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Original Research

# Unveiling the metabolic challenges in pulmonary arterial hypertension: Insights into thyroid, glycemic, lipid, and bone disorders

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ABSTRACT

This study aimed to evaluate the prevalence of thyroid, glycemic, lipid and metabolic bone disorders among adult patients with pulmonary arterial hypertension (PAH).

*Methods:* This was an observational cross-sectional clinical study with patients with PAH, matched by sex and age with a control group without PAH. All individuals were enrolled into a clinical assessment, metabolic workup, thyroid ultrasound, and bone densitometry protocol.

*Results:* The PAH group included 35 participants (34 females, 46 ± 15.5 years), and the control group, 40 (39 females, 41.8 ± 13.1 years). There was no difference in body mass index (BMI) between PAH and control group (27.5 ± 5.9 and 26.9 ± 4.3 kg/m$^2$, respectively, p = 0.63; 95 % CI: −1.8, 2.94), neither in physical activity time per week (60.3 ± 103.3 and 98.9 ± 137.6, respectively, p = 0.17; 95 % CI: −95.23, 18.06). Although there was no difference in the prevalence of insulin resistance between the PAH (51.4 %) and the control group (47.5 %), p = 0.74, patients with PAH had a higher median of glycated hemoglobin (A1c) than the control group (6.1 % and 5.57 %, respectively, p = 0.006; 95 % CI: −0.14, 1.22). PAH group presented lower mean total cholesterol (170.46 ± 35.51 mg/dL) and median LDL-cholesterol [105 (83–129) mg/dL, median (P25–P75)] levels than the control group [192.1 ± 34.44 mg/dL, p = 0.009; 95 % CI = −37.76, 5.52 and 121.6 (97–145) mg/dL, p = 0.012; 95 % CI: −34.08, 0.77, respectively]. It was found a higher prevalence of hypothyroidism (22.9 %) in PAH group than in control group (2.5 %), p = 0.007. We found hyperparathyroidism (HPT) among 8 patients of PAH group (23 %), but none in the control group. Considering bone mineral density disorders, 12 patients from PAH group presented low bone mass, osteopenia, or osteoporosis (34 %), and 8 individuals in the control group (20 %), p = 0.032, which represented a 2.13 higher relative risk for those conditions for the former group. The patients with HPT presented a higher creatinine level (0.98 ± 0.12 mg/dL) than the PAH patients with normal parathyroid hormone (0.76 ± 0.14 mg/dL), p = 0.0004; 95 % CI: 0.12, 0.33. The PAH group also presented lower total hip (-0.15 ± 1.25) and femoral neck (−0.14 ± 1.07) bone mineral density (BMD) Z-scores than the control group (0.50 ± 1.13, p = 0.021; 95 % CI: −0.18, −0.027 and 0.35 ± 0.94, p = 0.038; 95 % CI: −0.16, −0.01, respectively).

*Conclusion:* In this cohort, the findings of higher A1c levels, hypothyroidism prevalence, lower LDL and total cholesterol levels, and a higher prevalence of hyperparathyroidism, as well as lower total hip and femoral neck BMD Z-scores in the PAH group, compared to the control group and highlighting the dysregulation of various metabolic pathways in patients with HAP, suggesting the need for targeted interventions to enhance patient care. Additionally, they underscore the importance of gaining a deeper understanding of the mechanisms driving these changes and their potential pathophysiological connections to the disease.

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## 1. Introduction

Pulmonary arterial hypertension (PAH) is a clinical condition characterized by elevated pulmonary arterial pressure associated with increased pulmonary vascular resistance (PVR) and right ventricular overload [1]. PAH affects individuals of both sexes, across all age groups and ethnicities, with an estimated prevalence of 48–55 cases per one million adults, with a clear predominance among females [2,3]. Despite major therapeutic advances, PAH remains a serious limiting disease, with a three-year survival rate of around 80 % [4].

Several metabolic disorders have been reported in association with PAH, including disturbances in glucose metabolism, bone mineral density, lipid profile and thyroid function [5,6]. These factors collectively contribute to PAH decompensation [7,8].

Autoimmune hypothyroidism is estimated to affect 35–43 % of patients with PAH [9]. In the general population, epidemiological studies report a prevalence of 3.7 % for autoimmune hypothyroidism and 0.5 % for autoimmune hyperthyroidism [10]. These alterations in thyroid function significantly impact the prognosis of individuals with PAH due to their harmful effects on the heart contractility and output, and on pulmonary and systemic vascular resistance. Therefore, thorough monitoring and control of thyroid function in these patients is essential to minimizing the risk of worsening vascular involvement [6].

The association between insulin resistance and PAH has been described in approximately 56 % of individuals [11]. Elevated glycemic levels are believed to be linked to endothelial dysfunction, inflammatory cytokines release, higher levels of endothelin and reduced nitric oxide. These factors may contribute to the proliferation of smooth muscle cells in the pulmonary arterial territory, leading to vascular remodeling and increased pulmonary vascular resistance [7,12,13]. The inflammatory environment could also affect dysfunction and remodeling of the right ventricle [14,15]. Some data indicates that patients with PAH associated with insulin resistance (IR) or type 2 diabetes mellitus (T2D) have higher morbidity and mortality rates compared to those with PAH without IR or T2D [16].

The characteristic lipid profile described for PAH patients is represented by decreased HDL, LDL, and total cholesterol levels [17], alongside increased triglycerides (TG). An elevated TG/HDL ratio partly defines lipid-induced insulin resistance observed in PAH patients [18].

The bone physiology in this population may also be compromised, with a high prevalence of low bone mass and osteoporosis. Contributing factors include long-term glucocorticoids and calcium-depleting diuretics therapy, estrogen deficiency during perimenopausal and postmenopausal periods, smoking, low vitamin D levels, and insufficient dietary calcium intake, similar to trends observed in the general population [19,20].

Given the increased prevalence of metabolic disorders in patients with PAH and their negative impact on their health, coupled with the limited data on the Brazilian population, this study aimed to evaluate the thyroid, glycemic, lipid, and bone metabolic profiles of patients with PAH treated at a Brazilian tertiary hospital.

## 2. Materials and methods

This observational clinical study utilized an analytical cross-sectional design and was conducted at the Pulmonology Outpatient Clinic of the University Hospital of Brasília (HUB), between September 2022 and April 2023. The study included a convenience sample of 59 adults with PAH (PAH group) matched by sex and age with individuals without PAH who were recruited through hospital posters (control group).

To be included in the PAH group, patients needed a hemodynamically confirmed diagnosis of PAH, be over 18 years of age, have complete hemodynamic and clinical data records, and be in regular follow-up at the outpatient clinic. The control group included individuals without PAH, over 18 years of age, with no previous history of thyroid, glycemic, and/or metabolic bone dysfunction (including low bone mass and osteoporosis). Patients who did not undergo all proposed tests in the study and/or had other conditions that could affect the studied metabolic functions were excluded.

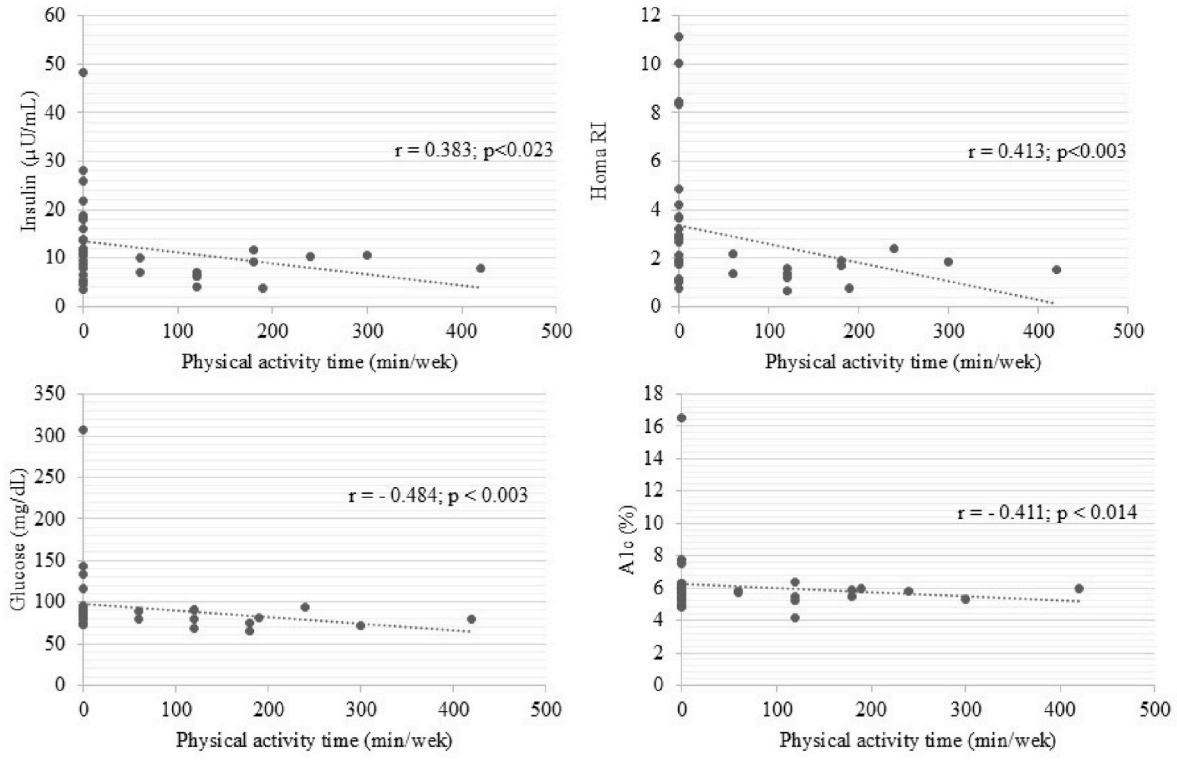


**Fig. 1.** Correlation between physical activity time and insulin and HOMA-RI. Correlation between distance walked in the walking test and glucose and A1c in the PAH group.

For hemodynamic assessment, it was adopted the criteria of the 6th World Symposium on Pulmonary Hypertension Association [21]. Clinical characterization of patients included the distance covered in the 6-min walk test (6MWT), B-type natriuretic peptide (BNP) or its precursor, NT-proBNP, levels, and their dyspnea classification according to the New York Heart Association functional class (FC-NYHA)/World Health Organization (WHO). The patients also reported the intensity and duration of their weekly physical activity, in minutes.

The study was approved by the Research Ethics Committee of the Faculty of Medical Sciences of the University of Brasília (CEP-FM/UnB) on September 2, 2022, under registration CAAE 60463422.6.0000.5558, position number: 5.622.834.

Demographic information, clinical assessments and details on physical activity (frequency, type, duration, and intensity performed during the week) were gathered through anamnesis, physical examination, laboratory tests, and imaging studies specially carried out for this study. Hemodynamic data, BNP or NT-proBNP levels and the 6MWT results were extracted from the patients' medical records. Metabolic laboratory evaluation, bone densitometry, and thyroid ultrasound were performed prospectively.

Thyroid function, glycemic and lipid profiles, and parameters related to bone and mineral metabolism were assessed through serum levels of thyroid stimulating hormone (TSH), free thyroxine (Free T4), triiodothyronine (T3), antithyroid peroxidase antibodies (ATPO), antithyroglobulin antibodies (ATT), thyrotropin receptor antibodies (TRAB), fasting glucose, insulin, glycated hemoglobin (A1c), cholesterol, triglycerides, calcium, phosphorus, magnesium, creatinine, alkaline phosphatase, parathyroid hormone (PTH), 25-OH-vitamin D, albumin. Additionally, glucose, calcium, phosphorus, magnesium, and creatinine were measured in spot urine samples for calculating their fraction of excretion.

Insulin resistance was defined for values of HOMA-IR $>$ 2.77 (homeostasis model assessment of *insulin resistance*), a TG/HDL ratio (triglycerides/high density lipoprotein cholesterol) of 3 or higher, or insulin levels 15.7 microU/mL or more [22–24]. HOMA-IR was calculated using fasting glucose and insulin with the formula: [fasting glucose (mg/dL) x 0.0555 x fasting serum insulin (mUI/L)/22.5] [25].

Hypothyroidism was defined by elevated TSH levels (higher than 10 mIU/L), with or without low free T4, while subclinical hypothyroidism was noted for TSH levels between the normal upper limit and 10 mIU/L. Hyperthyroidism was identified by suppressed TSH levels and elevated free T4, and subclinical hyperthyroidism by suppressed TSH and normal free T4. Since 10–15 % of individuals from the general population without thyroid disease also present anti-thyroid antibodies (anti-thyroid peroxidase - ATPO, and anti-tireoglobulin -TgAb), and weighting the limitations of TgAb as a marker of thyroid autoimmunity, we considered thyroid autoimmunity (Hashimoto thyroiditis or Graves' Disease) positive for ATPO levels greater than 200 UI/L [26] or anti-TSH receptor antibody (TRAB) levels above the reference range (Graves' Disease).

Lumbar spine (L1L4), total hip and femoral neck bone mineral density (BMD) were acquired through dual-energy X-rays absorptiometry (bone densitometry, DXA), following the 2023 International Society of Clinical Densitometry Official Position (ISCD) [27]. Evaluation included both total hip and femoral neck, with the total hip assessment covering a larger volume of bone, including trabecular bone, thus providing a more comprehensive and accurate evaluation of bone metabolism.

Given that the age range of the group extended from 18 to 74 years, and that T-scores of BMD are not meant to be used for women in the menacme period or men younger than 50 years, BMD Z-scores were used for comparing BMD of all individuals. This approach did not interfere on the accurate classification of low bone mass, osteopenia and osteoporosis, according to the ISCD guidelines.

Thyroid ultrasound with Doppler and DXA were conducted by the same professional at the HUB Radiology and Diagnostic Imaging Unit. The thyroid ultrasound assessed gland volume, echotexture, the presence of cysts and/or nodules, and blood flow using Doppler imaging. The ultrasound equipment used was a *PHILIPS® AFFINITI 50G* model with software version *1.5.8.916* and the densitometry machine was a *GE HEALTHCARE® LUNAR PRODIGY ADVANCE* model with software version *ENCORE 18*.

### 2.1. Statistical analysis

A minimum of 34 patients for each group was determined, based on assumed 70 % higher prevalence of thyroid disorders in the study group compared to the control group [28], with a power of 80 % and a type I error of 5 %. Data were expressed as mean ($\overline{X}$) and standard deviation score (SDS), and as medians (Med) and 25th and 75th percentiles (P25 and P75, respectively) for continuous variables with normal and non-normal distribution, respectively. The bootstrapping test was used to define the confidence interval for variables with a non-normal distribution. Normality was tested with the Shapiro-Wilk test. Categorical variables were expressed as absolute frequencies and percentages. The *t*-test for independent samples was used to compare normally distributed variables and the Mann-Whitney test to compare non-normal distributed variables between groups. For comparing mean from three or more subgroups, we used ANOVA. For the correlation analysis in PAH group, it was used Pearson's correlation coefficient for variables with normal distribution and Spearman's correlation for non-normal distributed variables. Relative risks (RR) and odds ratios (OR) were calculated to assess the strength of association in the groups.

The significance level was set at 0.05 for all tests. Data were analyzed using the Statistical Package for Social Science (IBM SPSS®) software version 27.0.

## 3. Results

Of the 104 individuals who met the inclusion criteria, 59 were in the PAH group, and 45 in the control group. After applying the exclusion criteria, the PAH group was reduced to 35 participants (ten excluded due to incomplete records or ongoing investigation, nine withdrew, four who did not belong to group 1 and one due to chronic kidney disease), while the final control group had 40 participants (two excluded due to previous diagnosis of hypothyroidism and three for T2D). The clinical-demographic data of the study participants are detailed in Table 1. In the PAH group, two participants had a prior diagnosis of hypothyroidism, two patients were former smokers and, in the control group, one individual was still a smoker.

Table 2 presents hemodynamic and functional characterization of PAH patients. Regarding PAH classification, there were 14 cases of collagenase, nine idiopathic, eight congenital, two schistosomiasis and two heritable types. Based on noninvasive parameters for PAH risk stratification (6MWT, BNP/NT-proBNP and FC-NYHA), 19 patients were classified as low-risk, 11 as low intermediate risk, four as high intermediate risk, and one as high risk [29].

The glycemic and lipid metabolism tests results are summarized in Table 3. The prevalence of insulin resistance in the PAH group was 51.4 %, while in the control group, 47.5 % ($p = 0.74$). The A1c levels were higher in the PAH group, [Med (P25-P75): 6.1 % (5.4–6) vs 5.47 % (5.3–5.6), $p = 0.006$; 95 % CI: −0.14, 1.22]. On average, the total cholesterol levels of the PAH group were lower compared to the control group, ($\overline{X} \pm$ SDS: 170.46 mg/dL ± 35.51 vs 192.1 mg/dL ± 34.44, $p < 0.05$; 95 % CI: −37.76, −5.52) (Table 3). Additionally, the prevalence of family history of T2D was higher among PAH patients (48.6 %) compared to the control group (20 %), $p = 0.01$.

In the PAH group, 22.9 % (eight patients) presented hypothyroidism, compared to 2.5 % (one patient) in the control group, $p = 0.007$. Regarding autoimmunity, only one patient with PAH tested positive for TRAb, but with normal FT4 and T3, and TSH near lower boundary level.

**Table 1**
Clinical and demographic characterization of the study participants.

| Characteristics | PAH Group (n = 35) | Control Group (n = 40) | p-value* | 95 % CI |
|---|---|---|---|---|
| Age (in years, $\overline{X}$ ± SDS) | 46 ± 15.5 | 41.8 ± 13.1 | 0.20 | −2.33, 10.78 |
| Sex: Female/Male, n | 34/1 | 39/1 | 0.92 | – |
| BMI (Kg/m$^2$, $\overline{X}$ ± SDS) | 27.5 ± 5.9 | 26.9 ± 4.3 | 0.63 | −1.8, 2.94 |
| Duration of disease (years) | 3.22 ± 2.89 | – | – | |
| Physical activity time (minutes per week, $\overline{X}$ ± SDS) | 60.3 ± 103.3 | 98.9 ± 137.6 | 0.17 | −95.23, 18.06 |
| Intensity of physical activity, n (%) | | | 0.17 | – |
| Sedentary | 23 (65.7) | 24 (60) | | |
| Low | 9 (25.7) | 5 (12.5) | | |
| Moderate | 2 (5.7) | 8 (20) | | |
| Vigorous | 1 (2.9) | 3 (7.5) | | |
| Use of sildenafil, n (%) | 34 (97.1) | – | – | |
| Use of ambrisentan, n (%) | 2 (5.7) | – | – | |
| Use of bosentan, n (%) | 26 (74.3) | – | – | |
| Use of furosemide, n (%) | | – | – | |
| Up to 80 mg/day | 13 (34.3) | – | | |
| More than 80 mg/day | 9 (25.8) | – | | |
| Use of prednisone, n (%) | 7 (20) | – | – | |
| Use of hydrochlorothiazide, n (%) | 5 (14.3) | – | – | |

$\overline{X}$: mean; SDS: standard deviation score; CI: confidence interval; BMI: body mass index; PAH: pulmonary arterial hypertension; T2D: type 2 diabetes mellitus.

**Table 2**
Clinical, functional and hemodynamic characterization of patients with PAH.

| Hemodynamic Characteristics of Patients with PAH | | |
|---|---|---|
| NYHA (n, %) | Class 1 | 11 (31.4 %) |
| | Class 2 | 13 (37.1 %) |
| | Class 3 | 10 (28.6 %) |
| | Class 4 | 1 (2.9 %) |
| 6MWT ($\overline{X}$ ± SDS) | Distance walked (m) | 400.69 ± 102.55 |
| | Initial HR (bpm) | 89.09 ± 14.77 |
| | Final HR (bpm) | 115.77 ± 20.22 |
| | Initial SatO2 (%) | 94 ± 4.01 |
| | Final SatO2 (%) | 89.37 ± 7.95 |
| Pro-BNP (pg/mL), $\overline{X}$ ± SDS | | 681.28 ± 189.56 |
| RHC | mPAP (mmHg) | 51.16 ± 15.93 |
| | LVEDP[a] (mmHg) | 7.38 ± 3.49 |
| | PAOP[a] (mmHg) | 11.14 ± 8.78 |
| | PVR (dyne.s/cm$^5$) | 12.19 ± 8.66 |
| | Cardiac Index (L/min/m$^2$) | 2.67 ± 1.12 |

NYHA: New York Heart Association; $\overline{X}$ ± SDS: mean ± standard deviation score; 6MWT: 6-min walk test; bpm: beats per minute; RHC: right heart catheterization; mPAP: mean pulmonary artery pressure; LVEDP: left ventricular end-diastolic pressure; PAOP: pulmonary artery occlusion pressure; PVR: pulmonary vascular resistance.
Normal values: NT-ProBNB (<125 pg/mL).
[a] Some patients underwent right and left catheterization with LVEDP measurement; in other patients, venous pressure was assessed by POAP.

No significant difference in TSH levels were observed between PAH (4.07 ± 4.91 mIU/L) and control groups (2.83 ± 2.01 mIU/L), p = 0.15; 95 % CI: 2.85, 6.12. Additionally, no difference was found in mean TSH levels among patients (p = 0.78) when grouped according to PAH risk stratification in four strata [29].

The mean thyroid gland volume was 6.37 cm$^3$ ± 3.08 in the PAH group and 7.11 cm$^3$ ± 2.5 in the control group (p = 0.26; 95 % CI: −2.02, 0.54). Additionally, 82.9 % of the PAH group and 90 % of the control group presented homogeneous echotexture p = 0.37. Cysts were present in 20 % of the PAH group and 25 % of the control group p = 0.6.

**Table 3**
Glycemic and lipid metabolism and thyroid characterization from patients in this study.

| Laboratory Tests | PAH Group n = 35 | Control Group n = 40 | p-value* | 95 % CI |
|---|---|---|---|---|
| Glucose (mg/dL), Med (P25-P75) | 93 (79–91) | 89 (82–93) | 0.27 | −8.83, 17.92 |
| Insulin (μU/mL), Med (P25-P75) | 12.1 (6.5–13.8) | 11.5 (7–14.1) | 0.92 | −2.88, 4.2 |
| HOMA-IR, Med (P25-P75) | 2.92 (1.38–3.23) | 2.6 (1.44–3.09) | 0.74 | −0.78, 1.36 |
| A1c (%), Med (P25-P75) | 6.1 (5.4–6) | 5.5 (5.3–5.6) | **0.006** | −0.14, 1.22 |
| Total Cholesterol (mg/dL), $\overline{X}$ ± SDS | 170.5 ± 35.5 | 192.1 ± 34.4 | **0.009** | −37.76, 5.52 |
| TG (mg/dL), Med (P25-P75) | 111 (74–142) | 114 (70–147) | 0.93 | −30.44, 23.61 |
| HDL (mg/dL), $\overline{X}$ ± SDS | 52.2 ± 16.4 | 56 ± 55.5 | 0.2 | −10.08, 2.83 |
| TG/HDL Ratio, Med (P25-P75) | 2.46 (1.31–3.09) | 2.26 (1.07–2.76) | 0.42 | −0.54, 0.95 |
| LDL (mg/dL); Med (P25-P75) | 105 (83–129) | 121.6 (97–145) | **0.012** | −34.08, 0.77 |
| TSH, $\overline{X}$ ± SDS | 4.18 ± 5.21 | 2.83 ± 2.01 | 0,78 | −0.42, 3.13 |
| Decreased, n (%) | 1 (2,9) | 0 | | |
| Normal, n (%) | 27 (77,1) | 34 (85) | | |
| Elevated, n (%) | 7 (20) | 6 (15) | | |
| Free T4, normal range, n (%) | 35 (100) | 40 (100) | 1 | |
| T3, n (%) | 35 (100) | 40 (100) | 1 | |
| ATPO positive, n(%) | 5 (14,3) | 4 (10) | 0,568 | |
| ATT positive, n (%) | 4 (11,4) | 0 (0) | **0,028** | |
| TRAB positive, n(%) | 1 (2,9) | 0 (0) | 0,28 | |

$\overline{X}$: mean; SDS: standard deviation score; Med: median; CI: confidence interval; A1c: **glycated hemoglobin; HDL:** high-density lipoprotein **TG:** triglycerides; **LDL:** low-density lipoprotein; Free T4: free thyroxine; T3: triiodothyronine; ATPO: antithyroid peroxidase antibodies; ATT: antithyroglobulin antibodies; TRAB: thyrotropin receptor antibodies.

The presence of nodules was 25.7 % in the PAH group and 47.5 % in the control group p = 0.37.

The PAH group had a higher median PTH values than the control group [Med (P25-P75): 62 (38.3–69.9) vs 37.59 (30.9–43.6), p < 0.001; 95 % CI: 51.95, 73.08]. However, there was no difference in serum calcium, albumin, 25-hydroxy-vitamin D and alkaline phosphatase, nor in urinary fractional excretion of calcium (Table 4). Eight patients in the PAH group had hyperparathyroidism - HPT (six normocalcemic and two hypercalcemic) and none of the control group. In an exploratory analysis, we found that t**he patients with HPT presented a higher creatinine and NT-proBNP levels 0.98 ± 0.12 mg/dL (p < 0.001; 95 % CI: 0.12, 0.33) and 2062.8 ± 1723.3 pg/mL (p < 0.001; 95 % CI: 1107.55, 2474.14), respectively than the PAH patients with normal parathyroid hormone 0.76 ± 0.14 mg/dL and 280.2 ± 292.2.**

The prevalence of BMD disorders, including low bone mass, osteopenia and osteoporosis was 43 % in the PAH group, compared to 20 % in the control group (p = 0.032), as shown in Table 5. Relative risk of presenting low bone mass, osteopenia or osteoporosis among PAH patients was 2.13 (95 % CI: 1.03, 4.44) higher than among the control group, with an odds ratio of 3 (95 % CI: 1.08, 8.35). Relative risk of PAH patients presenting osteoporosis was 1.14 (95 % CI: 0.24, 5.31) higher than the control group, with an odds ratio of 1.16 (95 % CI: 0.23, 5.82).

Additionally, on average, the total hip and femoral neck BMD Z-scores in the PAH group were lower than in the control group, ($\overline{X}$ ± SDS: −0.149 ± 1.247 vs 0.497 ± 1.132, p < 0.05; 95 % CI: −0.18, −0.027) and ($\overline{X}$ ± SDS: −0.137 ± 1.069 vs 0.353 ± 0.937, p < 0.05; 95 % CI: −0.16, −0.01), respectively, also shown in Table 5.

In PAH patients, moderate positive correlations were found between body mass index (BMI) and serum triglycerides/HDL ratio (r = 0.414; p

**Table 4**
Mineral and bone biochemical tests from the studied groups.

| Laboratory Tests | PAH Group n = 35 | Control Group n = 40 | p-value* | 95 % CI |
|---|---|---|---|---|
| Serum phosphorus (mg/dL), Med (P25-P75) | 3.9 (3.5–4.1) | 3.9 (3.5–4.2) | 0.99 | −0.26, 0.25 |
| Serum calcium (mg/dL), $\overline{X}$ ± SDS | 9.29 ± 0.64 | 9.32 ± 0.35 | 0.8 | −0.26, 0.2 |
| Serum alkaline phosphatase (U/L), Med (P25-P75) | 83 (62–100) | 72.7 (60–85) | 0.18 | −0.6, 21.81 |
| Serum albumin (g/dL), Med (P25-P75) | 4.3 (4.1–4.6) | 4.35 (4.2–4.5) | 0.56 | −0.29, 0.09 |
| 25-Hydroxyvitamin D (ng/mL), $\overline{X}$ ± SDS | 28.66 ± 10.23 | 29.18 ± 8.1 | 0.81 | −4.73, 3.7 |
| Parathyroid hormone (pg/mL), Med (P25-P75) | 62 (38.3–69.9) | 37.59 (30.9–43.6) | **<0.001** | 13.51, 35.39 |
| FE calcium (%), Med (P25-P75) | 0.63 (0.002–0.008) | 0.86 (0.004–0.012) | 0.065 | −0.004, 0.0001 |
| FE phosphorus (%), Med (P25-P75) | 0.13 (0.0006–0.0017) | 0.12 (0.06) | 0.516 | −0.0002, 0.0005 |

$\overline{X}$: mean; SDS: standard deviation score; Med: median; CI: confidence interval; FE: fractional excretion.
Reference ranges: serum calcium (8.8–2.2 mg/dL), serum alkaline phosphatase (female: 35–104 U/L; male: 40–129 U/L), serum phosphate (2.5–4.5 mg/dL), serum albumin (3.5–5.2 g/dL), 25-Hydroxy-D (20–80 ng/mL), PTH (15–65 pg/mL).

**Table 5**
Bone densitometry data from patients of the studied groups.

| | | PAH Group n = 35 | Control Group n = 40 | p-value* | 95 % CI |
|---|---|---|---|---|---|
| Female patients in menacme and males under 50 years old | Normal BMD n (%) | 17/20 (85 %) | 25/26 (96.2 %) | 0.18 | |
| | Low BMD n (%) | 3/20 (15 %) | 1/26 (3.8 %) | 0.18 | |
| Post-menopausal women and men 50 years old or older | Normal BMD n (%) | 3/15 (20 %) | 7/14 (50 %) | 0.089 | |
| | Osteopenia n (%) | 9/15 (60 %) | 4/14 (28.6 %) | 0.089 | |
| | Osteoporosis n (%) | 3/15 (20 %) | 3/14 (21.4 %) | 0.928 | |
| L1L4 BMD Z-score, $\overline{X}$ ± SDS | | −0.13 ± 1.67 | 0.56 ± 1.38 | 0.051 | −0.19, −0.009 |
| Total hip BMD Z-score, $\overline{X}$ ± SDS | | −0.15 ± 1.25 | 0.50 ± 1.13 | **0.021** | −0.18, −0.027 |
| Femoral neck BMD Z-score, $\overline{X}$ ± SDS | | −0.14 ± 1.07 | 0.35 ± 0.94 | **0.038** | −0.16, −0.01 |
| Normal bone mass (n) | | 20 | 32 | **0.032** | |
| Low bone mass/osteopenia (n) | | 12 | 5 | **0.024** | |
| Osteoporosis | | 3 | 3 | 0.86 | |

$\overline{X}$: mean; SDS: standard deviation score; CI: confidence interval; BMD: bone mineral densitometry.

= 0.013). Fasting glucose levels were positively correlated with triglycerides (r = 0.403; p = 0.017) and calcium (r = 0.469; p = 0.004). A1c levels were positively correlated with triglycerides/HDL ratio (r = 0.340; p = 0.046).

Among PAH patients, variables related to physical activity/capacity were also correlated with glycemic metabolism. Physical activity time was negatively correlated with serum insulin levels (r = −0.383; p < 0.023) and HOMA-IR (r = −0.413; p < 0.003). The 6MWT was negatively correlated with fasting glucose level (r = −0.484; p < 0.003) and A1c (r = −0.411; p < 0.014). BMI was positively correlated with L1L4 BMD Z-score (r = 0.522; p = 0.001) and total hip BMD Z-score (r = 0.389; p = 0.021) (see Fig. 1).

## 4. Discussion

In this study, we evaluated clinical, metabolic, and bone health parameters in PAH patients versus a control group. The PAH group demonstrated a higher prevalence of metabolic and bone health abnormalities, including increased insulin resistance and a significantly higher prevalence of hypothyroidism and hyperparathyroidism. Notably, PAH patients exhibited lower bone mineral density (BMD) and faced a 2.13-fold increased risk of low bone mass, osteopenia, or osteoporosis compared to the control group.

Patients in the PAH group, on average, had a low-risk profile based on hemodynamic assessment. Out of the 35 patients, 19 presented a low-risk, 11 low intermediate risk, four high intermediate risk and one high risk profile, as determined by the 6MWT performance, BNP/NT-proBNP levels and FC-NYHA classification. This profile contrasts with literature, where around 60 % of patients are classified as low/high intermediate risk [29]. This discrepancy might be attributed to the patients receiving specific vasodilator treatments and maintained adequate disease control.

The PAH group had higher levels of A1c, which may be linked to poorer prognosis due to higher cytokines production that can affect cardiac remodeling and contribute to greater vascular resistance [15]. In the PAH group, there were inverse correlations between A1c levels and fasting glucose with the distance covered in the 6MWT. This suggests that the physical capacity limitations in PAH patients may contribute to higher A1c levels, alongside potential genetic influences.

Although there was no difference in the prevalence of IR between the groups, data from Federal District (DF) overall population estimate a IR prevalence of 30.41 % [30], and 39.1 % for the Brazilian population, using the HOMA-IR method [31]. These rates were lower than the 51.4 % observed in the PAH group.

The observed lipid profile (lower LDL and total cholesterol compared with control group) aligns with current literature [32]. The reduced LDL-cholesterol described in the PAH population can be attributed to two main hypotheses: higher inflammatory levels in PAH patients, leading to increased LDL clearance [32], and right ventricular overload caused by PAH causing hepatic congestion, thereby contributing to reduced LDL production [32,33]. Interestingly, we did not find a higher TG/HDL ratio in PAH group, as reported in the literature. This may be explained by increased TG levels in the control group, possibly related to their lifestyle (mean BMI 26.9 ± 4.3 kg/m$^2$, 60 % of sedentarism).

The higher prevalence of hypothyroidism found in the PAH group (22.9 %) is consistent with other studies [28], which report rates from 19 to 24 %, significantly higher than the prevalence in the Brazilian general population, 5.7–7.4 % [34,35]. This rate also exceeded those described for other populations 2.5–9.5 % [28,36]. The absence of alteration in blood flow on thyroid Doppler ultrasound among PAH patients suggests that the chance of a low cardiac output in PAH does not directly impact their thyroid glands macro perfusion.

Increased PTH levels in patients with heart failure have been described in the literature as a marker of severity, with a well-established association with elevated BNP or NT-proBNP levels. In an experimental study, the administration of PTH to mice subjected to left ventricular overload led to remodeling with increased muscle thickness, increased internal cavity, and increased left ventricular mass when compared to the control group, indicating a deleterious effect of

elevated PTH levels on the heart. In our study, creatinine and NT-proBNP levels were higher in the subgroup with elevated PTH levels [37,38]. This result is in accordance with the literature and suggests that the relationship between PTH and right ventricular failure, due to high pulmonary vascular resistance, seems to behave similarly to that observed in the left heart failure [39].

Despite fiding a 43 % prevalence of BMD disorders, including low bone mass, osteopenia, and osteoporosis in the PAH group, and a relative risk 2.13 higher than the control group, literature on bone mass disturbances among patients with PAH is still scarce. Furthermore, the lower total hip and femoral neck BMD Z-scores in the PAH group suggest a negative impact of PAH on bone mineral density.

The moderate positive correlation between BMI and L1L4, and the total hip BMD Z-score in PAH group, can be attributed to the mechanic load on the bone, which is increased in overweight and obese patients [40]. In contrast to this positive effect of weight on bone mass, the inflammatory microenvironment prevalent in PAH, and worsened by obesity, physical activity limitations and/or pharmacological interventions may counteract that mechanical protection, leading to a lower bone mass compared to control group [41].

A prevalence of 69 % osteopenia and osteoporosis was reported in a cohort study, focusing severely affected patients evaluated for lung transplantation [20]. Another study, involving 32 class III and IV PAH Russian patients, described a positive correlation between lumbar spine and femoral neck BMD Z-scores and pulmonary vascular resistance [42]. In our study, however, no correlation between pulmonary vascular resistance, cardiac index, and right atrial pressure with BMD Z-scores was found.

This study has several limitations, such as the small sample size and temporal mismatch between assessment of RHC, NT-pro BNP/BNP, 6MWT evaluations, along with glucose, lipid, thyroid, bone metabolism and imaging.

Nevertheless, the data from this study reinforces the need for establishing a long-term protocol to monitor glycemic, lipid, thyroid, and bone metabolism in this patient group. Additionally, these findings could lead to a deeper understanding of the underlying mechanisms of such disorders and their potential pathophysiological links with PAH.

## 5. Conclusion

In our study, PAH patients presented higher levels of A1c, a greater prevalence of hypothyroidism and hyperparathyroidism, lower LDL and total cholesterol levels and lower total hip and femoral neck BMD Z-scores, compared to the control group. These findings underscore some potential systemic implications for PAH patients and highlight the importance of comprehensive monitoring and management of their metabolic and bone health.

## CRediT authorship contribution statement

**Odil Garrido Campos de Andrade:** Writing – review & editing, Writing – original draft, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Luiz Claudio Gonçalves de Castro:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Formal analysis, Conceptualization. **Veronica Moreira Amado:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

## Consent to participate

*Informed consent was obtained from all individual participants included in the study.*

## Ethics approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the University of Brasília in September 2022, under registration number CAAE 60463422.6.0000.5558.

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## 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 article.

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