intestinal edema and malabsorption due to venous congestion and a low

cardiac output.[2] In addition, diuretics and PAH-specific medications including prostacyclin may affect bowel function and renal clearance. Finally, anorexia is common in chronically ill patients. Although malnutrition is well recognized in end-stage disease, so far little is known of the nutritional status in PAH patients who are stable under treatment. While iron and vitamin D deficiencies have been described in PAH,[3–6] until now a comprehensive description of the nutritional status in PAH patients with vitamin and mineral status and nutritional intake is lacking. As a consequence, no evidence based dietary recommendations are available.

For this article, we aimed to provide a comprehensive assessment of the nutritional status, including vitamins and mineral levels and nutritional intake, and quality of life in PAH patients.

METHODS

Population

The data used in this study was derived from a prospective study testing a nutrition and lifestyle intervention in patients with pulmonary arterial hypertension (UPHILL study).

In total, 37 patients were included with the following inclusion criteria: idiopathic, hereditary or drug-related PAH, age <80 and >18 years, NYHA II or III and stable for at least 3 months, determined by a stable 6-min walk test (6MWT) with a difference of <10%, an estimated glomerular filtration rate and willing and able to sign the informed consent form. All participants provided written informed consent before any study-related procedures. The UPHILL study was approved by the medical ethics committee with approval number 2018.538 and complies with the Declaration of Helsinki.

Questionnaires

Nutrition

The Dutch version of the HELIUS (HEalthy LIfe in an Urban Setting) food frequency questionnaire (FFQ) was used to assess dietary intake of fluid, sodium, and sugar per day. This FFQ was developed at the Amsterdam UMC in collaboration with the National Institute for Public Health and the Environment (RIVM) and the Wageningen University.[7] The patients were given an online version of the FFQ and reported eating frequency and portion size of 238 food items they could have consumed in the previous 4 weeks. Average daily nutrient intake was calculated by multiplying the frequency of consumption by the consumed amounts and nutrient content per item using the NEVOtabel (supplement).

Quality of life

The SF-36 questionnaire was used for assessing QoL. The SF-36 is a set of generic, coherent, and easily administered QoL measures. These measures rely upon patient self-reporting and are widely utilized by managed care organizations for routine monitoring and assessment of care outcomes in adult patients.[8]

Blood analysis

All blood samples were drawn and pre-analytically processed according to the routine laboratory protocols. All analyses were performed by an ISO15189:2012 accredited medical laboratory. The hematology parameters were analyzed with a NX1000 analyzer (Sysmex), the routine blood chemistry parameters were analyzed with a Cobas8000 analyzer (Roche). The trace metals were determined with Atomic Absorption Spectroscopy (Shimadzu) and all vitamins were analyzed chromatographically with HPLC (Shimadzu). All reported results did comply with the criteria of the external quality surveys.

6MWT

The 6MWT was used to asses exercise capacity. This test is widely used for measuring response to therapeutic interventions in pulmonary and cardiac diseases. The 6MWT measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 min and is a useful measurement for functional capacity.[9]

Statistical analyses

Data are presented as mean ± (standard deviation or SD) for normally distributed data or as median [interquartile range or IQR] for non-normally distributed data. For non-normally distributed data, logarithmic transformation was performed before the analysis. Relationships between two continuous variables were assessed with Pearson's correlations. A p-value of <0.05 was considered statistically significant. Statistical analyses and graphical illustrations were generated in R studio (version 3.5.2).

TABLE 1 Patient characteristics

	Overall
n	37
Age - mean (SD)	47.92 (16.25)
Gender - *N*_male(%)	6 (16.2)
6MWT - mean (SD)	503.15 (122.66)
NTproBNP - median [IQR]	132.50 [78.18–257.25]
NYHA	II
BMI - mean (SD)	25.39 (4.34)
Therapy (%)	
Mono	6 (16.7)
Double	22 (61.1)
Triple	9 (22.2)
Endothelin antagonists - *N* (%)	27 (75.0)
Phosphodiesterase inhibitors - *N* (%)	33 (91.7)
Postacyclin p.o. - *N* (%)	7 (19.4)
Postacyclin i.v. - *N* (%)	5 (13.9)
Calcium antagonists - *N* (%)	3 (8.3)
Diuretics - *N* (%)	19 (52.8)
Vitamin K antagonists - *N* (%)	19 (52.8)

Abbreviations: 6MWT, 6-min walk test; BMI, body mass index; SD, standard deviation.

RESULTS

Patient characteristics

In total, we included 37 patients with a mean age of 48 ± 16 years. 16% of the subjects were males, the mean BMI was 25.39 ± 4.34, the median NTproBNP was 32.50 (IQR [78.18–257.25]), 61% received double therapy and the mean 6MWD was 503 ± 123 meters. Detailed patient characteristics and results can be found in Tables 1 and 2.

Intake

As shown in Figure 1a, 78% of patients had a fluid intake above 1500 ml and 31% had an intake above 2000 ml. The intake of fluid mostly came from tea, coffee, and water. As can be seen in Figure 1b, 87% of the females and all males in this population exceeded their advised daily sugar intake. Commonly chosen sugar-enriched products were: beverages, bakery, and candy. In this population 25% had an intake of sodium above 2300 mg and 56% had an intake below 1800 mg (Figure 1c). Intake of sodium mainly came from grain products, chips, salted nuts, and processed meat and fish. The reference values were derived from nutritional guidelines for patients with

TABLE 2 Dietary intake, QoL and 6MWT

	Females	Males
n	31	6
Dietary intake		
Fluid in ml (median [IQR])	1839.25 [1528.19–2162.00]	1576.53 [1533.40–2667.51]
Sodium in mg (median [IQR])	1569.72 [1101.05–2281.25]	1710.38 [1520.57–1979.38]
Sugar in grams (median [IQR])	40.20 [29.38–77.68]	107.04 [89.66–124.76]
SF-36		
Physical functioning (median [IQR])	50.00 [35.00–65.00]	55.00 [46.25–63.75]
Social functioning (median [IQR])	50.00 [37.50–62.50]	50.00 [50.00–50.00]
Role physical limitations (median [IQR])	50.00 [0.00–100.00]	75.00 [18.75–75.00]
Role emotional limitations (median [IQR])	66.70 [33.33–66.70]	66.70 [41.67–66.70]
Mental health (median [IQR])	60.00 [56.00–64.00]	64.00 [61.00–67.00]
Vitality (median [IQR])	45.00 [40.00–50.00]	42.50 [32.50–52.50]
Bodily pain (median [IQR])	89.80 [67.30–100.00]	100.00 [83.20–100.00]
Average health (median [IQR])	40.00 [35.00–50.00]	42.50 [36.25–52.50]
Health change (median [IQR])	50.00 [25.00–50.00]	50.00 [31.25–50.00]
6MWT		
Distance in meters (median [IQR])	499.50 [399.50–546.25]	635.00 [580.00–663.00]

Abbreviations: 6MWT, 6-min walk test; IQR, interquartile range; QoL, quality of life.

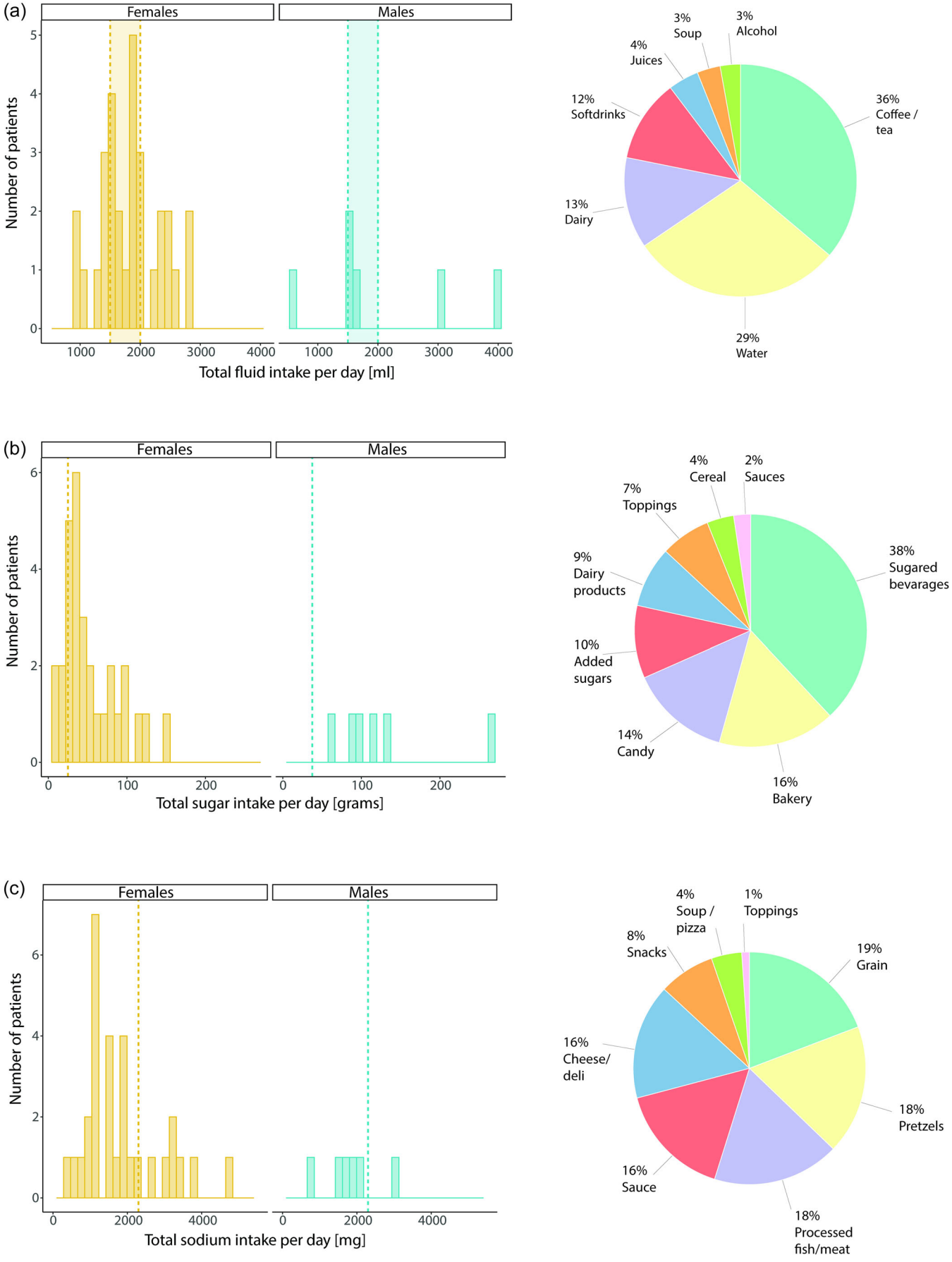

FIGURE 1 (See caption on next page)

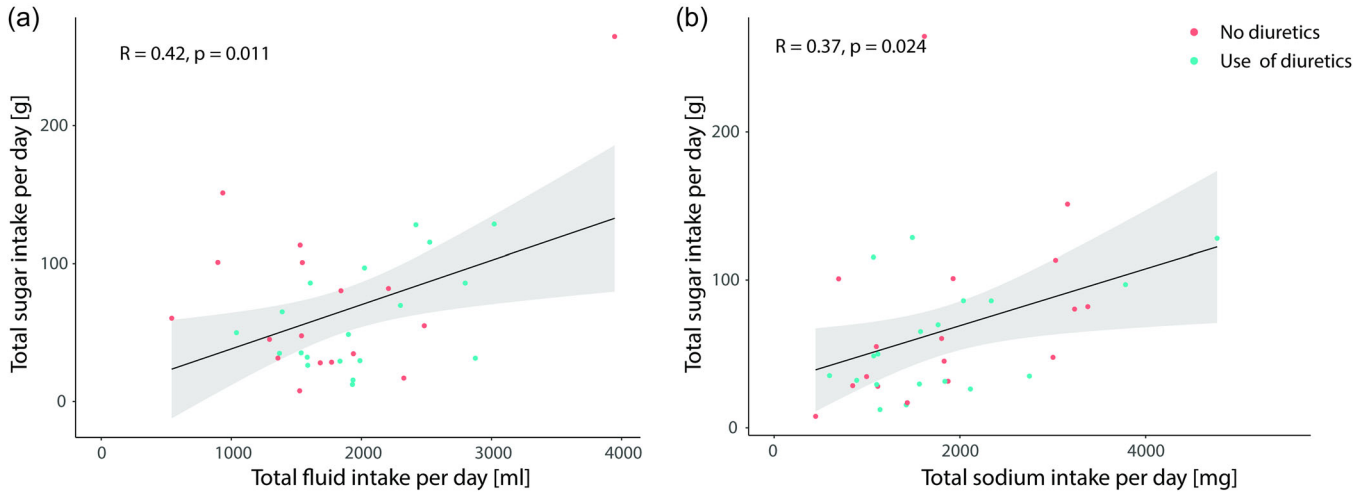

FIGURE 2 Correlations nutritional intake. Total sugar intake per day is closely associated with the total fluid intake (a) and total sodium intake (b) per day. No clear association with diuretic use could be observed. Red dots represent patients without diuretics. Blue dots represent patients with diuretic therapies.

cardiovascular disease from the American Heart Association.[10]

A significant correlation was found between the intake of sugar and fluid (Figure 2a); that is, the higher the consumption of sugar the more fluid was consumed. There was also a linear correlation between the intake of sugar and sodium (Figure 2b). There was no correlation found between fluid intake and use of diuretics.

Vitamin and mineral status

Serum vitamin analyses were performed in all patients and most outcomes were within normal range (Table 3). As illustrated in Figure 3a, only a minority of patients showed a low vitamin A level. Low vitamin K1 status was more prevalent, and was observed in 18 patients (60%) (Figure 3b) and there was no relation with the use of vitamin K antagonists. Vitamin K2 status was low in all patients. As expected, vitamin D deficiency was observed in 43% (Figure 3c), based on low 25-OH vitamin D values.

Vitamin B12 values were within reference interval (130–700 pmol/L) in the majority of patients (Figure 3d). However, to assess vitamin B12 deficiency, values should be interpreted in relation to methylmalonic acid (MMA) levels. This is because the circulating vitamin B12 species do not reflect the intracellular activity of vitamin B12-dependent enzyme systems.[11,12] It is therefore generally accepted that the functional vitamin B12 status is better reflected by the serum concentration of MMA and to a somewhat lesser extend homocysteine. Although the serum MMA concentration is age dependent, in guidelines a value of >350 nmol/L is commonly used as a cut-off criterium for a functional vitamin B12 deficiency. Interestingly, as can be observed in Figure 3e,f, 29% of patients' vitamin B12 values were >130 pmol/L in combination with MMA > 350 nmol/L. To correct for possible confounding by inflammation and reduced kidney function, relations are also shown for patients with an estimated glomerulus filtration rate <60 ml/min or CRP > 5 mg/L.

Serum mineral analyses were performed in all patients and most outcomes were within normal ranges, as can been seen in Table 3 and Figure 4a–c for selenium,

FIGURE 1 Fluid, sugar, and sodium intake per day. (a) Total fluid intake per day of male and female patients. Yellow/blue shaded square represent the amount of fluid intake that is advised by the American Heart Association (AHA). The pie chart demonstrates the distribution of sources of fluid intake. (b) Total sugar intake per day of male and female patients. The yellow dotted line represents the AHA-recommendation for females of 25 gram a day. The blue dotted line represents the AHA-recommendation for males of 37.5 grams a day. The pie chart shows sources of sugar intake of all patients. (c) Total sodium intake per day of male and female patients. The yellow/blue dotted lines represent the AHA-recommendation of 2300 mg sodium per day. The pie chart shows the sources of sodium intake of all patients. Pretzels are salty snacks such as nuts, chips, and salty biscuits.

TABLE 3 Blood analyses

	Females	Males	Reference values	
n	31	6		
General blood markers			Females	males
Erytrocytes (median [IQR])	4.70 [4.38–5.19]	5.50 [4.90–5.52]	3.8–5.3 × 10^{12}/L	4.4–5.9 × 10^{12}/L
Hematocrit (median [IQR])	0.44 [0.41–0.47]	0.47 [0.45–0.50]	0.36–0.48 L/L	0.42–0.51 L/L
Hemoglobine (median [IQR])	8.60 [8.30–9.55]	9.70 [9.30–9.80]	7.3–9.8 mmol/L	8.4–10.9 mmol/L
Leukocytes (median [IQR])	7.92 [7.19–8.94]	5.12 [4.85–5.25]	3.5–11.0 × 10^{9}/L	3.5–11.0 × 10^{9}/L
Trombocytes (median [IQR])	254.00 [221.00–301.00]	200.00 [195.00–260.00]	150–400 × 10^{9}/L	150–400 × 10^{9}/L
MCV (median [IQR])	92.50 [90.35–96.60]	89.90 [89.80–92.40]	83–98 fl	83–98 fl
Methylmalonic acid (median [IQR])	222.00 [186.75–442.75]	176.50 [136.00–288.25]	<350 nmol/L	<350 nmol/L
RDW (median [IQR])	46.00 [44.00–48.35]	40.45 [39.92–41.57]	37.0–48.0 fl	37.0–48.0 fl
ALP (median [IQR])	74.00 [61.00–87.00]	68.00 [60.75–79.00]	<120 U/L	<120 U/L
ALAT (median [IQR])	18.00 [13.75–24.00]	19.00 [16.50–22.25]	<0–34 U/L	<0–45 U/L
ASAT (median [IQR])	23.50 [20.75–27.50]	27.50 [24.75–32.50]	<0–31 U/L	<0–35 U/L
Bilirubine (median [IQR])	7.00 [5.33–10.18]	5.70 [5.00–11.00]	<17 μmol/L	<17 μmol/L
Gamma GT (median [IQR])	20.00 [17.00–43.00]	28.00 [21.00–37.25]	0–38 U/L	0–55 U/L
Creatinine (median [IQR])	71.00 [61.75–84.25]	79.00 [77.50–97.75]	45–84 μmol/L	59–104 μmol/L
EGFR (median [IQR])	79.00 [74.35–90.00]	90.00 [80.72–90.00]	>90 ml/min	>90 ml/min
Urea (median [IQR])	5.65 [4.50–6.53]	4.75 [4.45–5.20]	18–60 years: 2.1–7.1 mmol/L, >60 years: 2.9–8.2 mmol/L	18–60 years: 2.1–7.1 mmol/L, >60 year: 2.9–8.2 mmol/L
Albumin (median [IQR])	41.30 [39.20–42.60]	48.60 [48.60–48.60]	35–50 g/L	35–50 g/L
CRP (median [IQR])	2.00 [1.00–3.25]	1.00 [1.00–1.00]	<10 mg/l	<10 mg/L
Ferritine (median [IQR])	66.80 [27.60–161.00]	94.55 [65.18–112.75]	13–150 μg/L	30–400 μg/L
Ferritin saturation% (median [IQR])	20.50 [16.25–27.25]	27.50 [26.00–35.00]	20%–60%	20%–60%
TIBC (median [IQR])	62.50 [59.25–73.75]	63.50 [61.25–65.75]	45–81 μmol/L	45–81 μmol/L
Transferrin (median [IQR])	2.51 [2.36–2.95]	2.54 [2.46–2.61]	2.00–3.60 g/L	2.00–3.60 g/L
Cholesterol (median [IQR])	4.70 [4.20–5.39]	4.43 [4.14–4.73]	<6.0 mmol/L	<6.0 mmol/L
Chol_ratio (median [IQR])	3.60 [2.89–4.24]	3.24 [3.01–3.58]	<5.00	<5.00
HDL (median [IQR])	1.35 [1.13–1.68]	1.36 [1.22–1.48]	0.90–3.00 mmol/L	0.90–3.00 mmol/L
LDL (median [IQR])	2.80 [2.24–3.24]	2.63 [2.32–2.99]	<2.50 mmol/L	<2.50 mmol/L

TABLE 3 (Continued)

	Females	Males	Reference values	
Triglycerides (median [IQR])	1.30 [0.90–1.89]	1.29 [1.15–1.44]	<2.00 mmol/L	<2.00 mmol/L
T3 (median [IQR])	4.66 [4.30–5.10]	5.51 [5.43–5.51]	3.1–6.8 pmol/L	3.1–6.8 pmol/L
T4 (median [IQR])	16.85 [16.10–18.12]	16.05 [15.65–16.45]	12.0–22.0 pmol/L	12.0–22.0 pmol/L
TSH (median [IQR])	1.60 [1.28–2.25]	1.40 [1.04–3.00]	0.27–4.2 mU/L	0.27–4.2 mU/L
IgA (median [IQR])	2.06 [1.84–2.63]	1.72 [1.64–2.25]	0.70–4.00 g/L	0.70–4.00 g/L
Minerals				
Calcium (median [IQR])	2.38 [2.31–2.45]	2.40 [2.37–2.43]	2.20–2.65 mmol/L	2.20–2.65 mmol/L
Chloride (median [IQR])	102.10 [100.55–103.30]	101.65 [101.23–102.68]	97–107 mmol/L	97–107 mmol/L
Chrome (median [IQR])	7.50 [7.50–7.50]	7.50 [7.50–7.50]	<15.0 nmol/L	<15.0 nmol/L
Copper (median [IQR])	20.00 [18.00–22.00]	14.00 [13.00–16.00]	12–29 μmol/L	12–29 μmol/L
Iron (median [IQR])	13.15 [8.70–16.10]	17.55 [16.50–23.18]	10–25 μmol/L	14–28 μmol/L
Magnesium (median [IQR])	0.87 [0.84–0.91]	0.93 [0.90–0.94]	0.70–1.05 mmol/L	0.70–1.05 mmol/L
Phosphate (median [IQR])	1.06 [0.98–1.20]	1.05 [0.92–1.24]	0.80–1.40 mmol/L	0.80–1.40 mmol/L
Potassium (median [IQR])	4.18 [3.85–4.52]	4.38 [4.24–4.65]	3.2 –4.7 mmol/L	3.2–4.7 mmol/L
Selenium (median [IQR])	1.02 [0.92–1.20]	1.04 [1.03–1.06]	0.8–1.8 μmol/L	0.8–1.8 μmol/L
Zinc (median [IQR])	14.00 [13.00–15.00]	14.00 [14.00–15.00]	10–20 μmol/L	10–20 μmol/L
Sodium (median [IQR])	139.10 [138.45–140.25]	138.60 [138.02–139.33]	135–145 mmol/L	135–145 mmol/L
Vitamins				
A (median [IQR])	2.10 [1.75–2.45]	2.10 [1.57–2.40]	1.2–2.7 μmol/L	1.2–2.7 μmol/L
B1 (median [IQR])	148.00 [137.75–198.25]	153.50 [145.75–168.00]	85–175 nmol/L	85–175 nmol/L
B2 (median [IQR])	257.50 [239.75–290.75]	265.50 [230.50–291.50]	200–375 nmol/L	200–375 nmol/L
B6 (median [IQR])	91.00 [71.00–112.50]	118.00 [79.00–142.00]	59–179 nmol/L	59–179 nmol/L
B3 (median [IQR])	28.00 [26.00–31.00]	30.00 [29.00–36.00]	20–50 μmol/L	20–50 μmol/L
B12 (median [IQR])	380.00 [267.25–546.75]	463.50 [331.50–502.50]	130–700 pmol/L	130–700 pmol/L
Beta carotene (median [IQR])	0.60 [0.50–0.85]	0.60 [0.45–1.20]	0.3–1.9 μmol/L	0.3–1.9 μmol/L
D hydroxy (median [IQR])	58.60 [44.85–86.45]	43.75 [38.65–66.03]	43–168 pmol/L	43–168 pmol/L
E (median [IQR])	34.00 [28.50–38.50]	31.25 [30.12–32.75]	15–50 μmol/L	15–50 μmol/L
Folic acid (median [IQR])	17.80 [10.83–24.85]	14.85 [10.68–16.48]	>8.83 nmol/L	>8.83 nmol/L
K1 (median [IQR])	0.60 [0.50–1.10]	1.15 [0.60–1.88]	0.8–5.3 nmol/L	0.8–5.3 nmol/L

Abbreviation: ALP, alkaline phosphatase; ALAT, alaline transaminase; ASAT, aspartate transaminase; Chol_ratio, cholesterol ratio; CRP, C-reactive protein; eGFR, estimated glomerulus filtration rate; gamma-GT, gamma-glutamyl transferase; HDL, high-density lipoprotein; IgA, immunoglobulin A; IQR, interquartile range; LDL, low-density lipoprotein; MCV, mean corpuscular volume; RDW, red cell distribution width; T3, triiodothyronine; T4, thyroxine; TIBC, total iron binding capicity; TSH, thyroid stimulating hormone.

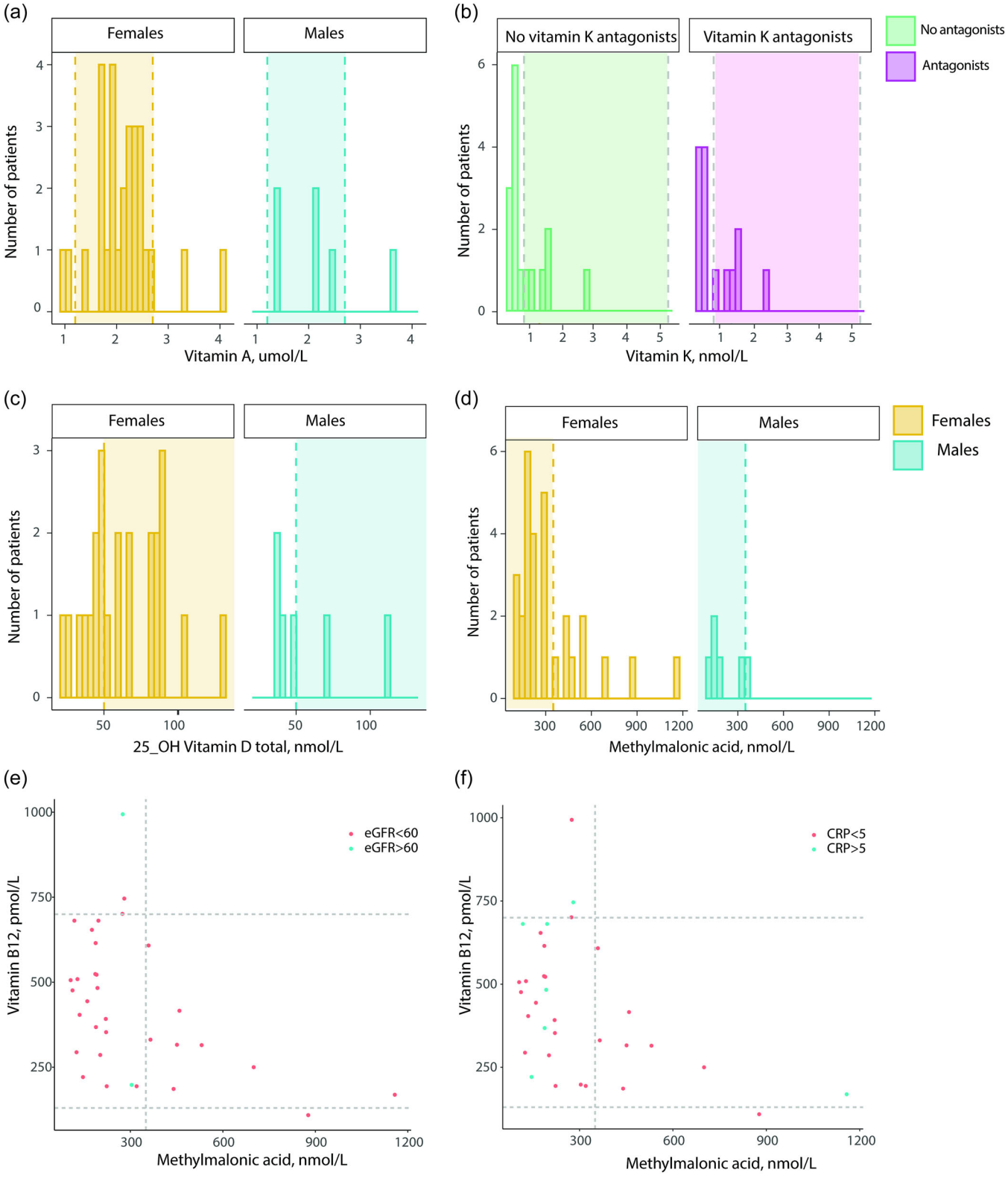

FIGURE 3 (See caption on next page)

copper, and magnesium. Transferrin saturation (Figure 4d) was < 20% in 32% of patients indicating iron deficiency. Selenium values < 100 ug/l were present in 41% of patients and related to vitality, a marker for QoL (Figure 4e). There were no further correlations found between QoL vitamin status or mineral status.

DISCUSSION

To assess the nutritional status in PAH we determined serum levels of vitamins and minerals and dietary intake. Using a combination of questionnaires and extensive blood analyses, we provide for the first time an overview of nutritional status in PAH patients (Figure 5) which is highlighted by newly found deficiencies in vitamin B12, K1, and selenium. In addition, we show that many PAH patients have elevated sugar and fluid intakes and a reduced sodium intake.

Intake

As compliance of dietary guidelines is measured through dietary intake, we subsequently investigated the nutrient intake of the patients with the HELIUS questionnaire. The HELIUS questionnaire is a large questionnaire with over 238 products to asses nutritional intake over the last four weeks. The HELIUS questionnaire has been described as suited for diverse populations, including urban settings, the elderly and patients with cardiovascular disease.[7,13,14]

We found a high intake of sugar, correlated to a high intake of fluid, and a low intake of sodium. High-glucose and insulin levels have been shown to increase salt and water retention and are closely associated with kidney dysfunction and PAH.[15–17] In addition, we observed a close correlation between fluid intake and sugar intake, confirming the notion of dietitians that sugar causes thirst. Fluid restriction is important in HF. We observed that 78% of patients exceeded fluid intake. The relation between sugar and fluid intake should be taken into account when designing novel dietary guidelines for PAH patients.

Interestingly, the sodium intake in this group can be considered low; 56% of the population had an intake below 1800 mg and even 5.6% had an intake below 500 mg sodium, which is the minimum reference value for vital functions. Nutritional advice in HF has always focused on lowering sodium intake and maybe this guideline has been taken too strictly in PAH. Recent studies question sodium guidelines.[18] As O'Donnel et al. conclude[19,20] a sodium intake below 3000 mg (100% in this population) is as worse as a sodium intake above 5000 mg when it comes to cardiovascular disease. To extend, patients with PAH often use diuretics which also deplete minerals. This raises the question of whether a low sodium intake is sensible.

The main intake of sugar and sodium came from ultra-processed foods (UPF), such as sugared beverages, snacks, and bakery.[21] In patients with pre-existing cardiovascular disease, a diet rich in UPF is associated with increased hazard of all cause and increased mortality.[22] As described, sugar and fluid intake were linearly related and sodium intake was too low in the majority of patients. We suspect that single dietary guidelines are followed too strictly and that patients will probably benefit more from general nutritional advice in relation to PAH. Further research is needed to investigate optimal communication of interventions.

Vitamin and mineral status

Although overall vitamin and mineral status was preserved in the majority of patients, in a subset of patients values below reference could be observed. As previously described by us and others, 32% of patients

FIGURE 3 Vitamins. Serum vitamin analyses was performed in all patients. (a) Vitamin A status for male and female patients. Shaded area represents normal limits. Only a minority of patients shows low vitamin A levels. (b) Vitamin K1 status for both males and females, divided for use or no use of vitamin K antagonists. Shaded area represents normal limits > 0.8 nmol/L < 5.3 nmol/L. In 60% of patients vitamin K1 values were lower than reference value. (c) Vitamin 25-OH D status for male and female patients. Shaded area represents normal limits > 50 nmol/L. In 43% vitamin D levels were lower than reference value. (d) Vitamin B12 status for male and female patients. The shaded area represents the normal values for vitamin B12 between 130 and 700 pmol/L. The majority of patients have vitamin B12 values between the normal limits. However, for evaluation of vitamin B12 deficiency, values should be interpreted in relation to methylmalonic acid levels (Wolffenbuttel BHR, Wouters HJCM, de Jong WHA, et al. *Association of vitamin B12, methylmalonic acid, and functional parameters*.). Reference value of methylmalonic acid is <350 nmol/L. As can be observed in (e–f), in 29% of patients vitamin B12 values >130 pmol/L in combination with methylmalonic acid >350 nmol/L. These patients are suspected for functional vitamin B12 deficiency. To test whether methylmalonic acid values were falsely increased due to kidney dysfunction (e) or systemic inflammation (f), relations are shown for patients with an eGFR<60 ml/min(red) or CRP > 5 mg/l(red). CRP, c-reactive protein; eGFR, estimated glomerulus filtration rate.

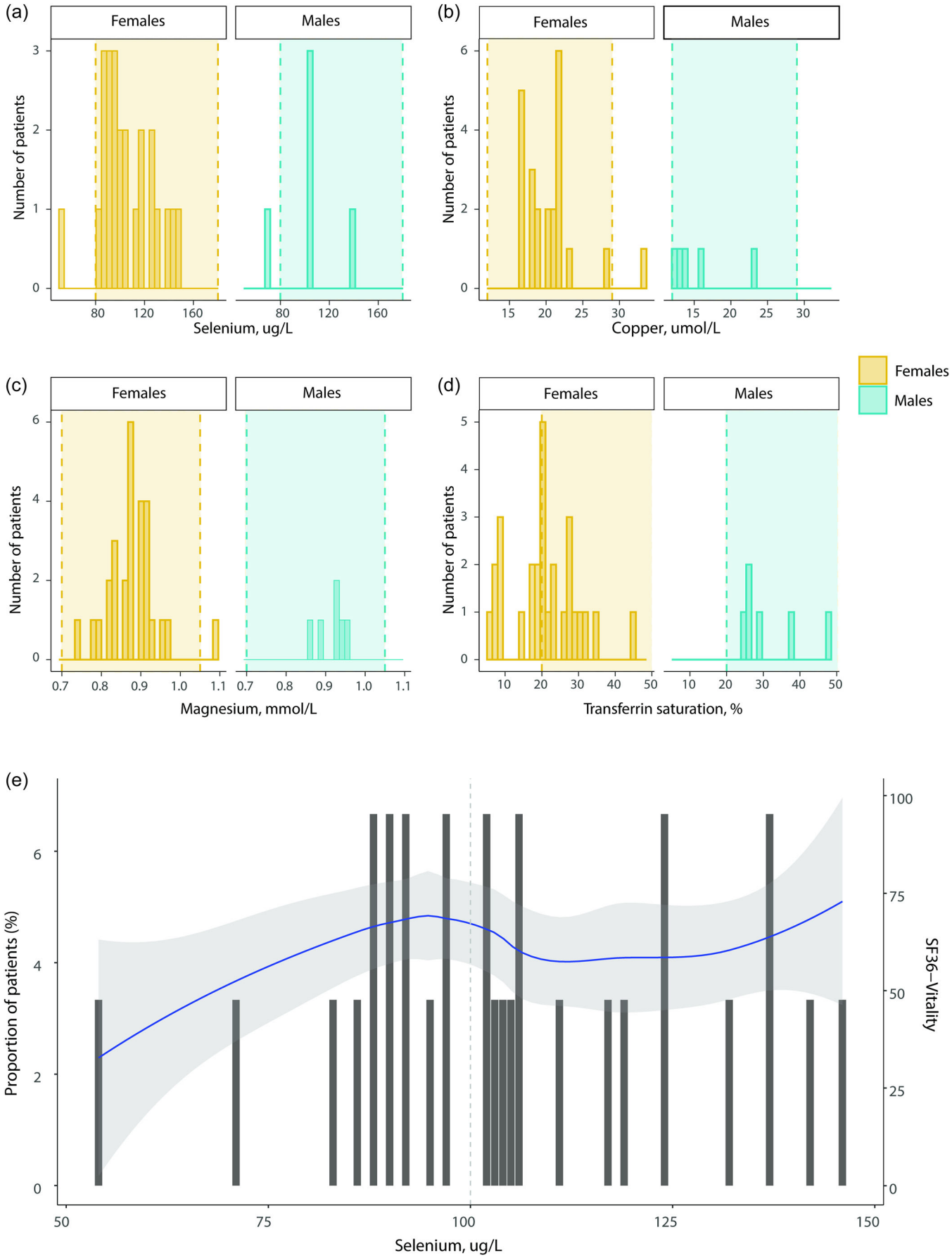

FIGURE 4 (See caption on next page)

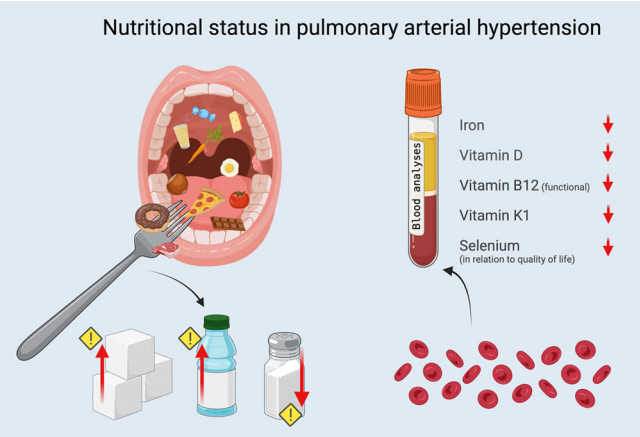

FIGURE 5 Graphical abstract, summary of findings.

had an iron deficiency and 43% a vitamin D deficiency.[3–6] An iron deficiency is common in heart failure,[23] and a vitamin D deficiency is described as a worldwide problem.[24] In 60% of our patients vitamin K1 deficiency was observed. In our study group vitamin K2 levels were too low to be detected, which is also described in the overall Dutch population.[25] A low vitamin K status is associated with increased cardiovascular risk.[25–27] In our cohort, half of the patients with vitamin K1 deficiency use vitamin K antagonists. This is line with previous findings demonstrating that vitamin K antagonists may influence serum level of vitamin K1.[28,29] However, we observed normal serum levels of vitamin K1 in patients with vitamin K antagonists as well (Table 1). Vitamin K1 is mainly provided by dietary intake of green leafy vegetables and is also produced by gut bacteria.[26] An explanation might be limited intake, however, another explanation is the altered microbiome.[30,31] For this, further studies to nutritional intake, the altered microbiome, and the clinical relevance of vitamin K1 are warranted.

In our study, we found a high MMA level in combination with normal vitamin B12 levels in 29% of the patients, which suggests deficiency of functional vitamin B12.[11,12] Adenosyl cobalamin (vitamin B12) is a co-factor of L-methymalonyl-CoA mutase, the enzyme that converts L-methymalonyl-CoA to succinyl-CoA. When there is a deficiency of adenosyl-cobalamin, excessive D-methylmalonyl-CoA (the precursor of L-methymalonyl-CoA) is converted into MMA.[32,33] In the overall population, a vitamin B12 deficiency has an estimated prevalence of 5%–10% up to 20%–30% amongst elderly and even higher in vegetarians and pregnant.[34,35] An international cohort concluded that a vitamin B12 deficiency was rare in heart failure, however, MMA levels were not analyzed.[36] Another study, that determined MMA levels in patients with heart failure, found a functional vitamin B12 deficiency in 43.8% of the population.[37] The increased MMA levels we observed, could indicate a problem in vitamin B12 absorption in PAH-patients, due to the frequent use of proton pump inhibitors in this population and an altered microbiome.[30,31] A functional vitamin B12 deficiency is characterized by, for example, fatigue, light headedness, tachycardia and cold extremities, which are overlapping features in PAH.[11,12] In addition, these overlapping features and normal serum levels of vitamin B12 results in a delayed recognition of a functional vitamin B12 deficiency. Further research is needed to understand the clinical relevance of a functional vitamin B12 deficiency in PAH.

Another observation of interest in our study was that 41% of the patients had selenium levels <100 μg/L. Although selenium values were within the limits of normal, a recent study[38] has suggested that in HF patients' selenium levels of 70 μg/L are already associated with worse survival and QoL. In our study, low selenium was also associated with reduced quality of life measured with the SF-36. We demonstrated an association with vitality, other components of the SF-36 had no correlation with selenium. Selenium is a strong antioxidant and an important regulator of mitochondrial function.[39] In PAH patients, further research should be performed to unravel the role of reduced selenium in PAH, its therapeutic potential and should demonstrate the role of dietary and/or supplementary intervention on selenium status.

Strengths and limitations

There are some limitations within our study. This is a small study including only 37 patients from a Dutch PAH

FIGURE 4 Minerals. Mineral analyses were performed in serum/plasma of all patients. As can be observed, values of Selenium (a), Copper (b), and Magnesium (c) remained within normal values for almost all patients. Transferrin saturation (d) was <20% in 32% of patients indicating iron deficiency (Beverborg NG, Klip IjT, Meijers WC, et al. Definition of iron deficiency based on the gold standard of bone marrow iron staining in heart failure patients. *Circ Heart Fail*; 11. Epub ahead of print 1 February 2018. DOI: 10.1161/CIRCHEARTFAILURE.117.004519.). Although selenium values were within the limits of normal a recent study has suggested that in heart failure patients selenium levels <100 ug/l are already associated with worse survival and quality of life. Similar results are observed in our patients, in which selenium value <100 μg/L was present in 41% of patients and related to vitality (e).

cohort. In addition, our patients had mild forms of PAH, evident from the low median NTproBNP values and high 6MWD. Nevertheless, we could observe mineral and vitamin deficiencies that deserve further investigation in larger multicentre cohorts of patients.

We could not include healthy subjects to compare blood levels and nutrient intake. Instead, we compared our findings to reference values from literature. Since there are different reference values for some vitamin- and mineral levels for males and females and for dietary sugar intake, we performed sex-stratified analyses to analyze this data. There were only 6 males included for this article and therefore this group was too small to compare with females for statistical analyses.

To determine nutritional intake, we used the HELIUS questionnaire which is a very large questionnaire with over more than 57 pages. Patients were asked to fill in their dietary habits over the previous 4 weeks. Patients may have been unaware of their actual nutritional intake or may have had problems with focussing on a load of questions. This may lead to under or overreporting, although former research has found the HELIUS questionnaire very suitable.[13,14]

To determine nutritional status, it is common to discuss BMI. Although in our group, the BMI was normal (mean 25.39 ± 4.34), we did not include it in our determination for nutritional status. BMI may not be the most reliable marker due to bias for fluid retention, which is common in PAH.

CONCLUSION

This is the first comprehensive study of nutritional status in PAH. Vitamin and mineral status were overall normal, besides common deficiencies of vitamin D and iron. However, evidence was found of previously unreported deficiencies in vitamin B12, vitamin K1 and selenium. Further research is needed to understand the clinical relevance. The intake of sugar and fluid was elevated and sodium intake was reduced. Sugar and fluid intake were linearly related. To lower fluid intake an effective reduction of refined sugar intake to a maximum of 37.5 g per day for males and a maximum of 25 g per day for females, as stated in AHA guidelines, is advised. There appears to be an unmet need for improvement in nutritional intake.

ETHICS STATEMENT

Documented informed consent for publication has been obtained from each patient.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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