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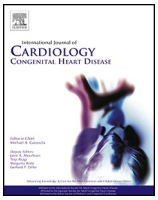

Vitamin D deficiency and secondary hyperparathyroidism in adult Fontan patients

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ABSTRACT

Background: The prevalence of vitamin D deficiency and secondary hyperparathyroidism (sHPT) in adult Fontan patients remains unstudied, and the role of vitamin D and parathyroid hormone (PTH) levels in assessing heart and circulatory failure in these patients is unclear.
Methods: We compared vitamin D deficiency and sHPT prevalence in adult Fontan patients (n = 35; mean age 33 ± 7.5 years) to adults with mild congenital heart disease (ACHD, n = 14). We analyzed associations between laboratory measurements, patient characteristics, and clinical events.
Findings: Vitamin D deficiency was highly prevalent in both Fontan patients and ACHD controls (76.5 % vs. 71.4 %, p = 0.726). sHPT was exclusively present in Fontan patients (31.4 %). PTH levels correlated with NYHA class (r = 0.412), O2 saturation (r = −0.39), systemic ventricular function (r = 0.465), and NT-proBNP levels (r = 0.742). 25-hydroxyvitamin D showed an inverse correlation with NYHA class and systemic ventricular function (both r ≤ −0.38). Fontan patients with sHPT had a higher incidence of prior hospitalization for worsening heart failure and atrial arrhythmias compared to Fontan patients without HPT or ACHD controls. (Hospitalization: Fontan with HPT vs. Fontan without HPT: OR 5.46 [95 % CI 1.25–23.86], p = 0.021; arrhythmia: Fontan with HPT vs. Fontan without HPT: OR 1.96 [95 % CI 1.13–3.4], p = 0.035; ACHD: OR 11.45 [95 % CI 1.7–77.28], p=<0.001). PTH showed significant correlation with inflammatory markers, particularly with GDF-15 (r = 0.8).
Conclusion: Our study is the first to demonstrate a high prevalence of vitamin D deficiency and sHPT in adult Fontan patients. As PTH strongly correlates with heart failure severity, it seems to be a promising biomarker in Fontan patients.

Abbreviations

25-OH-D3	25-hydroxyvitamin D3
95 % CI	95 % confidence interval
ACHD	adult congenital heart disease
AP	alkaline phosphatase
AST	aspartate aminotranferase
CHE	cholinesterase
CRP	C reactive protein
EF	ejection fraction
GDF-15	growth/differentiation factor 15
HbA1c	glycated hemoglobin A1C
NL ratio	neutrophil to lymphocyte ratio
NT-proBNP	N-terminal pro-B-type natriuretic peptide
NYHA	New York Heart Association
PLE	protein losing enteropathy
PTH	parathyroid hormone
RAAS	renin-angiotensin-aldosterone system
sHPT	secondary hyperparathyroidism
SpO2	oxygen saturation
yGT	gamma gamma-glutamyl-transpeptidase

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1. Introduction

Vitamin D deficiency is highly prevalent in the general population, with an estimated 30 % of adults in Germany being affected [1]. A study conducted in 307 601 UK Biobank participants found that vitamin D

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deficiency was associated with increased mortality [2].

According to the Endocrine Society's Practice Guidelines on Vitamin D, vitamin D deficiency is defined as a 25-hydroxyvitamin D level <20 ng/mL, insufficiency as 21–29 ng/mL and sufficiency as at least 30 ng/mL for maximum musculoskeletal health [3].

It has been shown that heart failure is associated with significantly lower vitamin D levels, particularly in the presence of concomitant renal disease.

Vitamin D deficiency is a predictor of poorer survival in heart failure patients [4,5]. Experimental data suggest that vitamin D deficiency may contribute to heart failure progression. Vitamin D receptor knockout mice showed elevated renin levels, leading to the subsequent activation of the renin-angiotensin-aldosterone system (RAAS) [6]. In humans, Forman et al. demonstrated that vitamin D deficiency is associated with increased angiotensin II levels [7]. In heart failure, RAAS activation results in hyperaldosteronism, which leads to an increased level of parathyroid hormone (PTH) due to fecal and renal calcium loss. Loop diuretics, commonly used in the treatment of heart failure, also contribute to secondary hyperparathyroidism (sHPT) by further increasing calcium loss [8]. PTH also directly increases aldosterone secretion via stimulating the adrenal PTH receptor and by potentiating angiotensin II induced aldosterone secretion [9].

PTH leads to an increased intracellular calcium concentration in cardiomyocytes, resulting in intracellular and mitochondrial calcium overload, oxidative stress, myocardial cell death, and ultimately, myocardial fibrosis [10,11].

Previous studies have shown that hyperparathyroidism is associated with an increased risk of new onset of heart failure as well as cardiovascular and all-cause mortality and a higher probability of hospitalization for heart failure [12–14]. PTH has also been discussed as a biomarker for heart failure, as it closely correlates with NT-proBNP levels [15].

To date, only one small observational study evaluated the prevalence of vitamin D deficiency and sHPT in adult patients with congenital heart disease [16]. In children after Fontan palliation only a few studies reported a high prevalence of vitamin D deficiency and sHPT [17–20].

Fontan patients are at increased risk of adverse events [21,22]. So far, no studies have been conducted on the prevalence of vitamin D deficiency and sHPT in adult Fontan patients, nor is it clear to what extent vitamin D and PTH can be used to assess heart and circulatory failure in these patients, which was the aim of our study.

2. Materials and methods

2.1. Study group

As part of a routine follow-up visit, we enrolled 35 Fontan patients in our study. Out of these patients, 11 (31.5 %) were female, and 24 (68.5 %) were male. The mean age of the patients was 33 ± 7.5 years, Table 1. Their initial diagnoses included tricuspid atresia, pulmonary atresia, hypoplastic left heart syndrome, double inlet left ventricle, partly in combination with D- or L-malposition of great arteries, and atrial or ventricular septal defects. Based on the NYHA class, 29 % of the patients belonged to class I, 54 % to class II, 17 % to class III. None of the included patients presented with class IV, Table 1.

As control we included 14 adults, with mild congenital heart disease (ACHD) who showed neither symptoms of heart failure nor NT-proBNP elevation. Of these patients, 7 (50 %) were male. The median age of the control group was 32 ± 12.4 years, Table 1. None of the patients were supplemented with vitamin D and there were no apparent symptoms of active infection observed in any of the patients.

We obtained clinical data from medical records, including the initial cardiac diagnosis, NYHA class, gender, age, height, weight, pulse oximetry, echocardiographic findings, hemodynamic measurements obtained by invasive heart catheterization, medications, history of pacemaker implantation, history of atrial or ventricular arrhythmia, resuscitation, hospitalization due to worsening heart failure, and secondary organ damage, such as liver fibrosis and renal failure. The authors secured Institutional Ethics waiver for this retrospective study reporting on clinical and anonymised data.

Table 1
Characteristics of Fontan patients and the control group (patients with mild ACHD). Plus–minus values are means ± SD.

Characteristic	Mild ACHD (n = 14)	Fontan (n = 35)	95%-CI
age *(yr)*	32 ± 12.4	33 ± 7.8	−6.86–8.12
male Sex *(no. - %)*	7 (50)	24 (68.5)	
body-mass index *(kg/m²)*[a]	23 ± 2.28	24.9 ± 4.42	−0.6–4.43
NYHA functional class *(median)*[c]	1	1.9	0.65–1.12
NYHA functional class *(no - %)*			
I (%)	14 (100 %)	10 (28.6 %)	
II (%)	0	19 (54.3 %)	
III (%)	0	6 (17.1 %)	
SpO2 *(%)*	98 ± 1.6	93 ± 2.62	−7.04-(−4.02)
active smoker *(no - %)*	1 (7.7)	4 (11.4)	
HbA1c (%)	5.06 ± 0.28	5.49 ± 0.423	0.17–0.67
vitamin D supplementation *(no. - %)*	0 (0)	3 (8.6)	
loop diuretics *(no. -%)*	0 (0)	0 (0) 7 (20)	
torasemide dose (mg)[b]	0	5.57 ± 13.76	0.84–10.3

NYHA: New York Heart Association; SpO2: oxygen saturation.
[a] The body-mass index is the weight in kilograms divided by the square of the height in meters.
[b] Exclusively torasemide prescribed.
[c] The New York Heart Association (NYHA) functional class ranges from I (no symptoms) to IV (symptoms at rest or on minimal activity).

2.2. Laboratory measurements

Serum levels of sodium, potassium, calcium, phosphate, liver function tests (alkaline phosphatase, y-glutamyltransferase, aspartate aminotransferase, alanate aminotransferase, cholinesterase, bilirubin), kidney function tests (creatinine clearance), albumin, thyroid stimulating hormone, HbA1c, lipid levels, complete blood count, as well as markers of systemic inflammation (CRP, GDF-15, IL-6) were measured using standard laboratory techniques.

The neutrophil to lymphocyte ratio, a marker of systemic inflammation, was calculated using data from the complete blood count (absolute neutrophil count/absolute lymphocyte count) [23].

Additionally, in order to examine vitamin D status and secondary HPT 25-hydroxyvitamin D, 1,25 dihydroxy Vitamin D, alkaline bone phosphatase, osteocalcin, and intact parathyroid hormone were measured using routine lab tests.

According to the Endocrine Society's Practice Guidelines on Vitamin D, vitamin D deficiency was defined as a 25-hydroxyvitamin D < 20 ng/mL [3]. Secondary hyperparathyroidism (HPT) was characterized by an intact parathyroid hormone (PTH) level exceeding 65 pg/mL alongside a normal serum calcium level. Only one Fontan patient exhibiting primary hyperparathyroidism, indicated by elevated serum calcium and elevated PTH levels, was identified in our study.

2.3. Statistical analysis

Data were analyzed using SPSS II version 28 (SPSS Inc, Troy, NY). Differences between groups in continuous and categorical variables were assessed using *t*-test or the $\chi 2$ test, respectively. Two-sided tests were used throughout. Pearson's correlation testing was performed to investigate associations between serum 25-hydroxyvitamin D levels, PTH, calcium, NT-proBNP, GDF-15, CRP, IL-6 and a broad range of other laboratory parameters. Spearman's correlation testing was used to

examine correlations between laboratory measurements and clinical outcome variables. Binary logistic regression calculated odds ratios. A value of P < 0.05 was considered to be significant.

3. Results

There was no significant difference in terms of gender, age, and body mass index between Fontan patients and the ACHD controls (all p > 0.132). All ACHD patients were classified as NYHA class I for heart failure, whereas Fontan patients had a median NYHA class II (95 % CI 0.65–1.12, p < 0.001), Table 1. In the Fontan group, 3 out of 35 patients were supplemented with vitamin D, while none of the patients in the ACHD group received vitamin D supplementation (p = 0.083).

Loop diuretics (torasemide) were exclusively prescribed to Fontan patients, with 7 out of 35 (20 %) patients receiving them (p = 0.17). Among Fontan patients with sHPT, 5 out of 11 (45.5 %) took loop diuretics, while only 2 out of 22 (9 %) Fontan patients without sHPT used this medication (p = 0.027). A positive correlation was observed between the torasemide dose and the serum PTH level (Pearson r = 0.858, p = 0.014).

It is noteworthy that there was a high prevalence of Vitamin D deficiency in both Fontan and ACHD patients, with 76.5 % of Fontan patients and 71.4 % of the ACHD control group showing Vitamin D deficiency (p = 0.726). sHPT was exclusively present in Fontan patients (31.4 %), (Fig. 2, Table 5).

Fontan patients with sHPT exhibited higher levels of systemic inflammation markers compared to Fontan patients without sHPT and ACHD controls. They showed elevated levels of CRP, GDF-15, and IL-6 compared to both ACHD controls (CRP: p=<0.001, GDF-15: p=<0.001, IL-6: p = 0.039) and Fontan patients without sHPT (CRP: p=<0.001, GDF-15: p = 0.001, IL-6: p = 0.012), see Fig. 1, Tables 4 and 5). Additionally, Fontan patients with sHPT had a significantly higher neutrophil to lymphocyte ratio, indicating increased systemic inflammation, when compared to Fontan patients without sHPT (p = 0.012) and ACHD controls (p=<0.001), see Fig. 1, Tables 4 and 5

Positive correlations were found between PTH and CRP (r = 0.434, p = 0.002), GDF-15 (r = 0.798, p < 0.001) and IL-6 (r = 0.5, p=<0.001). Notably, 25-hydroxyvitamin D only negatively correlated with CRP (r = −0.282, p = 0.05), but did not correlate with GDF-15, IL-6, or the neutrophil lymphocyte ratio, Table 2.

Fontan patients with sHPT exhibited significantly lower serum levels of 25-hydroxyvitamin D, albumin, and higher serum levels of AP compared to Fontan patients without sHPT (25-hydroxyvitamin D: p = 0.014, albumin: p < 0.001, AP: p = 0.003) or ACHD controls (25-hydroxyvitamin: p = 0.013, AP: p < 0.001, albumin: p = 0.014), Tables 4 and 5

Serum albumin and intact parathyroid hormone were inversely correlated (r = −0.596, p=<0.001), Table 2. Serving as a classic transport protein for calcium, reduced albumin levels were also associated with reduced serum calcium (r = 0.381, p = 0.007). Both, albumin and calcium were inversely related to GDF-15 (albumin: r = −0.573, p < 0.001; calcium: r = −0.35, p = 0.14). Low serum albumin levels were also associated with higher levels of CRP and IL-6 (CRP: r = −0.437, p = 0.002; IL-6: r = −0.507, p < 0.001), Table 2.

In addition, comparison between Fontan patients with sHPT and the ACHD control group revealed significant differences with regard to AST (p = 0.002), yGT (p = 0.033), bilirubin (p = 0.023), and CHE (p = 0.043), suggesting relevant hepatic congestion and consecutive organ dysfunction, Tables 4 and 5 Furthermore, increased levels of PTH were positively correlated with elevated liver function tests (AST: r = 0.377, p = 0,008, AP: r = 0.548, p < 0,001, yGT: r = 0.508, p < 0,001), Table 2.

In contrast to ACHD controls, Fontan patients with sHPT also showed significant changes in bone metabolism in terms of increased alkaline bone phosphatase (p = 0.017) as elevated PTH levels stimulate calcium mobilization from bone, Tables 4 and 5

Regarding kidney function, GFR was significantly lower in Fontan

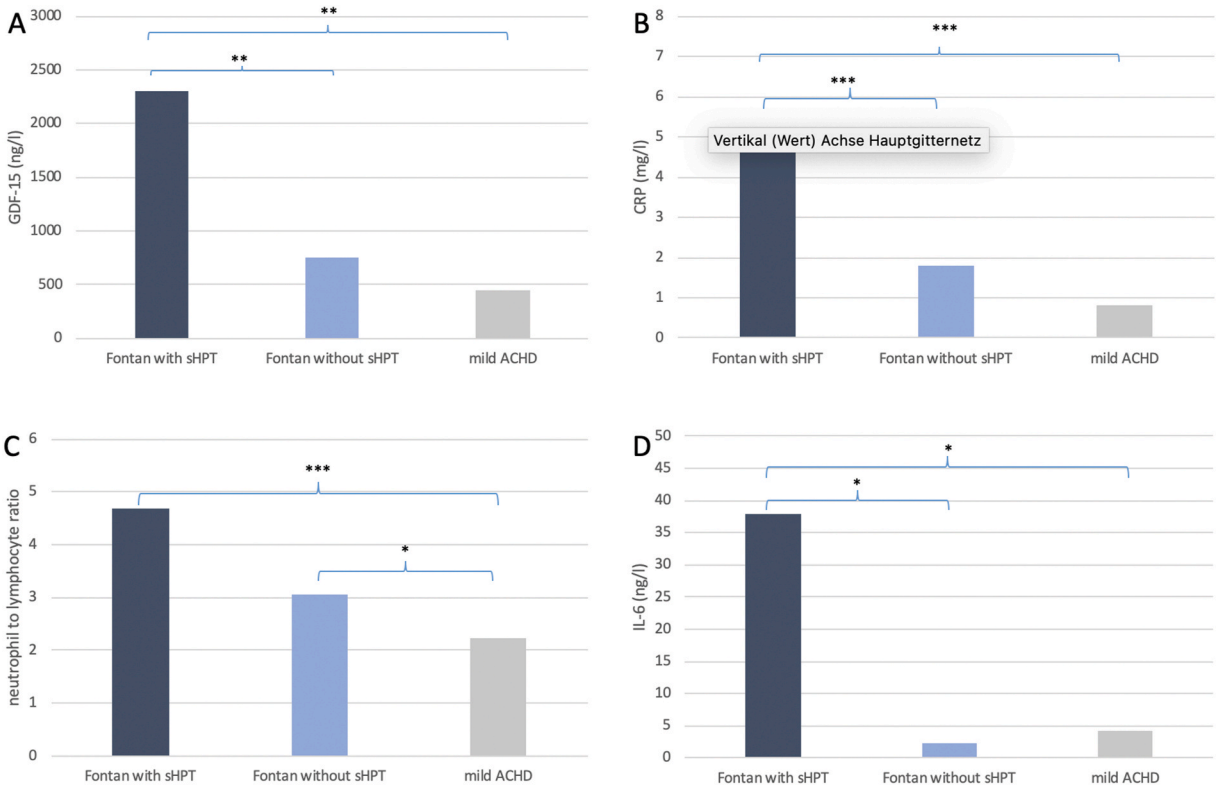

Fig. 1. Differences in parameters of systemic inflammation between Fontan patients with sHPT, Fontan patients without sHPT, and the mild ACHD group. A: GDF-15 (ng/l). B: CRP (mg/l). C: neutrophil to lymphocyte ratio. D: IL-6 (ng/l). Levels of significance depicted as follows: *p < 0.05, **p < 0.01, ***p < 0.001. ACHD: adult congenital heart disease; CRP: C reactive protein; GDF-15: growth differentiation factor 15; sHPT: secondary hyperparathyroidism; IL-6: interleukin-6.

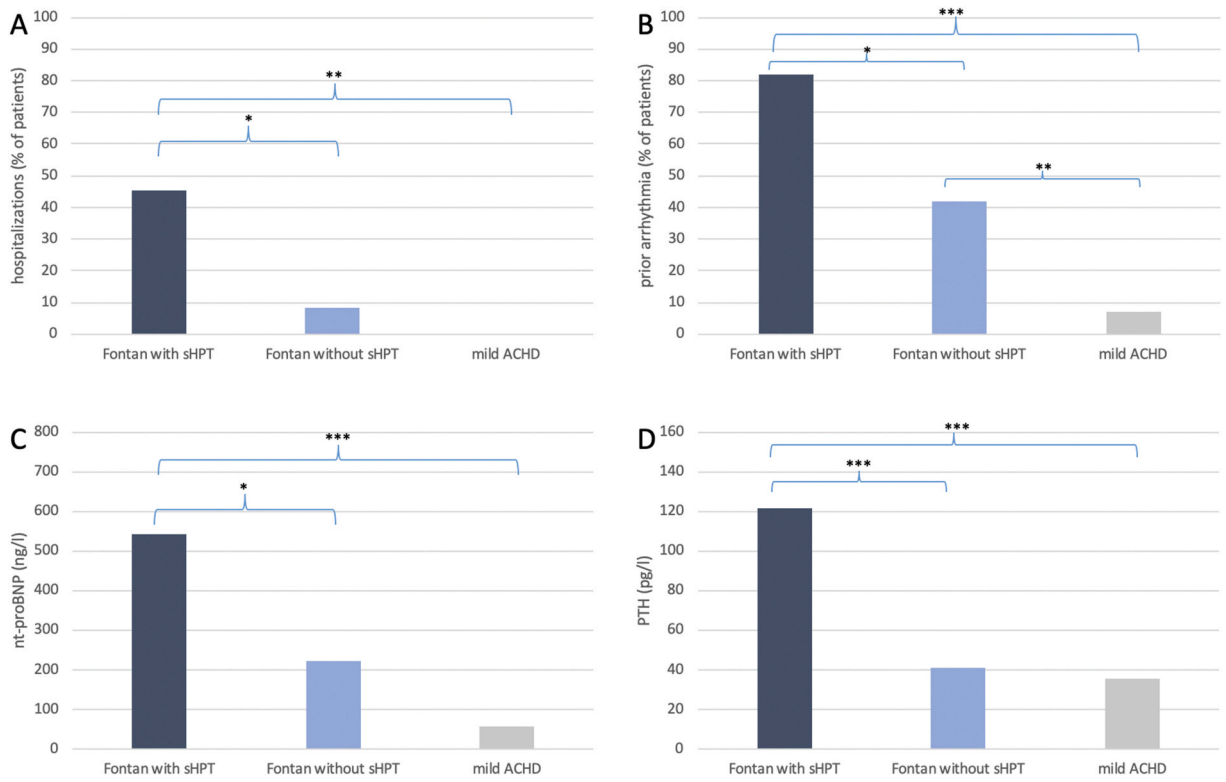

Fig. 2. A: Percentage of patients hospitalized due to worsening heart failure: 5 out of 11 (45.5 %) Fontan patients with sHPT were hospitalized, whereas only 2 out of 24 (8.3 %) Fontan patients without sHPT and none of the mild ACHD group were hospitalized. B: Percentage of patients with atrial arrhythmia: Atrial arrhythmia was present in 9 out of 11 (81.8 %) Fontan patients with sHPT, in 10 out of 24 (41.7 %) Fontan patients without sHPT, and in 1 out of 14 (7.1 %) mild ACHD controls. C: Fontan patients with sHPT showed significantly higher levels of NT-proBNP. D: PTH levels in the three patient groups. Secondary sHPT was defined as PTH> 65 ng/l, Levels of significance depicted as follows: *p < 0.05, **p < 0.01, ***p < 0.001. ACHD: adult congenital heart disease; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PTH: parathyroid hormone.

patients with sHPT compared to Fontan patients without sHPT (p = 0.016) or ACHD controls (p = 0,048), Tables 4 and 5. GFR was markedly associated with GDF-15 (r = −0.434, p < 0.001), PTH (r = −0.436, p < 0.002), and NT-proBNP (r = −0.495, p < 0.001), Table 2.

A positive correlation was observed between the torasemide dose and the serum PTH level (Pearson r = 0.858, p = 0.014).

NT-proBNP did not only show a strong correlation with PTH levels (r = 0.742, p= <0.001), but also with NYHA class (r = 0.412, p = 0.003), O2 saturation (r = −0.473, p = 0.003) and GDF-15 (r = 0.884, p=<0.001), Tables 2 and 3. PTH levels were inversely correlated with O2 saturation (r = −0.368, p = 0.009), Table 3.

There was also a clear association between systemic ventricular function and PTH levels. The more reduced systemic ventricular function, the higher were serum parathyroid hormone levels (r = 0.465, p=<0.001), Table 3. There was also a significant correlation between systemic inflammatory markers and ventricular function (GDF-15: r = 0.453, p = 0.012; IL-6: r = 0.33, p = 0.022; CRP: r = 0.456, p = 0.001; neutrophil to lymphocyte ratio: r = 0.329, p = 0.022), Table 3.

Interestingly, NT-proBNP did not correlate with 25-hydroxyvitamin D (p = 0.296), but NYHA class and systemic ventricular function showed an inverse correlation with serum 25-hydroxyvitamin D levels (NYHA: r = −0.402, p = 0.008; systemic ventricular function: r = −0.38, p = 0.024), Table 3.

7 of 35 Fontan patients had a history of hospitalization for worsening heart failure. Of the 7 hospitalized Fontan patients, 5 showed sHPT, suggesting a significantly higher probability of hospitalization when sHPT is present (Fontan with HPT vs. Fontan without HPT: 45.5 % vs. 8.3 %; OR 5.46 [95 % CI: 1.25–23.86] p = 0.021, Fig. 2. Also, Fontan patients with sHPT more often suffered from atrial arrhythmia than those without sHPT (OR 1.96 [95 % CI: 1.13–3.4], p = 0,035) or ACHD controls (OR 11.45 [95 % CI 1.7–77.28], p=<0.001), Fig. 2.

Additionally, in Fontan patients with sHPT NT-proBNP levels were significantly higher compared to Fontan patients without sHPT (95 % CI: 50.16–590.83, p = 0.015) or mild ACHD controls (95 % CI: 187.05–735.34, p < 0.001), Tables 4 and 5.

4. Discussion

This study found a remarkably high prevalence of vitamin D deficiency in adult Fontan patients and ACHD patients, with Fontan patients showing a trend towards a more severe deficiency. While vitamin D deficiency was found in the ACHD control group with a similar frequency as in Fontan patients, sHPT was exclusively present in almost one-third of Fontan patients.

Parathyroid hormone (PTH) plays a crucial role in bone metabolism and maintaining mineral homeostasis. Its effects include the calcium release from bone, absorption of calcium in the kidneys, and excretion of phosphate by the kidneys. Additionally, it stimulates the production of the active form of vitamin D (1,25-dihydroxyvitamin D) in the kidneys. This, in turn, reduces the excretion of calcium by the kidneys and enhances the absorption of both calcium and phosphate in the gastrointestinal tract [8].

Neurohormonal activation is a pathophysiological cornerstone of heart failure. Activation of the renin-angiotensin-aldosterone system results in hyperaldosteronism, which causes urinary and fecal excretion of calcium. Calcium loss results in hypocalcemia and the subsequent release of PTH from the parathyroid gland, leading to sHPT [15]. PTH also exerts a direct cardiotoxic effect by increasing intracellular calcium concentration, promoting oxidative stress, and ultimately causing myocardial cell death and fibrosis [11].

Table 2
Heatmap illustrating results of Pearson's correlation testing, which was conducted to investigate associations between laboratory parameters. R > 0.5 was considered indicative of a strong correlation. Levels of significance depicted as follows: *p < 0.05, **p < 0.01, ***p < 0.001.

	NT-proBNP	GDF-15	CRP	IL-6	NL ratio	PTH	calcium
NT-proBNP	1	0.884**	0.225	0.269	0.217	0.742**	0.157
GDF-15	0.884**	1	0.321*	0.397**	0.381**	0.798**	-0.35*
CRP	0.225	0.321*	1	0.316*	0.542**	0.434**	0.156
IL-6	0.269	0.397**	0.316*	1	0.121	0.500**	-0.28
NL ratio	0.217	0.381**	0.542**	0.121	1	0.265	0.227
PTH	0.742**	0.798**	0.434**	0.500**	0.265	1	-0.343*
calcium	0.157	- 0.35*	0.156	-0.28	0.227	-0.343*	1
25-OH-D3	-0.098	-0.26	-0.282*	-0.246	-0.116	-0.468**	0.194
creatine	0.52**	0.462**	0.333*	0.036	0.172	0.447**	-0.028
GFR	-0.495**	-0.434**	-0.277	0.111	-0.208	-0.436**	0.108
albumin	-0.365**	-0.573**	-0.437**	-0.507**	-0.232	-0.596**	0.381**
AST	0.478**	0.369**	0.307*	0.359*	0.247	0.377**	0.165
AP	0.542**	0.497**	0.553**	0.534**	0.215	0.548**	-0.144
yGT	0.472**	0.534**	0.411**	0.348*	0.274	0.508**	-0.1

	25-OH-D3	creatine	GFR	albumin	AST	AP	yGT
NT-proBNP	-0.098	0.52**	-0.495**	-0.365**	0.478**	0.542**	0.472**
GDF-15	-0.26	0.462**	-0.434**	-0.573**	0.369**	0.497**	0.534**
CRP	-0.282*	0.333*	-0.277	-0.437**	0.307*	0.553**	0.411**
IL-6	-0.246	0.036	0.111	-0.507**	0.359*	0.534**	0.348*
NL ratio	-0.116	0.172	-0.208	-0.232	0.247	0.215	0.274
PTH	-0.468**	0.447**	-0.436**	-0.596**	0.377**	0.548**	0.508**
calcium	0.194	-0.028	0.108	0.381**	0.165	-0.144	-0,1
25-OH-D3	1	-0.105	0.105	0.231	-0.128	-0.368*	-0.296*
creatine	-0.105	1	-0.822**	-0.156	0.379**	0.107	0.118
GFR	0.105	-0.822**	1	0.184	0.196	0.016	0.089
albumin	0.231	-0.156	0.184	1	0.049	-0.269	-0.002
AST	-0.128	0.379**	0.196	0.049	1	0.478**	0.45**
AP	-0.368*	0.107	0.016	-0.269	0.478**	1	0.611**
yGT	-0.296*	0.118	0.089	-0.002	0.45**	0.611**	1

25-OH-D3: 25-hydroxyvitamin D3; AP: alkaline phosphatase; AST: aspartate aminotransferase; CRP: C reactive protein; GDF-15: growth differentiation factor 15; interleukin-6, GFR: glomerular filtration rate; NL ratio: neutrophil to lymphocyte ratio; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PTH: parathyroid hormone; yGT: gamma gamma-glutamyl-transpeptidase.

Table 3
Heatmap illustrating Spearman's correlation testing, which was used to examine correlations between laboratory measurements and clinical outcome variables. R > 0.5 was considered indicative of a strong correlation. Levels of significance: *p < 0.05, **p < 0.01, ***p < 0.001.

	NT-proBNP	GDF-15	CRP	IL-6	NL ratio	PTH	calcium	25-OH-D3
NYHA	0.473**	0.622**	0.542**	0.454**	0.276	0.412*	-0.196	-0.402**
SpO2	-0.473**	-0.416**	-0.391**	-0.276	-0.428**	-0.368**	0.066	0.272
systemic ventricular function †	0.311*	0.453**	0.456**	0.33*	0.329*	0.465**	-0.328*	-0.38**

† The systemic ventricular function was categorized from grade 1 to 4, as follows: an ejection fraction (EF) greater than 50 % was classified as grade 1, an EF between 40 % and 50 % as grade 2, an EF between 30 % and 40 % as grade 3, and an EF less than 30 % as grade 4.
25-OH-D3: 25-hydroxyvitamin D3; CRP: C reactive protein; GDF-15: growth differentiation factor 15; interleukin-6, NL ratio: neutrophil to lymphocyte ratio; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; PTH: parathyroid hormone, SpO2: oxygen saturation.

Table 4
Results from Anova and Bonferroni multiple comparison tests between Fontan patients with sHPT, Fontan patients without sHPT, and mild ACHD controls. P < 0.05 was considered to be significant.

	mild ACHD vs. Fontan no sHPT			mild ACHD vs. Fontan with sHPT			Fontan with HPT vs. Fontan no sHPT		
parameter	p value	95%-CI		p value	95%-CI		p value	95%-CI	
age	1.000	-8.14	7.04	1.000	-5.88	12.3	.784	-4.46	11.98
sex	.949	-.5756	.2422	.765	-.7172	.2626	1.000	-.5033	.3821
weight	.949	-.5756	.2422	.985	-9.623	22.331	1.000	-13.245	15.632
BMI	.750	-1.761	4.870	.293	-1.269	6.676	1.000	-2.441	4.738
NYHA	<.001	.29	1.21	<.001	.63	1.74	.113	-.07	.93
SpO2	<.001	-7.27	-3.28	<.001	-8.47	-3.70	1.000	-2.97	1.35
NT-proBNP	0.318	-83.98	415.39	<.001	187.05	785.34	.015	50.16	590.83
CRP	.564	-.898	2.986	<.001	2091	6744	<.001	1.271	5.476
GDF-15	1.000	-542.92	1149.33	<.001	847.92	2875.38	<.001	642.35	2474.55
IL-6	1000	-28.81	25.08	.039	1.3	65.87	.012	6.27	64.63
NL ratio	.279	-.3770	20570	<.001	.9963	39124	.012	.2967	29.319
AST	.124	-1.00	11,85	.002	3.38	18.77	.148	-1.30	12.61
yGT	.021	11.21	174.14	.033	6.57	201.77	1.000	-76.71	99.70
AP	.070	-1.11	39.50	<.001	25.25	73.56	.003	8.75	51.68
CHE	.499	-21.990	.6097	.043	-3.3799	-.0385	.398	-23.995	.5703
bilirubin	.428	-3.74	14.99	.023	1.37	23.82	.284	-3.18	17.11
albumin	.206	-.89	6.25	.014	-9.39	-.84	<.001	-11.66	-3.93
PTH	1.000	-20.379	30.734	<.001	55.483	116.720	<.001	53.254	108.594
25-OH-D3	1.000	-7.310	5.378	.013	-16.825	-1.623	.014	-15.127	-1.389
bone alkaline phosphatase	.864	-2.697	6.807	.017	.975	12.282	.085	-.451	9.598
HbA1c	.021	.043	.695	.004	.146	.926	.739	-.186	.519
creatine	1.000	-12.07	15.65	.038	.71	33.93	.040	.52	30.54
GFR	1.000	-12.17	13.97	.048	-31.39	-.08	.016	-30.78	-2.49

25-OH-D3: 25-hydroxyvitamin D3; AP: alkaline phosphatase; AST: aspartate aminotransferase; BMI: body mass index; CHE: cholinesterase; CRP: C reactive protein; GDF-15: growth differentiation factor 15; interleukin-6, GFR: glomerular filtration rate; HbA1c: glycated hemoglobin A1C; NL ratio: neutrophil to lymphocyte ratio; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association; PTH: parathyroid hormone; SpO2: oxygen saturation; yGT: gamma gamma-glutamyl-transpeptidase.

Several former studies, including probands with both primary and secondary hyperparathyroidism, found that HPT is linked to an elevated risk of new onset of heart failure, a heightened probability of hospitalization for heart failure, as well as an increased risk of both cardiovascular and all-cause mortality [12–14].

Moreover, studies in elderly patients have found that elevated PTH levels are associated with higher NYHA class, decreased left ventricular function, and increased NT-proBNP levels [24,25]. Additionally, several studies have linked increased PTH levels to atrial arrhythmia [26,27].

Consistent with these findings, our study revealed that Fontan patients with sHPT had a higher frequency of prior hospitalization and atrial arrhythmias than both, Fontan patients without sHPT and ACHD controls, suggesting that the presence of sHPT indicates advanced disease severity associated with a higher probability of adverse outcome.

Our study also found that PTH levels were significantly correlated with markers of systemic inflammation, including GDF-15, IL-6, and CRP. The strongest correlation was observed between PTH and GDF-15. Elevated GDF-15 levels have been linked to an increased risk of cardiovascular disease. Moreover, these levels may serve as valuable indicators for assessing the chronic disease burden and hemodynamic status in individuals with heart failure [28]. In Fontan patients, GDF-15 could potentially aid in the early detection of abnormal function [29].

GDF-15 is produced by various cardiovascular and non-cardiovascular cell types, suggesting its significant prognostic value in the context of long-standing Fontan circulation burdened by a diverse range of organ dysfunctions. These dysfunctions encompass metabolic alterations like cachexia, diabetes mellitus, or fatty liver disease, as well as the development of conditions such as liver fibrosis/cirrhosis (Fontan-associated liver disease- FALD), hepatocellular carcinoma, renal impairment, and protein-losing enteropathy [30,31].

Our data show, that PTH levels correlated with inflammatory markers, renal function, dosage of torasemide, low serum albumin and calcium. However, vitamin D levels did not significantly correlate with renal function or inflammatory parameters.

sHPT can be exacerbated by vitamin D deficiency, a condition present in 76.5 % of our Fontan patients. Experimental data suggest that vitamin D deficiency may contribute to heart failure progression. In particular, studies using vitamin D receptor knockout mice showed increased renin levels, leading to activation of the renin-angiotensin-aldosterone system and subsequent cardiac hypertrophy, hypertension, and salt and water retention [6]. Forman et al. demonstrated that in humans, vitamin D deficiency is associated with increased levels of

Table 5
Mean laboratory values in the mild ACHD group, Fontan patients with sHPT, and Fontan patients without sHPT.

parameter	mild ACHD	Fontan with HPT	Fontan without HPT
nt-proBNP (ng/l)	55.71 ± 20.63	541.91 ± 587.86	221.42 ± 167.59
CRP (mg/l)	0.76 ± 0.35	5.18 ± 4.28	1.81 ± 1.66
GDF-15 (ng/l)	445.71 ± 85.58	2307.36 ± 2112.25	748.29 ± 326.76
IL-6 (ng/l)	4.21 ± 8.69	37.8 ± 68.42	2.35 ± 1.44
NL ratio	2.23 ± 0.85	4.69 ± 2.39	3.07 ± 1.16
AST (U/l)	23.29 ± 6.59	34.36 ± 9.07	28.71 ± 7.61
yGT (U/l)	28.93 ± 41.23	133.1 ± 78.87	121.6 ± 123.87
AP (U/l)	70.23 ± 18.51	119.64 ± 28.35	89.42 ± 23.91
CHE (kU/l)	7.92 ± 1.42	6.21 ± 2.2	7.12 ± 1.42
Bilirubin (μmol/l)	10.5 ± 4.85	23.09 ± 20.04	16.13 ± 7.97
Albumin (g/l)	45.57 ± 2.71	40.45 ± 6.41	48.25 ± 3.8
PTH (pg/ml)	35.51 ± 11.44	121.62 ± 62.75	40.69 ± 9.23
25-OH-vitamin D3 (ng/ml)	17.78 ± 6.21	8.56 ± 7.34	16.81 ± 8.36
bone alkaline phosphatase (μg/l)	12.01 ± 5.29	18.64 ± 6.15	14.06 ± 5.4
HbA1c (%)	5.1 ± 0.28	5.6 ± 0.45	5.43 ± 0.42
Creatine (μmol/l)	77.5 ± 14.01	94.82 ± 24.73	79.29 ± 13.18
GFR (ml/min/l)	102.64 ± 14.14	86.91 ± 21.83	103.54 ± 13

25-OH-D3: 25-hydroxyvitamin D3; AP: alkaline phosphatase; AST: aspartate aminotransferase; CHE: cholinesterase; CRP: C reactive protein; GDF-15: growth differentiation factor 15; interleukin-6, GFR: glomerular filtration rate; HbA1c: glycated hemoglobin A1C; NL ratio: neutrophil to lymphocyte ratio; NT-proBNP: N-terminal pro-B-type natriuretic peptide; PTH: parathyroid hormone; yGT: gamma gamma-glutamyl-transpeptidase.

angiotensin II, which can lead to hyperaldosteronism and perpetuate the cycle of sHPT [7]. Additionally, both vitamin D deficiency and sHPT lead to an increased release of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α, further promoting systemic inflammation. Nevertheless, according to the VITAL study, supplementation with vitamin D did not lead to a reduced incidence of invasive cancer or cardiovascular events compared to placebo [32].

Malnutrition, malabsorption, and renal failure are also potential contributors to secondary HPT [33]. Malnutrition and malabsorption are frequently observed in Fontan patients [34]. The main hemodynamic feature after Fontan surgery consists of a constantly elevated central venous pressure. Neurohumoral activation and increased systemic resistance is constantly present, even in the absence of symptoms of heart failure and ventricular dysfunction [35]. As a result, venous hypertension and increased systemic resistance result in decreased perfusion of the gastrointestinal vasculature, resulting in chronic gut inflammation and protein-losing enteropathy. Protein-losing enteropathy occurs in 3–18 % of Fontan patients and leads to intestinal protein loss and nutrient malabsorption [36].

As albumin acts as a major transport protein for calcium, diminished serum albumin levels reduce the transport capacity for calcium ultimately leading to hypocalcemia. This, in turn, can cause sHPT [37]. Moreover, chronic venous congestion can lead to liver dysfunction and impaired synthesis of 25-hydroxyvitamin D, which results in decreased calcium absorption and sHPT suggesting that the Fontan associated chronic liver disease might be of great importance in the development of secondary HPT.

In our study, Fontan patients with sHPT exhibited significantly elevated levels of liver function tests (AST, AP, yGT) in comparison to the mild ACHD control group, suggesting underlying liver disease and hepatic congestion. Additionally, Fontan patients with sHPT had significantly lower levels of albumin compared to both Fontan patients without sHPT and the control group.

We also found a highly significant inverse correlation between serum albumin and PTH. Specifically, when albumin levels were reduced, we observed a corresponding decrease in serum calcium as expected.

Additionally, albumin was inversely correlated with inflammatory markers, such as GDF-15, CRP, and IL-6. Systemic inflammation causes aggravation of malabsorption resulting in decreased albumin levels, which is a major finding in protein losing enteropathy. Diminished serum albumin levels, subsequent hypocalcemia and sHPT may lead to osteopenia and even pathologic bone fractures [38]. Children and young adults with Fontan circulation show lower volumetric trabecular bone mineral density, cortical structure and muscle deficits [19].

Fontan patients with sHPT showed mildly decreased renal function (as per KDIGO stadium G2), in contrast to Fontan patients without sHPT or ACHD controls, who demonstrated normal renal function. Renal failure may also contribute to secondary sHPT, being associated with renal calcium loss, elevated serum phosphate levels, and impaired conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D [33].

Overall, the presence of sHPT indicates advanced disease severity and represents an important co-morbidity in Fontan patients. Fontan patients with sHPT demonstrated significantly elevated liver function tests, lower albumin levels, worse kidney function, more elevated NT-proBNP levels, and higher inflammatory serum markers compared to both Fontan patients without sHPT and the mild ACHD group. However, further studies with a larger study population are necessary to definitively establish a statistical causation between these parameters, clinical outcomes and variables, and the presence of sHPT and vitamin D deficiency.

Further studies are warranted to clarify, whether the treatment of Vitamin D deficiency or Vitamin D prophylaxis might improve outcome.

4.1. Limitations

There are some limitations of our study. Our study is a single center study with a relatively small study population, which precluded the ability to conduct multivariate linear regression analysis to evaluate the independent effects of variables on the occurrence of sHPT.

Subjective evaluation of functional capacity using NYHA class may overestimate the true functional status. Additionally, spiroergometry data was limited, as exercise testing in the year prior to study inclusion was only conducted in 37 % of Fontan patients and 14.3 % of participants with mild ACHD due to the Covid-19 pandemic. Despite its limitations, NYHA class represents an accepted parameter in the majority of studies involving adult congenital heart disease (ACHD).

In addition, the subjects' eating behavior and time outdoors were not recorded. Serum renin, angiotensin, and aldosterone levels as well as fecal alpha-1-antitrypsin levels were not measured.

5. Conclusion

Adult patients with impaired Fontan circulation exhibit significantly higher levels of PTH and lower levels of 25-hydroxyvitamin D compared to patients with well-functioning Fontan circulation or ACHD controls.

Fontan patients may develop sHPT due to a failing Fontan circulation. Chronic low cardiac output and venous hypertension lead to an activation of the renin-angiotensin-aldosterone system and hyperaldosteronism, causing direct renal and gastrointestinal calcium loss, which further deteriorates sHPT. Impaired renal function and vitamin D deficiency may exacerbate sHPT. Elevated levels of PTH were found to be associated with increased systemic inflammation, which, in turn, aggravates PLE and heart failure. PTH could potentially serve as a marker for heart and circulatory failure in Fontan patients.

5.1. Perspective

Further studies are needed to investigate the prognostic value of vitamin D deficiency and sHPT in Fontan patients. Additionally, the

potential effects of vitamin D supplementation on heart failure in this patient population should be elucidated in future studies.

CRediT authorship contribution statement

Friederike Löffler: Writing – review & editing, Writing – original draft, Visualization, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Justus Christian Garlichs:** Writing – review & editing, Data curation. **Sabrina Uehlein:** Writing – review & editing. **Lena Löffler:** Writing – review & editing. **Holger Leitolf:** Writing – review & editing. **Christoph Terkamp:** Writing – review & editing. **Johann Bauersachs:** Writing – review & editing, Supervision, Resources, Project administration. **Mechthild Westhoff-Bleck:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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